Principles and Practice of
Geriatric Medicine

Fourth Edition

Volume 2

Principles and Practice of Geriatric Medicine, 4th Edition. Edited by M.S. John Pathy, Alan J. Sinclair and John E. Morley.
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In memory of my wife, Norma Mary, for her enduring support and encouragement and to my children, Aidan, Anne, Sarah, Helen and Damian for graciously accepting the limitations of my time.

- M.S. John Pathy

In loving memory of my parents, to whom I owe so much, and to my wife, Caroline, for her unflinching support throughout these last two years during the preparation of this textbook.

- Alan J. Sinclair

To all my older friends and patients who have taught me geriatrics, to my wife Pat and my children Robert, Sue and Jacqueline who have supported me throughout my career and to my grandchildren Amanda, Conor, Katelyn, Nicole and Paige who are my eternal joy and my hope for the future of elder care.

- John E. Morley

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Preface

"I offer no apology for the publication of this volume. The subject is one of the highest importance, and yet it has been strangely overlooked during the last half-century by the physicians of all countries."

-George Edward Day
(1815–1872)

George Day's introduction to his textbook *Disease of Advanced Life*, published in 1848, regrettably remains appropriate for textbooks published over 150 years later. Modern physicians can still fail to recognize the differences in disease presentation and management between middle-aged and older adults. It is our hope that this Fourth Edition of "Principles and Practice of Geriatric Medicine" will help increase the awareness of geriatric principles and improve the treatment of older individuals. John Pathy's original vision for the first edition was to provide, in a single volume, a comprehensive reference source for all those involved in the medicine of old age. We have endeavored to adhere to this vision, but inevitably the size of the textbook has grown. While in any text of this size some overlap with general texts of medicine will occur, the emphasis is on those assessments and disorders that are particularly of relevance to older persons.

Over the seven years since the last edition of this text was published, there have been dramatic advances in our understanding of the pathophysiology of disease as it interacts with the physiological processes of aging. There has been a continuing validation of assessment tools for older persons and the development of some new ones. Large-scale studies of the efficacy of various geriatric systems such as Acute Care for the Elderly Units, Geriatric Evaluation and Management Units, and Home Care Systems have been carried out. All of these have demonstrated the value and cost-effectiveness of the geriatric specialist approach to managing older people. In comparison, most studies assessing Coronary Care Units and Intensive Care Units have failed to come close to demonstrating the effectiveness that has been shown for geriatric units. Despite this, all major hospitals have highly expensive critical care units, while fewer have developed geriatric units. The last decade has also seen an increased awareness of the need to enhance the quality of long-term care. This increase in geriatric knowledge has been recognized by the addition of nearly 40 new chapters in this edition. In addition, many of the previous chapters have been totally rewritten to allow the recognition of the changes that have occurred in our understanding of the care of older persons.

Previous editions of this textbook were edited by a single person, John Pathy. With the rapid increase in geriatric knowledge and John's desire for the Fourth Edition to reflect the input of other academic minds, he has added two new editors to share the burden with him, namely, Alan Sinclair and John Morley. This has allowed a more even distribution of the editing tasks, though John Pathy has continued to carry the lion's share. In recognition of the globalization of the world, in general, and geriatrics, in particular, one of the new editors, John Morley, is from the United States, while Alan Sinclair draws on his European experiences. In addition, a major effort has been made at the end of the text to recognize the differences (as well as the similarities) of geriatrics as it is practiced around the world. The enormous good fortune the editors had in recruiting a stellar class of contributors from around the world has, we hope, allowed this text to be truly representative of a global view of geriatric medicine. From the beginning, John Pathy has made this a goal of his text, and the editors feel that this edition has truly achieved an international view of old-age medicine as originally developed by Marjorie Warren and her colleagues in the United Kingdom.

The general outline of the text still follows that of the first edition. The first sections provide a general perspective of old age, the processes of aging, and social and community perspectives. The chapter on preventive medicine now focuses on issues of particular importance to older persons. In Part III "Medicine in Old Age", the section "Eating Disorders and Nutritional Health" has been increased to recognize the increased importance and understanding of nutrition in old age. Chapters on frailty, sarcopenia, palliative care, and women's health have been added to recognize the increasing importance of these issues in older persons. The final part on "Health Care Systems" focuses first on the emergence of continuous quality improvement, geriatric systems and evidence-based medicine as the foundation of high-quality geriatric medicine. The development of novel education systems is discussed. Finally, unique aspects of geriatric care around the world are examined.

In an attempt to improve the readability of the text, we have asked the authors to make liberal use of tables and figures, and key points have been added at the end of each chapter. References have been limited, and at the beginning of the reference list, authors identify a few key references to allow for further reading. The new editors have tried to keep the easy reading style of the previous editions, but, as can be

imagined, this has been a difficult task as we have increased the number of contributors from around the world.

Overall, we hope our readers enjoy and learn from this textbook; for the three of us, it has been a true labor of love. We particularly would like to thank our contributors for the excellent job they have done. We would also like to thank Layla Paggetti from John Wiley & Sons for her tireless efforts in making sure this book came to fruition. Finally, we would like to thank our families for their forbearance. This book is dedicated to all those who care for older persons.

M.S. John Pathy, Alan J. Sinclair, John E. Morley
December 2005

Preface to the Third Edition

With an increasingly aging population in both the industrialized and developing world, the health care needs of older people can no longer be dismissed by society.

A national provision for geriatric medical services was initially a British phenomenon that was later adopted by other European nations. On the other hand, the USA has long been at the forefront of much gerontological research. During the past decade, however, clinical practice and teaching in geriatric medicine has also moved forward at a phenomenal pace. The balance in this new edition reflects and emphasizes these changes.

Those familiar with the previous editions will note that this edition has been published as a two volume set. This has been necessitated by the addition of 27 new chapters and the reorganization of and increase in the number of clinical chapters. The original objective of providing an authoritative text on the medicine of old age has been maintained thanks to the distinguished panel of nearly 200 international contributors.

It is with deepest regret that I record the deaths of Professor Verna Wright and Professor Frank Benson.

Dr John Morris, Dr Arup Banergee and Dr Brian Williams have generously provided editorial advice on the gastroenterology, haematology and cardiology sections respectively.

The sustained support of Michael Osuch and Lewis Derrick of John Wiley & Sons is gratefully acknowledged.

It is hoped that these two volumes will encourage and inform all those whose clinical practice brings them into contact with elderly patients.

Preface to the Second Edition

In this new edition my priority was not only to revise and update, but to reorganize and restructure to make the information as accessible and useful to the reader as possible. The result is that not only have we included some 45 distinguished new contributors, and indeed several entirely new topics, but about 50% of the book has been rewritten almost from scratch, with the remainder heavily revised and updated, and the entire content radically reorganized into what I believe is a more practical and logical format. New subjects now considered to be at the forefront of practice, and some published here for the first time, are covered, and I am delighted to welcome the following group of new authors:

Professor D. Armstrong, Dr C.A. Bar, Dr W.H. Barker, Dr A.J. Bayer, Professor M. Bergman, Dr E.T. Bloom, Dr D.G. Clements, Dr K.J. Collins, Dr I.G. Finlay, Dr P. Finucane, Dr C. Freer, Dr S.R. Gambert, Professor A.M. Gelb, Ms J.E. Griffiths, Dr J.T. Hartford, Ms A.E. Helfand, Dr S.J. James, Mr D.F. Jessett, Dr R.A. Kane, Professor H. Katsunuma, Professor H. Kesteloot, Dr J. Lubinski, Dr L.M. Luxon, Professor W.J. Maclennan, Dr S.S. McCachren, Professor J.F. Macias-Nunez, Dr S.E. Mathers, Dr K. Morgan, Dr J.G. O'Brien, Dr M.E. Piper, Dr J. Powell, Ms H.G. Prince, Dr T. Pullar, Dr D.S. Rosenthal, Dr H.R. Silberman, Dr I.C. Stewart, Dr R. Strong, Professor M. Swash, Professor C.G. Swift, Professor W.A. Wallace, Dr M.F. Wilkins, Dr W.G. Wood, Dr A.M. Woods, Professor V. Wright.

It is with deepest regret, however, that I must record the death of three contributors:

Professor A.N. Exton-Smith, Dr R.A. Griffiths and Sir Alan Parks.

I express my sincere appreciation to Dr A.J. Bayer for his invaluable assistance with some of the chapters, to my secretary, Mrs Shirley Green, for her meticulous typing, checking of references and collating material, and to the Department of Medical Illustration, University of Wales College of Medicine, for undertaking the additional illustrations for the revised chapter on rehabilitation in the elderly. It is a pleasure to acknowledge the high standard of general editorial services provided by Dr Lewis Derrick, Desk Editor, and the continuing support of Mrs Verity Waite, Publishing Editor in Medicine, John Wiley & Sons.

Preface to the First Edition

In some parts of the world, notably Europe, North America and Japan, the impact of an expanding elderly population resulting from an era of unprecedented reduction in the diseases of early life has already had a dramatic effect on the epidemiology of disease. Within the foreseeable future no nation will escape a similar increase in the number of its elderly citizens with similar changes in the disease profile of its society. In the developed industrial nations Governments and medical schools, recognizing this phenomenon, are increasingly encouraging teaching and research in the medicine of later life. The objective of this textbook, written by authors of international repute, is to provide in a single volume a comprehensive reference source for all who are involved in the medicine of old age. Some overlap with textbooks of general medicine is inevitable but appropriate emphasis and attention is given to those disorders which are of particular relevance to the elderly.

Whilst this is primarily a clinical textbook, an account is given of the fundamental changes associated with aging which are so inextricably interlinked with diseases that their study is essential to our understanding and management of elderly sick and disabled people.

Equally important for those treating and caring for the old is an understanding of the influence, for good or ill, of the social environment within which the elderly have to function and its effect on their health.

Knowledge of programmes aimed at the promotion and maintenance of health, early detection of its impending breakdown and the organization and provision of services for health care are additional essential components of a complete account of the medicine of old age.

The early chapters of the book provide a general perspective of old age and the process of aging. Preventive aspects together with accounts of nutrition and sleep in the elderly and the interpretation of biochemical data in older patients, precede the main clinical section which occupies the greater part of the text. The later chapters cover rehabilitation, the management of the dying patient and aspects of the delivery of health care.

I acknowledge with gratitude the willing help of my colleagues, Dr Deirdre Hine and Dr D. Gwyn Seymour who read through much of the text and provided valuable criticisms and suggestions; and to my secretaries Mrs Lorraine Spriggs who did much of the typing and the arduous task of checking references, and Mrs Sylvia Bevan. I am indebted to Dr Ralph Marshall and his team in the Department of Medical Illustration at the University Hospital of Wales for preparing a number of figures and photographs.

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Historical Perspectives

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INTRODUCTION

The broad subject of old age has attracted the attention of writers and philosophers for many centuries. It contains the interrelated topics of the theories of aging, of how to increase longevity, and the medical management of sick elderly people. Initially, the first two themes attracted most attention. It was not until the twentieth century that literature relating to medical care came to the fore. This chapter concentrates on the twentieth-century developments in medical care of the elderly (geriatric medicine), mainly from a British perspective since much of the pioneering work was carried out in the United Kingdom.

THE EARLIER WRITERS ON OLD AGE

Early writers such as Hippocrates, Cicero, Galen, Roger Bacon, and Francis Bacon discussed old age in general terms pointing to features such as skin changes, reduction in physical strength, and deteriorating memory, sight, and hearing. None were sure of the cause(s) of old age. Theories ranged from incorrect diet, loss of heat to loss of moisture. Although the basis of growing old was unclear, several philosophers thought that a healthy old age could be promoted by keeping active, eating sensibly, and exercising regularly.

Later, British writers of the eighteenth and nineteenth centuries, such as Sir John Floyer, Sir John Hill, Sir Anthony Carlisle, Professor George Day, and Sir John Sinclair, wrote about old age and how life might be prolonged, but devoted limited attention to medical management of disease in older people. They generally considered it impossible to turn an elderly man into a young person, but agreed that much could be done to make later life healthy. Lifestyle was important. They recommended wise eating of easily digestible foods taken at regular intervals, exercising regularly, ensuring good sleep, keeping clean, wearing warm clothing, and avoiding constipation. In 1863, Dr Daniel Maclachlan, medical superintendent at the Royal Hospital Chelsea, criticized the lack of English literature relating to old age and pointed out that precise diagnosis could be difficult in older people because several diseases could exist simultaneously. In 1882, the English translation of Jean Martin Charcot's *Clinical Lectures of the Diseases of Old Age* was published, which described an extensive range of subjects including the overt signs of old age, rheumatism, gout, arthritis, fever and its feeble response in older people, respiratory infections, cerebral hemorrhage, and cerebral softening. However, his contribution to treatment and management was limited. The early twentieth-century English writers such as Sir Henry Weber, Dr Robert Saundby, G. Stanley Hall and Sir Humphry Rolleston continued to describe old age, but again medical management received little attention. Maurice Ernest's writing in 1938 pointed out that until the nineteenth century only superficial knowledge existed of how the body worked.

THE BIRTH OF MODERN GERIATRIC MEDICINE

Modern geriatric medicine commenced in the United States. Although American writers in the nineteenth century, such as Dr Benjamin Rush, had published on the subject of old age, the real impetus for advance came later when a young medical student, Ignatz Nascher (1863–1944), an immigrant to America from Vienna, was taken to an almshouse to see some interesting cases. An old woman hobbled up to the medical teacher with a complaint. The class was told that she was suffering from old age and that nothing can be done for her. This remark impressed him so strongly that after qualification he took up the study of the diseases of old age. His lifetime work on the subject resulted in his becoming known as the "father of geriatric medicine". His publication of *Geriatrics* in 1916 was followed by others including Dr Malford Thewlis, who published the first edition of his book, *Geriatrics,* in 1919; Dr Edmund Cowdry's whose *Problems of Aging* appeared in 1939; and

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Dr Alfred Worcester who published a series of lectures in 1940 called *The Care of the Aged, the Dying, and the Dead.* Dr Nathaniel Shock, in 1951, published the first edition of his classification of geriatrics and gerontology but pointed to the scarcity of material. In 1942 the American Geriatrics Society was formed with a membership of physicians, while in 1945 the Gerontological Society of America was created with a multidisciplinary membership. Each of the societies produced its own journal in 1946. Unfortunately, this momentum for change was not sustained, partly because physicians saw little attraction in the subject. Interest was not reignited until the 1960s when Medicare and Medicaid were introduced.

Thus it was that leadership and instruction in modern geriatric medicine in the postwar era passed to the United Kingdom (UK), where the achievements of a handful of pioneers were becoming known.

BRITISH DEVELOPMENTS

Health care in the United Kingdom goes back to that provided by the monasteries until they were dissolved in 1536. After the dissolution many of the aged and infirm, who could not be managed at home with the help of family members, were left uncared for. The Poor Law Relief Act of 1601 attempted to remedy these problems. Parishes levied a rate on all occupiers of property to provide work for the unemployed and accommodation for the lame, old, and blind. Workhouses were built for these purposes, but were made as unpleasant as possible to discourage people from entering them. Infirmaries were established to look after sick inmates of the workhouses. Outdoor relief was available for the poor but this was curtailed in 1832.

Hospitals did not become central to health care until the nineteenth–twentieth centuries, by which time two different types of hospitals were evolving: the voluntary hospitals and the workhouse/municipal infirmaries (Abel-Smith, 1964). Voluntary hospitals, some of which dated back to the tenth century, were financed from endowments, subscriptions, fees, and fund raising. They had a high reputation with good nursing and medical staff, and acted as a base for clinical teaching of medical students. They were reluctant to admit the chronic sick fearing that their beds could become blocked because these patients were slower in improving and there could be social problems preventing their discharge. An important consequence was that medical students rarely saw them and, therefore, were not taught about the diseases of old age or how to manage the mixture of medical and social problems they would meet after qualification.

Workhouse infirmaries were funded by local rates. They gradually became long-stay institutions for the chronic sick. Examples of unsatisfactory conditions and poor care in workhouses and infirmaries surfaced in the 1860s and resulted in visits by the *Lancet* commissioners and the inspectors of the Poor Law Board. The 1869 report of the *Lancet* Sanitary Commission was damning, stating "The fate of the "infirm" inmates of crowded workhouses is lamentable in the extreme; they lead a life which would be like that of a vegetable, were it not that it preserves the doubtful privilege of sensibility to pain and mental misery" (Anonymous, 1869).

In 1929 the Local Government Act came into force, which aimed to correct the existing bipartite system of health care of "one part for the pauper and the other part for the nonpauper". However, Charles Webster concluded that health services between the two world wars were ramshackle and uncoordinated, with hostility between sections of the service, increasingly chaotic funding, and with a hospital service which was unevenly distributed and limited in rural areas (Webster, 1993).

Further reform came in 1948 with the creation of the National Health Service (NHS) which rearranged British health care into a tripartite system. First, there was the hospital service which was formed by the nationalization of 1143 voluntary and 1545 municipal hospitals. It became the dominant partner in the Service. Second, there were the general practitioner and the ophthalmic, pharmaceutical, and dental services. The third arm, which was managed by the local authorities, included health centers, health visitors, and ambulance services. Their immensely valuable home help and meals-on-wheel services did not really "take off" until some years later. Importantly, health care for all became free of charge.

Voluntary and charitable organizations made important contributions to the care of the older person and research into old age. In 1943 the Nuffield Foundation was created, one of whose objectives was the care of the aged and the poor. This support led to the formation of the National Corporation for the Care of Old People in 1947. The Foundation also stimulated major research into the causes of old age (Gerontology). These moves to assist older people became increasingly important as the proportion of older people in the population steadily increased. In 1841, the over-65-year-old people comprised 4.5% of the population, which rose to 4.7% in 1901, 7.8% by 1921, 9.6% by 1931 and reached 10.5% in 1947.

AN OVERVIEW OF EARLY GERIATRIC MEDICINE IN THE UNITED KINGDOM

Modern geriatric medicine in the United Kingdom dates from 1926 when Dr Marjory Warren was appointed to the West Middlesex Hospital, where her interests were initially surgical. However, in 1935 the Hospital took over control of the adjacent old Poor Law institution and Warren was put in charge of 874 patients. The situation she found was described in the first of her many articles on the modern treatment of the chronic sick (Warren, 1943). At about the same time, three other British doctors were also keen to improve the medical care of the elderly: Dr Eric Brooke, Mr Lionel Cosin, and Dr Trevor Howell. Like her, they, too, applied classification, diagnosis, and treatment to their elderly patients, which had been previously missing. After the war, a further wave of

enthusiasts, such as Lord Amulree, Drs John Agate, Charles Andrews, Ferguson Anderson (later Professor), Bill Davison, Hugo Droller, Norman Exton-Smith (later Professor), Tom Wilson, and Lyn Woodford-Williams, began to make their mark with many publications.

These newly appointed postwar consultants in geriatric medicine had to embark on a steep learning curve. In the early days, they had the responsibility for very large numbers of inpatients, sometimes many hundreds, who were often kept in bed for no discernable medical reason, which could ultimately lead to a totally bedridden state. Generally there was a massive waiting list for admission, often precipitated by the death or illness of the carer or the person's inability to prepare meals for him/herself. These new consultants learnt that illness and the presentation of disease in the older person differed from that of younger people, that more time was required to recover, that prescribing drug therapy required great care, that extensive teamwork was needed for successful rehabilitation, and that local social service support was usually essential to provide alternative accommodation or domiciliary support services. They had to provide a service although they lacked adequate resources and staffs, had poor ward accommodation, inadequate investigative/treatment facilities, and were not always based on the main hospital site. They had to fight antagonism and resistance from their fellow consultants and some hospital management committees. One chairman of such a committee refused a consultant geriatrician the use of empty beds in general medical wards: "Over my dead body", he said. When he died the geriatrician got the beds. Another consultant had to fight for proper washing facilities in the wards and for curtains to be placed around the beds of elderly patients. Yet others had to struggle to get heating installed in the wards and repairs made to the leaking ward roofs.

Important studies of the elderly living at home or in residential homes appeared shortly after the war. Dr Joseph Sheldon, a general physician, published *The Social Medicine of Old Age* in 1948, which was the result of his research into the health of the elderly living in the community in Wolverhampton. In 1955, Professor William Hobson and Dr John Pemberton published *The Health of the Elderly at Home,* which was a study of older people living at home in Sheffield. In 1962, Professor Peter Townsend published *The Last Refuge*, a seminal study of old people living in residential homes.

The British Ministry of Health, which was created in 1919, and its medical officers supported the newly emerging style of medical care of the sick elderly patient with official circulars, memoranda, meetings, and documents. These highlighted its firm belief in modern management of elderly patients and the drive to establish a geriatric unit in every health district. The ministry organized surveys of hospitals in England and Wales, which were to be the basis of the forthcoming NHS. The reports, published in 1945, were generally very critical of services and accommodation for the chronic sick. "The worst and oldest buildings were set aside for the chronic sick" (Jones *et al.*, 1945). "The buildings are old, dark, devoid of modern sanitary conveniences, death traps in the case of "fire", and unfit for the nursing of the chronic sick" (Bevers *et al.*, 1945). "The first essential is that every patient should be thoroughly examined and treated with a view to restoring a maximum degree of activity" (Gray and Topping, 1945). Later, Lord Amulree and Dr Edwin Sturdee, both medical officers of the Ministry, presented a paper on the care of the chronic sick to the Parliamentary Medical Committee in 1946 (Amulree and Sturdee, 1946). In it they stated, "not only is the problem of the treatment of the chronic sick not being met, but also most people do not realize there is a problem". In 1957, Dr Christopher Boucher, a Principal Medical Officer at the Ministry, published the result of an important survey of services available to the chronic sick and elderly (Boucher, 1957). However, the ministry realized that it could not force change, but could only use persuasion to improve proper medical services for older people (Godber, 1991). Perhaps this was why that, even in 1978, 42 health districts in England still lacked geriatric beds in general hospitals.

The British Medical Association played its part in planning the medical care of older people with a series of very specific reports. A coordinated geriatric service was recommended to the newly created Regional Health Authorities, supported by a wide range of domiciliary services, which would be needed by the infirm elderly to enable them to stay at home for as long as possible (British Medical Association, 1947, 1948, 1955).

However, commentators looked back to the old Poor Law and the new NHS with mixed feelings (Webster 1988, 1991; Thane 1993, 2000). They pointed out that while the old Poor Law system had given a coordinated personal service to its clients, the tripartite structure of the NHS service led to lack of cooperation and coordination between the arms of the service. Chronic and mental services received a smaller share of capital and revenue, and clear guidelines for the treatment of old people were lacking. The political will to produce a nationwide effective geriatric service was lacking. On the other hand, the new service did provide the less well off with forms of care to which previously they had only limited entrée, and the elderly now had access to consultant services.

THE EARLY PIONEERS IN GERIATRIC MEDICINE

In 1935, *Dr Marjory Winsome Warren*, CBE, MB (1897–1960), was placed in charge of 874 patients from the adjacent Public Assistance Institution. These included 16 maternity patients and about 144 "mental observation" patients, who were subsequently transferred to their appropriate departments. She assessed and examined the remainder. She described the situation as follows:

> Having lost all hope of recovery, with the knowledge that independence has gone, and with a feeling of helplessness and frustration, the patient rapidly loses morale and self respect and develops an apathetic. . .temperament, which leads to laziness and faulty habits, with or without incontinence. Lack of interest in the surroundings,

confinement to bed. . .soon produces pressure sores. . .inevitable loss of muscle tone make for a completely bedridden state. . .[leading to] disuse atrophy of the lower limbs, with postural deformities, stiffness of joints, and contractures. . .in this miserable state, dull, apathetic, helpless, and hopeless, life lingers on, sometimes for years.

(Warren, 1946)

She criticized the medical profession: "It is surprising that [it] has been so long awakening to its responsibilities towards the chronic sick and aged, and that the country at large should have been content to do so little for this section of the community" (Warren, 1946).

She recognized the importance of the environment in helping patients recover. She improved ward lighting, arranged repainting of the wards from the previous drab color to cream, replaced old-fashioned beds, provided modern bedside lockers, bed tables, and headphones, as well as bright red top blankets, light colored bedspreads, and patterned screen curtains. Wards were equipped with handrails attached to the walls, and suitable armchairs provided. Floors were no longer highly polished and steps were avoided. Special chairs and walking sticks and frames were provided for arthritic and heart patients. Some equipment she designed herself is still used today. She was the first British geriatrician to publish admission, death, and discharge data. By 1948, Warren reported that the general medical staff acknowledged that their "chronic" elderly patients actually did better in the geriatric unit than in their own wards.

Mr Lionel Zelick Cosin, FRCS (1910–1993), came from a surgical background to the care of the elderly chronic sick (Cosin, 1991). At the outbreak of war, he was drafted to Orsett Lodge Hospital in Essex, which had been upgraded to an Emergency Medical Service Hospital in 1939. He became responsible for 300 chronic sick patients in addition to his surgical commitments. He found that they were fed and kept clean but no other treatment was given. When ordinary admissions restarted in 1944, he admitted elderly women with fractured femurs, successfully operated on them, gave them rehabilitation, and discharged them home.

In 1950, he was invited to establish a geriatric unit at Cowley Road Hospital in Oxford, where he became its first clinical director and established the first day hospital in the United Kingdom. He classified, diagnosed, and treated his elderly patients. He reorganized inpatient accommodation, creating an acute geriatric ward for investigation, treatment, and physiotherapy as well as a long-stay annex ward for the permanently bedfast, long-stay wards for the frail ambulant, and "residential home" type of accommodation for the more robust patients. These methods resulted in the average length of stay falling from 286 days to 51 days. The proportion remaining in hospital longer than 180 days declined from 20 to 7%. Admissions increased from 200 a year to 1200 through the same number of beds. The average age of the patients increased from 68 to 75 years. Approximately 10% of his patients became permanent bedfast (Cosin, 1956).

Dr Eric Barrington Brooke, FRCP (1896–1957), became the first medical superintendent of newly built, 800 bedded, St Helier Hospital in Carshalton. The building was hit several times by enemy bombs, his superintendent's house was destroyed by a flying bomb in 1944, and he was severely wounded and lost an eye but he returned to duty in due course. In 1953, he was appointed consultant physician to the Southampton group of hospitals.

His approach to his long waiting list for admissions was different from others because he had few hospital beds. He devised a scheme of managing patients at home with a domiciliary "inpatient service" supplemented by increased use of the outpatient department. The process began with a home visit made by a member of the hospital-based geriatric team. These revealed that only one in three of the patients on the list required admission on a short-term basis for investigation and treatment, terminal care, or to provide holiday relief for caring relatives. Where appropriate, he arranged for a coordinated home-based service with district nurses, home helps, domiciliary occupational therapists, a laundry service, and the Red Cross library. The local Women's Voluntary Service set up a hot "meals-on-wheels" domiciliary service. He viewed the general practitioner as the key member of the whole support scheme.

Dr Trevor Henry Howell, FRCP Ed. (1909–1988), first encountered elderly patients when he was a general practitioner before the war. What puzzled him was what represented "normal" for age and what represented disease. After his war service, he established a geriatric research unit at Battersea Hospital in London before becoming medical superintendent at Queen's Hospital, Croydon. He kept meticulous records of his patients, which formed the basis of over 300 papers and four books that he wrote. He kept a handwritten record of every book he read, every patient he saw, and every postmortem held on his patients. Like his colleagues, he firmly supported teaching medical students. He and Sturdee were the driving force behind the creation in 1948 of the Medical Society for the Care of the Elderly, which later became the British Geriatrics Society. Howell was its secretary for many years.

THE SECOND WAVE OF GERIATRICIANS

These were led by *Lord Amulree*, KBE, MD, FRCP (1900–1983), who, prior to his appointment as geriatric physician to University College Hospital and St Pancras Hospital in London in 1949, had worked at the Ministry of Health on aspects of care of the older person. This had brought him in touch with all the early pioneers. His appointment in geriatric medicine was, for a long time, the only one at a London teaching hospital. He and his staff classified, diagnosed, and treated elderly inpatients. Assessment visits were made to old people who were on the waiting list for admission. This ensured either appropriate placement of patients in hospital or that the necessary home support was arranged to enable the person to continue to stay at home. The result was a considerable shortening in the average inpatient length of stay, increased patient/bed turnover, and a reduced the waiting list.

Amulree was unique amongst geriatricians in having a "wide-angled" view of the care of elderly people. This resulted from his experience as a clinician, as a medical officer of the Ministry of Health and a Liberal peer in the House of Lords, where he spoke on matters relevant to the care of the elderly. He wrote extensively and his work included one of the first comprehensive articles on care of the elderly (Amulree, 1951). He is possibly best remembered for his maxim "Adding Life to Years", as well as his stature, wisdom, and willingness to help colleagues. He was President of the British Geriatrics Society for 25 years. When all his achievements are taken into account, there is a case for calling him "the father of British geriatric medicine".

Professor Norman Exton-Smith, CBE, FRCP (1920–1990), was based at the Withington Hospital in London, before moving to University College Hospital and St Pancras Hospital when Lord Amulree retired. Like others he made detailed assessment of his clinical management of sick elderly people. His style of medical management of inpatient care increased patient turnover and reduced their length of stay. He adapted progressive patient care to fit the needs of geriatric medicine. He led and/or encouraged research work, imbuing enthusiasm in his research team, registrars, and colleagues. He established a research unit at St Pancras Hospital and supported work in subjects such as thermoregulation, control of the autonomic nervous system, falls, osteoporosis, osteomalacia, fractures of the femur, nursing of the elderly patient, pressure sores, nutrition of the older person, meals on wheels, terminal care, predicting mortality, and cognitive assessment. He wrote many papers, a substantive textbook on geriatric medicine, and coauthored several books.

Exton-Smith considered the components of an effective geriatric department that included having a sufficient number of beds, both in total and in the District General Hospital; practicing progressive patient care; having adequate medical and nurse staffing; consulting with other consultant colleagues; making home visits; having a day hospital; and having good coordination with primary care and local authority services to produce a successful planned discharge. He thought that approximately half to two-thirds of all geriatric beds should be in the main hospital where the main diagnostic and treatment facilities were based, while the remainder should be in smaller units near the patients' home.

Professor Sir William Ferguson Anderson, OBE, FRCP (Glasgow, Edinburgh, and London), (1914–2001), was a strong advocate on behalf of older people. In 1965, he was appointed David Cargill Professor of Geriatric Medicine in the University of Glasgow. He firmly believed in the speciality as an academic discipline and the need to teach medical students about old age. He took geriatric medicine into the community, notably in Rutherglen, where he established health centers for the elderly. He wrote extensively, and his textbook *Practical Management of the Elderly* went into five editions. He lectured in many countries spreading the message of the achievements of British geriatric medicine, was a visiting professor to many countries, a major advisor to several medical charities for the elderly, and a superb charismatic ambassador for the speciality.

GERIATRIC MEDICINE IN THE HOSPITAL

Home visits were considered essential in the early days of the speciality. They were initiated by the geriatrician to assess patients on the waiting lists from a medical and social point of view, to gauge priority for admission, to ensure that right patients were admitted to the right bed, to reduce misplacement of elderly patients in inappropriate wards or local authority accommodation and help some patients remain at home with local authority domiciliary support. Knowledge gained at visits was often useful when planning discharge, and often assisted rapport with both patient and relatives. These visits revealed that the true list was often substantially shorter than the "paper" list because some patients had died, moved, recovered, or had been admitted elsewhere since being placed on the list. As waiting lists decreased, so the need for home visits began to disappear. However, domiciliary visits, made by the consultants at the request of the general practitioner, continued.

Progressive patient care was widely practiced throughout the United Kingdom. It was a concept first developed in America in an attempt to overcome a shortage of skilled nurses. It involved moving patients from ward to ward, or sometimes within wards, as they improved or required further treatment. Most were admitted first to the initial treatment ward. From there patients could be discharged home, or moved to the continuation care wards, where they would be divided further into two groups: continued rehabilitation or continued nursing care. From those wards the patients could be discharged, moved to a halfway house to await a place in a welfare home, or returned home. The disadvantage of the system was that beds were not always used to maximum efficiency and nursing continuity was lost as patients moved from ward to ward. On the other hand, it was argued that it helped patients' morale to be moved on as they improved.

A *consultative service* provided by geriatricians to consultant colleagues was another important feature of the new style geriatric service. An excellent example of such collaboration, involving the general and geriatric physicians, resulted in a reduction in mean and median durations of stay in general medical wards (Burley *et al.*, 1979). The mean stay for females over 65 years in general wards was reduced from 25 to 16 days and for the over 85s from 50 to 19 days. These changes were not due to increased transfers to the geriatric wards. Collaboration was particularly important for the orthopedic surgeons to assist the rehabilitation of elderly women after operations for a fractured neck of the femur. A thriving example, which achieved wide recognition, was created in Hastings by Dr Robert Irvine and Mr Michael Devas.

Day hospitals were one of the major innovations in modern geriatric medicine and are viewed by many geriatricians as an essential part of their service. These facilities provided rehabilitation, physical maintenance, follow-up care after discharge from hospital, and allowed minor medical procedures to be undertaken without the need for inpatient admission. The Department of Health and Social Services recommended 2 places/1000 for those over 65 years with the usual size of

a day hospital being 20–40 places per day (Department of Health and Social Security, 1971). They are generally open 5 days a week and require one session of consultant time, two sessions of junior doctor time, ten whole-time equivalent nurses and a rehabilitation team to provide a service for 30-day patients.

Transport has been a major limiting factor in day hospital efficiency. One psychogeriatrician with a large rural area thought patients spent almost as long in the ambulance as at the hospital and wondered if a new form of psychiatric day care should be created called *transport therapy*: "the patient is jogged along the countryside for several hours. . .the hospital became irrelevant and to travel happily becomes more important than to arrive. Meals can be taken at a friendly transport cafe, always provided there is a greater-than-average provision of functioning lavatories" (Arie, 1975). Other delays can result from the considerable time taken to use the tail lift to "load" patients into the ambulance, and the diversion of day hospital ambulance to other duties.

The efficiency and effectiveness of day hospitals has been much debated with criticism targeted at inadequate audit of their function, poor working policies and insufficient consultant input. Unfortunately, reliable data is difficult to obtain. Simple attendance rates are difficult to assess, since they depend on the size of the unit, the availability of transport, public holidays, and staff shortages. Properly designed trials are bedeviled by methodological limitations of the studies. Patients usually attend for different reasons and the number attending individual day hospitals may be small. Day units have different roles in different localities, and there can be difficulties in defining the control groups. The Royal College of Physicians of London reviewed 13 research studies including 6 randomized controlled trials, only two of which were based in the United Kingdom (Research Unit of the Royal College of Physicians, 1994). Unfortunately, they tended to give contradictory results depending on the nature of the treatment received by the control groups.

Long-stay care, for those geriatric patients who fail to recover, has its own special requirements (*A Better Home Life*, 1996). The pace of life is slower but the patients need to be kept as mentally and physically active as possible to prevent institutionalization. Different nursing skills are required. The accommodation needs to be designed to take account of the fact that it is likely to be the patient's home for several years and, therefore, it needs to be appropriately designed. Within the last 20 years or so, much of the long-stay care, which used to be part of the NHS, has been transferred into the private/voluntary sector.

GERIATRIC MEDICINE IN THE COMMUNITY

General practitioners have a pivotal role in elderly care. They provide free medical service for all those on their list of patients and act as first line of referral when the person becomes ill. They can obtain medical support from the geriatric service or the local social service department. Regular review of their patients over the age of 75 years has been promoted.

However, older people may not consult their general practitioner about their symptoms because they may feel that little could be done for them. Case-finding programs, which involve a search for untreated disability, have been revealing. Programs in Scotland found that general practitioners were largely aware of the major disorders affecting the elderly at home but were much less aware of minor disorders such as problems with sight, hearing, and care of toenails, which can have a major impact on quality of life and for which treatment can produce benefit (Williamson *et al.*, 1964). Another major Scottish innovation was the creation of successful health centers to provide a "walk-in" medical assessment and treatment for elderly people (Anderson and Cowan, 1955).

An effective social service department is an essential component of any geriatric service, since it can provide an extensive range of domiciliary care, such as home helps, meals on wheels, occupational therapy, appliances, and visits from the local social worker. Many provide residential homes for those who cannot manage at home even with maximum support and day centers for those who require diversional activities. The local social service departments liaise with voluntary organizations such as Age Concern, old people's clubs, and church organizations. However, many of these services were inadequate in the early days of the NHS and took time to develop.

TEACHING GERIATRIC MEDICINE

The teaching of medical students about the medical care of sick elderly people had long been recommended, but it was not until 1949 that Lord Amulree was appointed to University College Hospital, a London teaching hospital. Further advance had to wait until 1965 when Sir Ferguson Anderson became the first UK Professor of Geriatric Medicine. After this, progress was slow but by 1998 almost all the London teaching hospitals had a professorial chair in the speciality, and increasing numbers of chairs in geriatric medicine have been made in the country as a whole. These academic departments were usually based on an active geriatric unit with good community links. The curricula vary but could include biological and sociological gerontology as well as clinical geriatric medicine. Postgraduate research courses leading to the degrees of M.Sc. and Ph.D. have been set up. Some universities have a cluster of associated chairs, as the University of Manchester with two chairs in geriatric medicine, one each in cognitive gerontology, old-age psychiatry, gerodontology, biological gerontology, and social gerontology.

However, research of attitudes of medical students toward the elderly has shown that they tend to lose their initial

interest and empathy for older people as they train and qualify. A survey of their attitudes before qualification showed that they had empathy for, and a "bedside interest in", the elderly, which disappeared after graduation when the doctors considered their career prospects (Gale and Livesley, 1974). Parkhouse and McLaughlin (1976) found that no doctor, who had graduated in 1974, wished to enter geriatric medicine. Lambert *et al.* (1996) showed that little had changed in a review of career preferences among newly qualified doctors: preferences for geriatric medicine remained very low at 0.9%, well below general medicine and surgery, although above genetics. Factors blamed included the prejudice of medical teachers against geriatric medicine; poor image/role of the geriatrician, and mediocre working conditions. As a result, recruitment of medical staff into the speciality was poor. The Royal College of Physicians responded in 1972 and 1977 with a range of recommendations, including integration of geriatric medicine with general medicine, appointment of consultant physicians with a special interest in geriatric medicine, and rotation of junior training posts between the two specialties (Royal College of Physicians of London, 1972, 1977). The College also introduced the Diploma of Geriatric Medicine in 1986 to encourage general practitioners to gain interest in the care of older people.

ACHIEVEMENTS OF GERIATRIC MEDICINE

As the new style treatment methods were applied to the previously neglected chronic sick, clear evidence emerged of its effectiveness, particularly in hospitals. Official health data sources, such as Hospital In Patient Enquiry (HIPE) data collection, the Office of Health Economics, and Health and Personal Social Services Statistics for England, showed that the number of deaths and discharges of elderly people, and patient turnover from geriatric wards, steadily increased while the average and median lengths of stay decreased. In 1980, the Chief Medical Officer for England and Wales was able to report "the average length of stay for patients in hospital departments of geriatric medicine is steadily diminishing – more so than in any other hospital speciality. Only 10% remain in hospital for more than 6 months; the median length of stay is only 21.7 days" (Department of Health and Social Security, 1980). Progress was such that in 1984 the Nuffield Provincial Hospital Trust was able to comment "It [geriatric medicine] has established its expertise and has had notable success in developing and raising the standards of services for the old" (Batchelor, 1984). Concomitant with these developments, individual geriatricians began to create differing styles of practice: while some did not take emergency admissions, others took increasing numbers of acutely ill patients, and still others reintegrated with general medicine, taking part in unselected acute medical take and joint ward rounds with their general physician colleagues.

GERONTOLOGY: THE SCIENCE OF THE AGING PROCESS

Interest in gerontology in the United Kingdom was stimulated by the support of charitable foundations and the enthusiasm of a few individuals. The Nuffield Foundation created a medical and biological Research Committee, which gave grants to Howell for his research, to Dr Alex Comfort to work with Sir Peter Medawar at Birmingham and later at University College London, and to Professor Sir Frederick Bartlett at the University of Cambridge to establish a research unit to investigate the psychological aspects of aging. The Nuffield and the Ciba Foundations supported Vladimir Korenchevsky (1880–1959), a Russian biologist, who had studied under Pavlov and Metchnikoff. His enthusiasm for the science of aging culminated in his becoming director of the Oxford Gerontological Institute. He was a driving force behind the creation of the International Association of Gerontology (IAG). The Ciba Foundation supported the IAG, which held its first meeting in 1950 in Liege, Belgium. The first meeting of the clinical section of the IAG was held in Sunderland in the United Kingdom in 1958 and was chaired by Dr Oscar Olbrich. A later meeting was held in Manchester in 1974, which was organized by Professor Brocklehurst. The Ciba Foundation maintained its interest in old age by establishing a series of special colloquia in London, which were attended by many international experts on aging, and supported the British Society for the Research in Ageing, which was founded by Korenchevsky.

PROBLEM AREAS

The birth of geriatric medicine in the United Kingdom was hampered by the indifference of the medical profession to elderly patients for many reasons. The care of the aged and infirm lacked the dramatic appeal of acute illness in the young. Physicians questioned why elderly people should be put through extensive rehabilitation when they had only a few years to live. Complete recovery was rarely possible and the result was often disproportionate to the effort required. Chronic sick patients were often accommodated in poorly equipped and staffed hospitals. General physicians feared "bed blocking" if they admitted elderly patients, appeared uninterested in deciding what was normal or abnormal in this age-group, in learning what treatment could achieve, were displeased at the diversion of resources from general medicine to geriatric medicine, and were unenthusiastic about the considerable social/nonmedical components of geriatric medicine. Geriatricians were viewed as "second-rate" physicians.

Another concern was the quality of care given to the elderly in hospital. This culminated in the publication in 1967 of *Sans Everything: a Case to Answer,* which alleged inappropriate care in hospitals for the elderly and mentally ill. Official investigations found that the complaints were inaccurate, vague, lacking in substance, misinterpretations,

or overemotional (Martin, 1984). Following yet another allegation of improper care in a unit for the mentally subnormal in 1967, the Secretary of state for Health created the Hospital Advisory Service (HAS) in 1969, which was to act as his "eyes and ears". It was to be responsible only to him and was to be independent of the Department of Health. Visits to hospitals for the elderly and mentally ill started in 1970 and were carried out by teams of "in-post" professionals: consultant geriatricians or psychiatrists, senior nurses, paramedical staff, administrators, and later social workers. It is best considered as a form of "peer review". Later its remit was extended to cover community services, at which time it was renamed the Health Advisory Service.

The development of specialist service for the elderly mentally ill lagged behind that of the physically ill. Not infrequently, these patients were inappropriately admitted to geriatric wards, where staff had limited experience in managing them. Sometimes they were admitted to large general mental hospitals where the general psychiatrists did not welcome them. The ministry was aware of the problems presented by these patients and published advisory documents (e.g. Ministry of Health, 1950; Department of Health and Social Security, 1972). Eventually, guidelines were introduced to ensure admission to an appropriate ward: assessment by a multidisciplinary team was recommended. Joint assessment units with input from the local authority, psychiatrists, and the geriatrician were set up, although they tended to silt up owing to the failure to move the patients on to suitable ward or accommodation. Psychogeriatric day hospitals were opened, which provided a useful community function. Local authority residential homes were encouraged to take more mentally ill patients. However, it was not until the 1970s that consultant psychogeriatricians were appointed.

Another source of debate was the term *geriatrics* and its allied words. The word *gerocomy,* attributed to Galen, was used for the medical care of the elderly and was adapted to *geroncology* for their sociological aspects. In 1903, Metchnikoff invented the word *gerontology* for the biological study of the aging process. Nascher is generally credited with coining the word *geriatrics* (Nascher, 1916). "The term was... derived from the Greek, *geron*, old man and *iatrikos*, medical treatment. The etymological construction is faulty but euphony and mnemonic expediency were considered of more importance than correct grammatical construction". Howell pointed out at least one author who had confused *gerontology* (the science of old age) and *geriatrics* (the care of the aged). The word *gerontology* has been attacked as a barbarous misspelling and the word *geratology,* the study of old age, has been suggested instead. The founders of the Medical Society for the Care of the Elderly did not use the word *geriatrics* since it was, in 1940s, almost unknown. Many UK hospital geriatric units, aware of the public's perception of *geriatrics* as being apparently synonymous with *senility*, now call themselves "Department for the Medical Care of the Elderly" or "Care of the Elderly Department".

KEY POINTS

- In spite of interest in old age, enlightened medical treatment of the elderly sick patient did not start until the twentieth century.
- Classification of patients and modern treatment methods showed that the majority of those admitted to elderly care wards could be discharged.
- Community studies found unreported minor illness in older people, which could have a major impact on the quality of life if left untreated.
- University authorities were slow to implement the education of medical students about the medical and social aspects of illness in the older person.
- Powerful charitable foundations supported research into the causes of aging.

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PART I

Human Aging: A Biological Perspective

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2

A Biological Perspective on Aging

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INTRODUCTION

The biological perspective on aging is important for what it tells us about why and how the body becomes progressively more vulnerable to disability and disease as we grow older. Although there is significant variability in how aging affects individuals, certain underlying processes appear to follow a fairly common course. Furthermore, humans share features of aging with a wide range of other animal species. Thus, research that is being done on factors that influence aging in these species may throw light on at least some aspects of human senescence.

WHY AGING OCCURS

One of the questions of greatest interest for biological gerontologists is the nature of the genetic contribution to longevity. How do genes act on the aging process? How did the relevant genes evolve?

It is clear on several grounds that aging and longevity are influenced by genes (Finch and Tanzi, 1997). Firstly, the life spans of human monozygotic twin pairs are statistically more similar than life spans of dizygotic twins, pointing clearly to a role for genetics. Secondly, there are significant differences in life span between different genetically inbred strains of any given laboratory animal, such as the mouse. Third, studies of simple organisms like fruit flies, nematode worms, and yeast have identified gene mutations that affect duration of life. However, although genes influence longevity, it has also been shown that genes account for only about 25% of the variance in human life span (Finch and Tanzi, 1997; Cournil and Kirkwood, 2001).

The nature of the genetic contribution to the aging process has received much attention, both from the perspective of evolutionary theory and through experimentation. The evolutionary angle is valuable because it can tell us a great deal about the kinds of genes that are likely to underlie the aging process (Kirkwood and Austad, 2000). Although it is widely supposed that aging evolved as some kind of evolutionary necessity – to clear older generations out of the way as a form of inbuilt population control – there is in fact scant evidence that aging plays such a role in nature, or that such an evolutionary pressure could have worked. The reason is simple: animals in nature die young. Only rarely do they survive long enough to reveal significant aging. Out of a population of newborn wild mice, for example, nine out of ten of them will be dead before 10 months even though half of the same animals reared in captivity would still be alive at 2 years (Austad, 1997). Thus, aging in mice is seen only in protected environments, and a similar statement would have applied to primitive human populations, before the advent of civilization.

The fact that aging is rarely seen in natural animal populations speaks tellingly against any suggestion that aging evolved as a genetically programmed means to limit population size and avoid overcrowding. Instead of being programmed to die, organisms are genetically programmed to survive. However, in spite of a formidable array of survival mechanisms, most species appear not to be programmed well enough to last indefinitely. The key to understanding why this should be so, and what governs how long a survival period should be catered for, comes from looking once more at the data from survival patterns in wild populations. If 90% of wild mice are dead by 10 months, any investment in programming for survival much beyond this point can benefit at most 10% of the population. This immediately suggests that there will be little evolutionary advantage in programming long-term survival capacity into a mouse. The argument is further strengthened when we observe that nearly all of the survival mechanisms required by the mouse to combat intrinsic deterioration (DNA damage, protein oxidation, etc.) require metabolic resources. Metabolic resources are scarce, as is evidenced by the fact that the major cause of mortality for wild mice is cold, due to insufficient energy to maintain body temperature. From a Darwinian point of view, the mouse will benefit more from investing any spare

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resource into thermogenesis or reproduction than into better DNA repair capacity that it needs.

This concept, with its explicit focus on evolution of optimal levels of cell maintenance, is termed *the disposable soma theory* (Kirkwood, 1977, 1997). In essence, the investments in durability and maintenance of somatic (nonreproductive) tissues are predicted to be sufficient to keep the body in good repair through the normal expectation of life in the wild environment, with some measure of reserve capacity. Thus, it makes sense that mice (with 90% mortality by 10 months) have intrinsic life spans of around 3 years, while humans (who probably experienced something like 90% mortality by age 50 in our ancestral environment) have intrinsic life spans limited to about 100 years. The distinction between somatic and reproductive tissues is important because the reproductive cell lineage, or germ line, must be maintained at a level that preserves viability across the generations, whereas the soma needs only to support the survival of a single generation. As far as is known, all species that have a clear distinction between soma and germ line undergo somatic senescence, while animals that do not show senescence, such as the freshwater Hydra, have germ cells distributed throughout their structure.

The above argument clearly identifies the level of extrinsic mortality as the principal driver in the evolution of longevity. If the level of extrinsic mortality is high, the average survival period is short and there is little selection for a high level of maintenance. Any spare resources should go instead towards reproduction. Consequently, the organism is not long-lived even in a protected environment. Conversely, if the level of extrinsic mortality is low, selection is likely to direct a higher investment in building and maintaining a durable soma. Studies comparing the biochemistry of cellular repair among long- and short-lived species bear this prediction out. Cells from long-lived organisms exhibit greater capacity to repair molecular damage and withstand biochemical stresses than cells from short-lived species (Kapahi *et al.*, 1999; Ogburn *et al.*, 2001).

The disposable soma theory provides a bridge between understanding not only why aging occurs but also how aging is caused in molecular and cellular terms. It thus extended earlier considerations by Medawar (1952), who suggested that because organisms die young there is little force of selection to oppose the accumulation within the genome of mutations with late-acting deleterious effects, and by Williams (1957) who suggested that genes with beneficial effects would be favored by selection even if these genes had adverse effects at later ages. This is known as *the theory of antagonistic pleiotropy*, the term pleiotropy meaning that the same gene can have different effects in different circumstances.

By combining the insights from the mutation accumulation, antagonistic pleiotropy, and disposable soma theories, evolutionary biology has established a solid basis to explain why aging occurs. The four cornerstones of this basis are: (i) there are no specific genes for aging; (ii) genes of particular importance for aging and longevity are those governing durability and maintenance of the soma; (iii) there may exist other genetically determined trade-offs between benefits to young organisms and their viability at older ages; and (iv) there may exist a variety of gene mutations with late deleterious effects that contribute to the senescent phenotype. It is clear that multiple genes probably contribute to the aging phenotype and a major challenge is therefore to identify how many of each category exist, and which are the most important.

HOW AGING AFFECTS TISSUES

The evolutionary explanation of aging, as summarized above, leads to a number of clear predictions about the nature of the underlying mechanisms that lead eventually to age-related frailty, disability, and disease (and eventually to increasing mortality). In its essence, aging is neither more nor less than the progressive accumulation through life of a variety of random molecular defects that build up within cells and tissues. These defects start arising very early in life, probably even *in utero*, but in the early years both the fraction of affected cells and the average burden of damage per affected cell are low. However, over time, the faults increase, resulting eventually in age-related functional impairment of tissues and organs.

This view of the aging process makes clear the life-course nature of the underlying mechanisms. Aging is a continuous process, starting early and developing gradually, instead of being a distinct phase that begins in middle to late life. The view also helps us reexamine the sometimes controversial relationship between "normal aging" and age-related disease. In an extreme version of this view, the term "normal aging" is reserved for individuals in whom identifiable pathology is absent, whereas specific age-related diseases, such as Alzheimer's disease, are seen as distinct entities. An obvious difficulty that arises, however, when any attempt is made to draw a line between normal aging and age-related disease is that as a cohort ages, the fraction of individuals who can be said to be aging "normally" declines to very low levels. Whether the word "normal" can usefully be applied to such an atypical subset is debatable.

In a clinical context, it often makes sense to try and draw a distinction between normal aging and disease, since this may have implications for treatment. However, if our aim is to understand the mechanisms responsible for age-related conditions, such a distinction can obscure what is really going on and impede progress toward developing novel interventions that are targeted at "upstream" processes.

The majority of chronic, degenerative conditions, such as dementia, osteoporosis, and osteoarthritis, involve the progressive accumulation of specific types of cellular and molecular lesions. Since the aging process, as we have seen, is caused by the general accumulation of such lesions, there may be a much greater overlap between the causative pathways leading to normal aging and age-related diseases than has hitherto been recognized. In the case of osteoporosis, for example, progressive bone loss from the late 20s onwards

is the norm. Whether an individual reaches a critically low bone density, making him or her highly susceptible to fracture is governed by how much bone mass they had to start with and by their individual rate of bone loss. The process that leads eventually to osteoporosis is thus entirely "normal", but what distinguishes whether or not this process results in an overtly pathological outcome is a range of moderating factors. In the case of Alzheimer's disease, most people above age 70 have extensive cortical amyloid plaques and neurofibrillary tangles (the so-called "hallmarks" of classic Alzheimer's disease) even though they may show no evidence of major cognitive decline (Esiri *et al.*, 2001). In this instance, what determines whether or not the diagnosis of Alzheimer's disease is called for may be not so much the presence of lesions as which specific targets are affected.

MECHANISMS OF CELLULAR DAMAGE

Aging is highly complex, involving multiple mechanisms at different levels. Much recent evidence suggests that an important theme linking several different kinds of damage is the action of reactive oxygen species (ROS; also known as "free radicals") which are produced as by-products of the body's essential use of oxygen to produce cellular energy (Martin *et al.*, 1996; von Zglinicki *et al.*, 2001). Of particular significance are the contributions of ROS-induced damage to cellular DNA through (1) damage to the chromosomal DNA of the cell nucleus resulting in impaired gene function, (2) damage to telomeres – the protective DNA structures that appear to "cap" the ends of chromosomes (analogous to the plastic tips of shoelaces), and (3) damage to the DNA that exists within the cell's energy-generating organelles, the mitochondria, resulting in impaired energy production.

DNA Damage and Repair

Damage to DNA is particularly likely to play a role in the life-long accumulation of molecular damage within cells, since damage to DNA can readily result in permanent alteration of the cell's DNA sequence. Cells are subject to mutation all the time, both through errors that may become fixed when cells divide and as a result of ROS-induced damage which can occur at any time. Numerous studies have reported age-related increases in somatic mutation and other forms of DNA damage, and have suggested that an important determinant of the rate of aging at the cell and molecular level is the capacity for DNA repair (Promislow, 1994; Burkle *et al.*, 2002).

Although DNA damage may take many forms, it is estimated that oxidative damage is among the most important, accounting for large numbers of oxidative hits per cell per day. A key player in the immediate cellular response to ROS-induced DNA damage is the enzyme poly(ADP-ribose) polymerase (PARP). Grube and Bürkle (1992) discovered a strong, positive correlation of PARP activity with the species life span, cells from long-lived species having higher levels of PARP activity than cells from short-lived species. In a similar vein, it was found that human centenarians, who have often maintained remarkably good general health, have a significantly greater poly(ADP-ribosyl)ation capacity than the general population (Muiras *et al.*, 1998).

Telomeres

In many human somatic tissues a decline in cellular division capacity with age appears to be linked to the fact that the telomeres, which protect the ends of chromosomes, get progressively shorter as cells divide (Kim *et al.*, 2002). This is due to the absence of the enzyme telomerase, which is normally expressed only in germ cells (in testis and ovary) and in certain adult stem cells. Some have suggested that in dividing somatic cells, telomeres act as an intrinsic "division counter", perhaps to protect us against runaway cell division as happens in cancer but causing aging as the price for this protection (Campisi, 1997). Erosion of telomere length below a critical length appears to trigger activation of the same kinds of cell cycle checkpoint, especially the p53/p21/pRb system, as are involved in the more general cellular response to DNA damage.

While the loss of telomeric DNA is often attributed mainly to the so-called "end-replication" problem – the inability of the normal DNA-copying machinery to copy right to the very end of the strand in the absence of telomerase – it has been found that stress, especially oxidative stress, has an even bigger effect on the rate of telomere loss (von Zglinicki, 2002). Telomere shortening is greatly accelerated (or slowed) in cells with increased (or reduced) levels of stress. The clinical relevance of understanding telomere maintenance and its interaction with stress is considerable. A growing body of evidence suggests that telomere length is linked with aging and mortality (e.g. Cawthon *et al.*, 2003). Not only do telomeres shorten with normal aging in several tissues (e.g. lymphocytes, vascular endothelial cells, kidney, liver), but also their reduction is more marked in certain disease states. For example, there appears to be a 100-fold higher incidence of vascular dementia in people with prematurely short telomeres (von Zglinicki *et al.*, 2000). Viewed together with the observation that oxidative stress accelerates telomere loss, the intriguing possibility arises that prematurely short telomeres *in vivo* are an indicator of previous exposure to stress and may therefore serve as a prognostic indicator for disease conditions in which oxidative stress plays a causative role (von Zglinicki, 2002).

Mitochondria

An important connection between oxidative stress and aging is suggested by the accumulation of mitochondrial DNA (mtDNA) deletions and point mutations with age (Wallace, 1992). Mitochondria are intracellular organelles, each carrying its own small DNA genome, which are responsible for

generating cellular energy. As a by-product of energy generation, mitochondria are also the major source of ROS within the cell, and they are therefore both responsible for, and a major target of, oxidative stress. Any age-related increase in mutation of mtDNA is likely to contribute to a progressive decline in the cell and tissue capacity for energy production. Age-related increases in frequency of cytochrome c oxidase (COX)-deficient cells have been reported in human muscle (Müller-Höcker, 1989; Müller-Höcker *et al.*, 1993; Brierley *et al.*, 1998) and brain (Cottrell *et al.*, 2000), associated with increased frequency of mutated mtDNA.

Until recently, the evidence for age-related accumulation of mtDNA mutations came mainly from tissues such as brain and muscle where cell division in the adult, if it occurs at all, is rare. This led to the idea that accumulation of mtDNA mutation was driven mainly by the dynamics of mitochondrial multiplication and turnover within nondividing cells (Kowald and Kirkwood, 2000). However, recent work has revealed a strongly age-dependent accumulation of mtDNA mutations in human gut epithelium, which has the highest cell division rate of any tissue in the body (Taylor *et al.*, 2003). Thus, it appears that mtDNA mutation accumulation may be a widespread phenomenon.

Proteins

So far, we have concentrated on damage to DNA. However, damage can also affect any of the macromolecules that make up the cell, as well as those that form extracellular structures such as cartilage and bone. In particular, damage to protein molecules occurs to a considerable extent, and accumulation of faulty proteins contributes to important age-related disorders such as cataract, Parkinson's disease, and Alzheimer's disease. In some ways, the accumulation of defective proteins is harder to explain than the accumulation of DNA damage, since individual protein molecules are subject to a continual cycle of synthesis and breakdown. Thus, damage to any individual protein molecule should be cleared as soon as that molecule is degraded. The exceptions occur when the defective protein molecules become resistant to breakdown, for example, because they form aggregates large enough to withstand the normal removal systems. It is the buildup of such aggregates that is commonly linked with cell and tissue pathology.

Interactions between Mechanisms

We have so far considered a number of distinct mechanisms that can contribute to cellular aging. For each of these, there is evidence supporting the hypothesis that it is indeed an agent of senescence. However, the extent of the contribution to senescence almost invariably appears too small for the mechanism to be a sufficient explanation of age-related degeneration. The obvious solution to this "conundrum" is that cellular aging is multicausal and that the various mechanisms all play their part. For example, a buildup of mtDNA mutations will lead to a decline in the cell's energy production, and this will reduce the capacity to carry out energy-dependent protein clearance. In recent years, novel methods based on computer modeling of interactions and synergism between different aging mechanisms have begun to build a better integrated picture of how cells breakdown with age (Kirkwood *et al.*, 2003).

METABOLIC FACTORS INFLUENCING AGING

Numerous opportunities exist to test the evolutionary prediction that in safe environments (those with low extrinsic mortality) aging will evolve to be retarded, whereas aging should evolve to be more rapid in hazardous environments. Field observations comparing a mainland population of opossums subject to significant predation by mammals, with an island population not subject to mammalian predation, found the predicted slower aging in the island population (Austad, 1993). What is interesting from the metabolic perspective is to understand how these ecologically driven effects are mediated at the level of cellular and molecular mechanisms.

The disposable soma theory predicts that the proportional effort devoted to cellular maintenance and repair processes will vary directly with longevity. For instance, the long-lived rodent species *Peromyscus leucopus* exhibits lower generation of ROS, higher cellular concentrations of some antioxidant enzymes, and overall lower levels of protein oxidative damage than the shorter-lived species *Mus musculus* (Sohal *et al.*, 1993). A direct relation between species longevity and rate of mitochondrial ROS production in captive mammals has also been found (Ku *et al.*, 1993; Barja and Herrero, 2000), as has a similar relationship between mammals and similar-sized but much longer-lived birds (Herrero and Barja, 1999). Markers of glycoxidation, the nonenzymatic modification of reducing sugars, are also found to accumulate more slowly in long-lived, as opposed to short-lived, mammals (Sell *et al.*, 1996).

Of particular significance in terms of metabolic factors influencing aging rates has been the discovery that insulin signaling pathways appear to have effects on aging that may be strongly conserved across the species range (Gems and Partridge, 2001). Insulin signaling regulates responses to varying nutrient levels and so the discovery of the major role for these pathways in aging fits well with the central concept of the disposable soma theory, namely, that aging results from and is controlled by the metabolic allocation of the organism's metabolic resources to maintenance and repair.

One of the clearest examples of how metabolic signaling affects aging and longevity comes from a study on genes of the insulin signaling pathway in *Caenorhabditis elegans* (Murphy *et al.*, 2003). When threatened with overcrowding, which the larval worm detects by the increasing concentration of a pheromone, it diverts its development from the normal succession of larval molts into a long-lived, dispersal

form called *the dauer larva* (Larsen *et al.*, 1995). Dauers show increased resistance to stress and can survive very much longer than the normal form, reverting to complete their development into adults should more favorable conditions be detected. An insulin/IGF-1-like gene, *daf-2*, heads the gene regulatory pathway that controls the switch into the dauer form, and mutations in *daf-2* produce animals that develop into adults with substantially increased lifespans (Kenyon *et al.*, 1993). In common with other members of the evolutionarily conserved insulin/IGF1 signaling pathway, *daf-2* also regulates lipid metabolism and reproduction. The *daf-2* gene product exerts its effects by influencing "downstream" gene expression, in particular via the actions of another gene belonging to the dauer-formation gene family, *daf-16*, which it inhibits (Kimura *et al.*, 1997).

It was shown by Murphy *et al.* (2003) that more than 300 genes appeared to have their expression levels altered by *daf-16* regulation. This large number suggests that, as predicted by the evolutionary theory, many genes are involved in determining longevity. The genes modulated by *daf-16* turned out to be a heterogeneous group although several broad categories could be discerned. The first category comprised a variety of stress-response genes, including players like antioxidant enzymes. A second group of genes encoded antimicrobial proteins, which are important for survival in this organism because its death is commonly caused by proliferation of bacteria in the gut. A miscellaneous third group included genes involved in protein turnover, which is an important cellular maintenance system. Thus, the metabolic regulation of the rate of aging in *C. elegans* is mediated through genetic effects on a diverse array of survival mechanisms, exactly as the disposable soma theory predicted.

By this point, it will be seen that, from a range of studies at the genetic, cellular, and molecular levels, both in humans and a variety of other organisms, a picture is clearly emerging of the main elements of the biological science of human aging (Figure 1). These elements are the result of the relentless role of biochemical *stresses*, such as exposure to ROS, driving a gradual but progressive accumulation of *damage* to cells, tissues, and organs. The process is not entirely passive, since the rate of accumulation is strongly resisted by maintenance and repair processes, which are controlled by *genes*. Furthermore, the regulation of these genes may, at least in some organisms, be influenced by metabolic factors, for example, responding to levels of nutrition. This picture is one that readily accommodates the role of at least five major elements contributing to the individuality of the human aging process: genes, nutrition, lifestyle (e.g. exercise), environment, and chance. The recognition of this interplay of factors is likely to be crucial for integrating biological, clinical, and social gerontology. For example, environment is often defined by social factors such as housing, transport, and income. Poor environments may adversely affect an individual's opportunities to do the optimal things for healthy aging in terms of nutrition, lifestyle, and so on. In particular, a poor environment can reinforce a tendency for the older person to suffer social isolation, which in turn can exacerbate psychological and physical deterioration. On the positive side, the understanding that we now have of the biological science of human aging supports the idea that the aging process is much more malleable than has hitherto been recognized. This opens the way to a range of interventions that may improve health in old age and extend quality life.

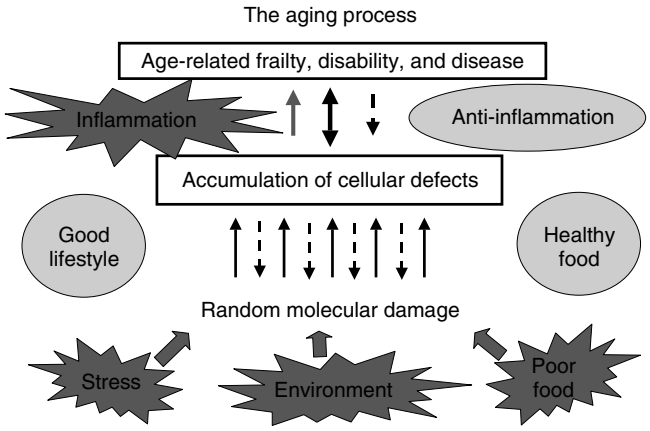

Figure 1 The aging process is driven by a life-long accumulation of molecular damage, resulting in gradual increase in the fraction of cells carrying defects. After sufficient time has passed, the increasing levels of these defects interfere with both the performance and functional reserves of tissues and organs, resulting in age-related frailty, disability, and disease. Stress, adverse environment, and poor nutrition can increase the rate at which molecular damage arises. Molecular damage is partially countered by cellular maintenance and repair systems (dashed arrows). Accumulation of cellular damage can cause inflammation, which can exacerbate the development of overt age-related frailty, disability, and disease. This may be countered by anti-inflammatory factors (dotted arrow)

KEY POINTS

- There is no biological program specifically to cause aging.
- The body is programmed for survival but our survival mechanisms, which evolved to cater for the typical longevity of our evolutionary ancestors, are insufficient to prevent damage from accumulating.
- Aging is caused by the life-long accumulation of subtle molecular and cellular faults, a process that probably begins *in utero*.
- Multiple mechanisms contribute to the buildup of damage that causes aging, and there are multiple maintenance and repair systems working to combat this buildup of damage. It is the genetic setting of these maintenance and repair systems that explains the genetic contribution to human longevity (which explains about 25% of the variation in human life span).
- The rate at which damage accumulates, and thus the aging process itself, is malleable through the actions of factors such as nutrition, lifestyle, and environment.

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3

Immunity and Aging

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INTRODUCTION

Protozoa floating in the Cambrian sea many billion years ago could have been the first cell-like living organisms on earth resembling today's *Amoeba*. From such unicellular organisms, it took billions of years for the evolution of a wide variety of multicellular organisms. One necessary condition for the survival of these organisms, including Protozoa, is that each one must be able to maintain its identity by discriminating itself from many others in the same environment. It is interesting to note that this ability to discriminate "self" from "non-self" is the basic function of the immune system. Leukocytes in higher vertebrates as mammals are quite similar to Cambrian Protozoa in terms of appearance and function and constitute a major component of the immune system. In a broad sense, they can be categorized into granulocytes, macrophage (monocytes), and lymphocytes.

Animals are equipped with three types of defense systems against invading pathogenic microbes. One is a physical barrier composed of skin and mucosal surface of gastrointestinal and respiratory tract. This barrier is reinforced by humoral substances containing lysozymes or acid. Second is a natural (innate) immune system composed of granulocytes, macrophages, dendritic cells, and natural killer (NK) cells. Granulocytes and macrophages can nonspecifically ingest and kill microbes by lytic enzymes in lysozymes. NK cells can nonspecifically kill tumor cells and virus-infected cells. The importance of granulocytes is illustrated by the fact that people suffering from drug-induced hypo- or agranulocytosis occasionally die within a week after the onset of the disease. Third is an acquired (specific) immune system. Its major component is lymphocytes, but many of their functions are helped by macrophages, dendritic cells, and NK cells. Unlike natural immune system, killing of microbes by acquired immune system is specific to a certain type of microbe (a specific antigen); therefore, there are countless numbers of clones of lymphocytes corresponding to the countless numbers of antigens in the environment and each clone of lymphocytes can specifically react to a corresponding antigen, resulting in proliferation of specific effector cells or production of specific antibody. Moreover, the immune reaction retains memory analogous to that of the nervous system, and the sequence of generation of effector cells and antibody production occurs very quickly upon subsequent infections by the same microbes. However, immunological functions are known to decline with age in many mammals, including humans (Makinodan and Kay, 1980; Hirokawa, 1992; Linton and Dorshkind, 2004), and the decline occurs more in the acquired immune system than in the natural immune system. It is of clinical importance that with a decrease of immunologic vigor, the incidence of various age-associated diseases such as infections, cancers, and vascular diseases increases. Table 1(a) shows causes of death observed in 3000 autopsy cases in geriatric institutions in Geneva, Switzerland (Mac Gee, 1993). The most prevalent fatal condition was bronchopneumonia. The same observation was also seen in Tokyo Metropolitan Geriatric Hospital, Japan (Table 1b). Infections such as bronchopneumonia compose almost 40% of the direct causes of death in autopsy cases over 60 years of age, although a variety of antibiotics are available. The occurrence of severe acute respiratory syndrome (SARS) in the winter of 2003 clearly indicated the immune deficient state of the elderly. Fatality rate increased with age in SARS (Hong Kong, China), occurring in more than 50% in people 65 years and over (Table 1c). These results suggest that elderly people whose immune functions are at an exceptionally high level can live longer and become centenarians. They also underscore the importance of age-related decline of immune functions. Regarding infection, there is a hypothesis that chronic antigenic stimulation could lead to an increasing prevalence of senescent, dysfunctional T cells, and therefore contributes to more general alterations in the immune system (Pawelec *et al.*, 2004).

A related serious problem of our society is acquired immune deficiency syndrome (AIDS), and AIDS is due

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 ISBN 0-470-09055-3

Table 1a Causes of death in a hospitalized geriatric population: An autopsy study of 3000 patients

Bronchopneumonia	42.9%
Malignant neoplasms	28.1%
Pulmonary thromboembolism	21.2%
Acute myocardial infarction	19.6%
Urinary tract infection	12.3%
Acute cerebrovascular disease	6.5%
Internal hemorrhage	5.5%
Congestive cardiac failure	3.3%

The data, based on 3000 consecutive autopsies (1758 females/1242 males: mean age 80.3 years) performed from 1972 to 1992 in Geneva Geriatric Instutitions (Mac Gee W).

Table 1b Major causes of death in autopsy cases of elderly persons at Tokyo Metropolitan Geriatric Hospital

	People over 60 years (%)	People over 70 years (%)
Infections	39.2	27.6
Vascular diseases in brain and heart	29.7	43.1
Malignancies	18.7	22.4
Others	12.4%	6.9%

The data, based on 923 autopsy cases (570 females/353 males) over 60 years of age.

Table 1c Fatality rate of SARS increased with age in Hong Kong

Age	Fatality rate (%)
24 years and under	0
25–44 years	6
45–64 years	15
65 years and over	52
Total	14–15

Source: WHO report. Consensus document on the epidemiology of severe acute respiratory syndrome (SARS). 17 October 2003 http://www.who.int/csr/sars/guidelines/en/. Reproduced by permission of the World Health Organization.

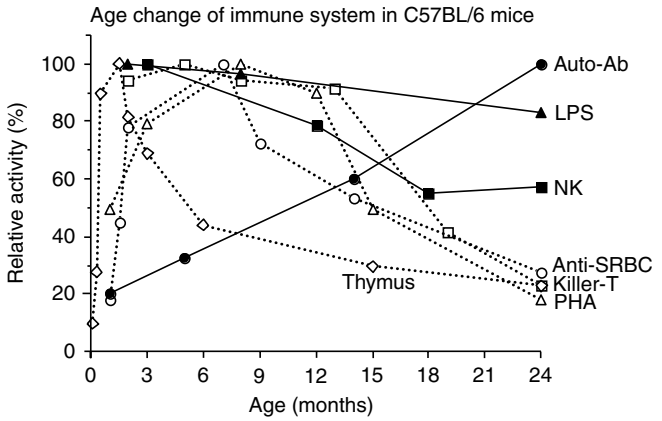


Figure 1 Age-related changes in the immune functions of C57BL/6 mice. Age-related decline is seen in three kinds of T cell-dependent immune functions: mitogenic response of spleen cells to phytohemagglutinin (PHA, closed triangle), cytolytic T cell activity (killer T, open squares), and anti-SRBC antibody response (anti-SRBC, open circles). Thymic involution (open diamonds) precedes the decline of these T cell-dependent immune functions. Proliferative activity of B cells (LPS, closed triangles) declines very slightly with age. Activity of natural killer (NK) cells (closed squares) declines moderately. Production of autoantibody (auto-Ab, closed circles) increases with age (Reprinted from Archives of Gerontology and Geriatrics, **19**: 171, Hirokawa *et al.*, Copyright 1994, with permission from Elsevier)

to insufficiency of $CD4^+$ helper T cells caused by HIV infection. With most elderly people, a much wider range of nonspecific immunological deficiency occurs. This chapter will outline how the immune functions decline with age in humans and animal models.

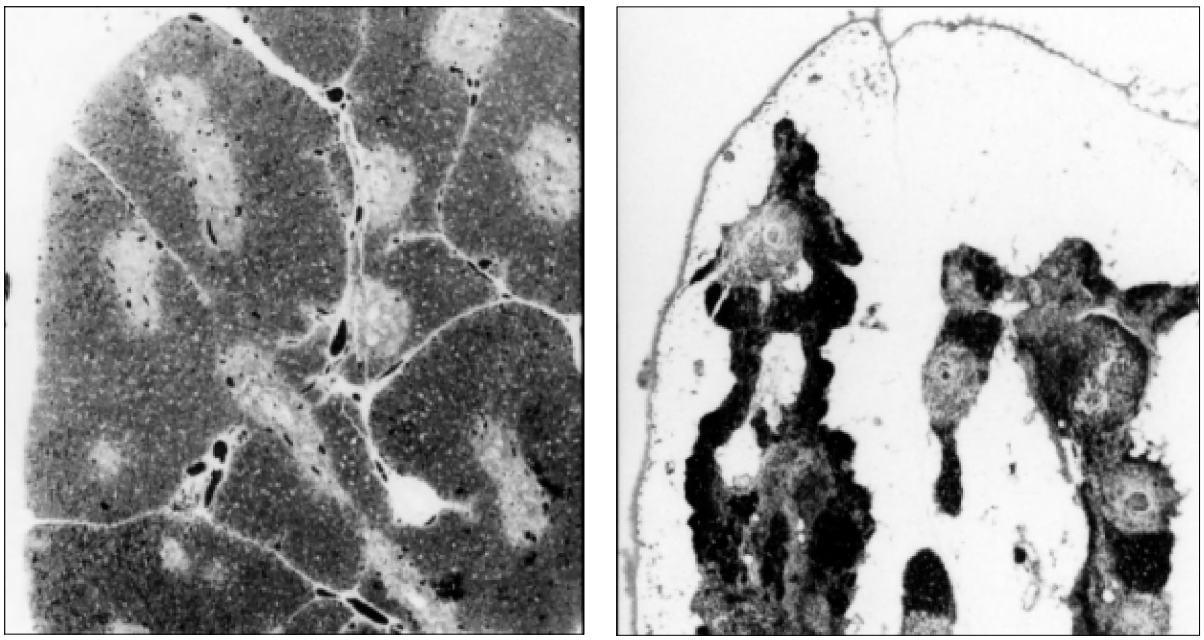
SENESCENCE OF IMMUNE SYSTEM

1. *T cell-dependent immune system is most susceptible to aging*

The natural immune system is already functioning at the time of birth and does not show a pronounced age-related change during the course of life in healthy individuals. On the other hand, the acquired immune system is immature and does not function well in the early stage after birth. Its activity develops quickly by exposure to innumerable antigens, including microbes in the environment, peaks at puberty, and starts to gradually decline thereafter. Studies in several long-lived mouse strains and humans performed in several laboratories, including ours (Makinodan and Kay, 1980; Hirokawa, 1992; Linton and Dorshkind, 2004; Deng *et al.*, 2004), indicate that: (a) decline primarily occurs in T cell-dependent immune functions such as T cell-dependent antibody formation, cytolytic T cell activity, T cell proliferative response to various mitogens and tuberculin skin test; (b) all these changes are preceded by thymic involution; (c) activity of NK cells also declines with age, but the magnitude of the decline is less than that of T cells; (d) there is a marginal decline in B cell mitogenic response to lipopolysaccharide (Figure 1); and (e) transition of pro-B cells into pre-B cells and migration of newly made B cells to the spleen from bone marrow are reduced in old individuals. Considering the fact that T cells are mainly produced in the thymus, a causal relationship appears to exist between thymic involution and subsequent age-related decline in T cell functions. Physiologically, the major reason why T cells are more susceptible to aging than other immune cells is that the recruitment of T cells is quite limited, as the thymic capacity to provide T cells to peripheral lymphoid tissues declines quickly after puberty. The situation is quite different in B cells, dendritic cells, and macrophages, which are constantly replenished by the bone marrow throughout life.

2. *Lymphoid and hemopoietic tissues*

As cells composing the acquired immune system are mainly located in lymphoid tissues, we will see how lymphoid tissues change with age.



(a) (b)

Figure 2 Histology of the thymus from newborn (a) and 28-years-old male (b) The thymus from newborn maintains the basic structure of thymus, composed of cortex and medulla. By contrast, the thymus from a young adult male is composed of a large amount of fatty tissue and fragments of thymic tissues

(a) Thymus
The Thymus is the key organ for the development of T cells. Thymic involution is generally known to occur after puberty. However, an early sign of involution such as fatty infiltration could be observed as early as 5 years of age, and the number of thymic epithelial cells starts to decline shortly after birth. Normal thymic architecture of cortex and medulla, as seen in the newborn stage, completely disappears in the thymus of people over 20 years of age due to extensive fatty infiltration (Figure 2). In a normal mouse strain (mean life span about 2 years), the thymic size peaks at 4–6 weeks and gradually declines, but without fatty infiltration. As will be seen in the later section, the thymic capacity to provide T cells to the periphery is high in the newborn stage and quickly declines thereafter. Nevertheless, Douek *et al.* (1998) reported that thymocytes were still proliferating in the thymus of human adults and newly generated T cells were being exported to peripheral lymphoid tissues. From a structural viewpoint, thymic fragments of human adults are composed of cortical and medullary portions and they provide T cells to the periphery, although very low in number (Shiraishi *et al.*, 2003) and less functional. This will be discussed later.

(b) Spleen
Splenic weight decreases in elderly people, but unlike the thymus, the onset of the decrease is at about the seventh decade, far later than that of thymus. It is composed of red pulp and white pulp. The latter portion occupies about 20% of total spleen and is mainly responsible for immune reactions. Germinal centers are well developed in white pulp of the young spleen, but rarely seen in that of the old spleen (Figure 3).

(c) Lymph node
The size of the lymph node is most prominent in the first decade in humans, as with the case of the thymus. Thereafter, lymph nodes are less conspicuous or not palpable in healthy individuals. Lymph nodes become swollen at the time of infection, but the magnitude of swelling is less prominent in elderly people than in the young. As is seen in the spleen, there is a profound reduction of the germinal center reaction in the lymphoid tissues of the aged. As the germinal center is necessary for generation of high affinity antibodies, the absence of germinal center is considered a cause for the compromised humoral responses in aging (Zheng *et al.*, 1997).

(d) Mucosal lymphoid tissue
The intestine contains a considerable amount of lymphoid tissue, produces a large amount of immunoglobulin (Ig) A, and plays a major role in the protection against infectious diseases of the intestinal tract. There are accumulating data showing that deficits are found in the intestinal mucosal immune responses of elderly humans and old animals (Schmucker, 2002). Nasal-associated lymphoid tissue is important for the protection of respiratory infections, and its function is also impaired with the advancement of age. It is important to note that the production of IgA antibody in nasal mucosa is efficiently enhanced by local administration of antigen, not by systemic injection of antigen

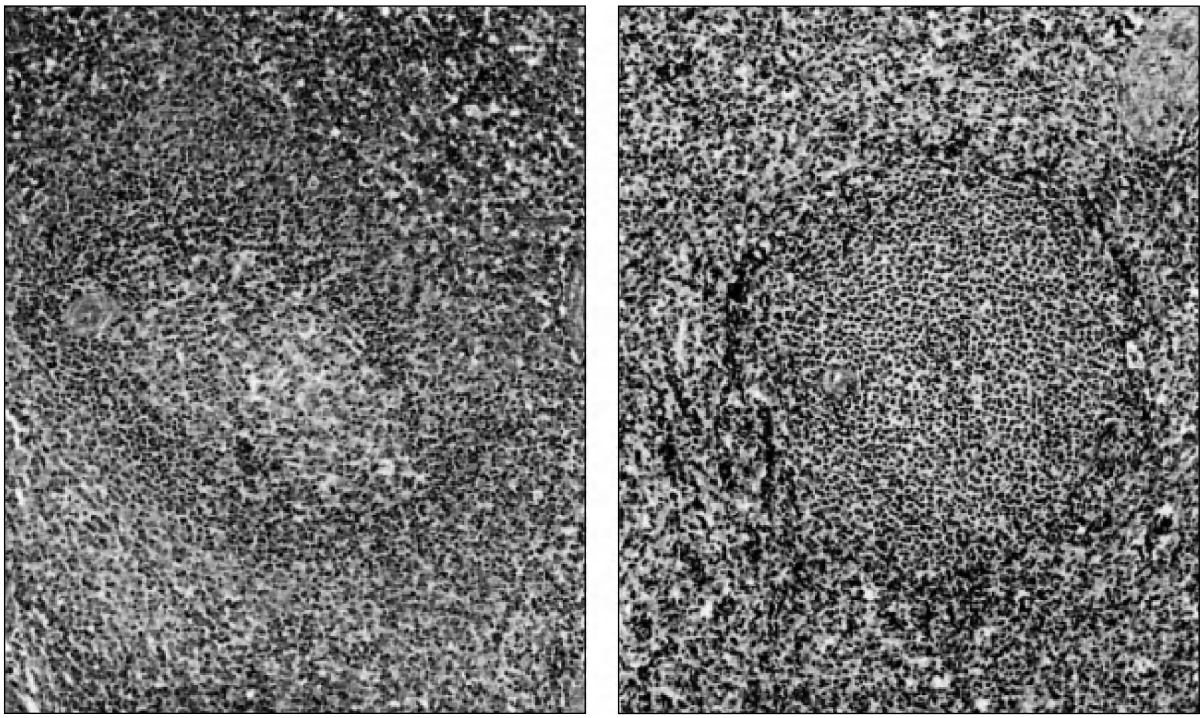


Figure 3 Histology of white pulp of spleen from 36-year-old male (a) and 83-year-old male (b). Formation of germinal center is observed in (a), but not in (b)

Table 2 Concentration of IgA antibody in the nasal mucosa is efficiently increased by intranasal immunization of antigen, not by other routes

Immunization route	in → in		iv → ip	
Age of mice	3 m	18 m	3 m	18 m
Ig A levels in nasal mucosa	172 ± 17	54 ± 20	2 ± 0.8	2 ± 0.8
Ig G levels in serum	30364 ± 2370	11230 ± 4584	162481 ± 14322	111903 ± 7488

Levels of antibodies, ng/mouse.
in, intranasal immunization; iv, intravenous immunization; ip, intraperitoneal immunization.
in → in, antigen was first intranasally given and a booster 3 weeks later by the same route;
iv → ip, antigen was first intravenously given and a booster 3 weeks later by ip.
Antigen; Influenza virus vaccine (A/PR/8/34) mixed with cholera toxin B.
Asanuma *et al.* (2001).

(Table 2). Thus, efficient protection against influenza could be accomplished by intranasal local administration of vaccine.

(e) Bone marrow

The Bone marrow is a primary source of hematopoietic and lymphoid cells. An apparent age-related decrease of red bone marrow is observed in humans and rats, but not in mice. Proliferative activity assessed by Ki-67-positive cells was high in the middle-aged group and declined slightly in the elderly group. Apoptosis was relatively low in the young and middle-aged group, but significantly increased in the elderly group (Figure 4). These data suggest that hypocellularity in the bone marrow of elderly people could be ascribed partly to the increase in apoptosis and decrease of proliferative capacity. Interestingly, plasma cells, or IgA, and IgG containing cells increase in human bone marrow, with a concomitant increase of these immunoglobulins in serum. In aged mice, bone marrow, and not spleen, becomes the major site of immunoglobulin production.

3. *Serum immunoglobulins*

Despite age-related atrophy of lymphoid tissues, such as spleen, lymphoid tissues, and thymus, the level of serum IgA and IgG gradually increases with age, but that of IgM does not change. Increased level of serum immunoglobulin is consistent with an increase in immunoglobulin synthesizing plasma cells in lymphoid tissues and bone marrow, and with a decrease in the rate of degradation. Although serum immunoglobulin level increases with age, immunoglobulins

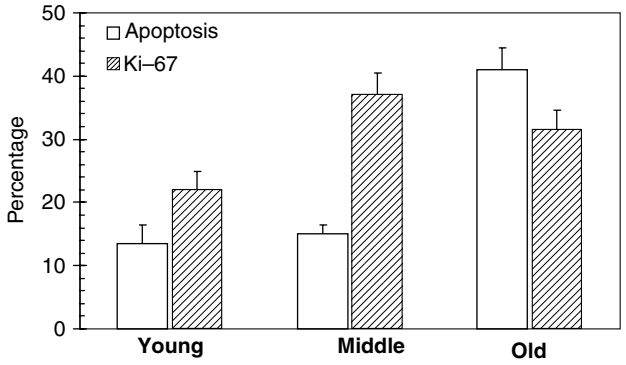


Figure 4 The percentage of apoptotic cells and proliferating cells in human bone marrow of 3 different age-groups. The percentage of apoptotic cells was determined by the terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) method. The Ki-67^+ cells indicate cells in the proliferating phase. Vertical bars indicate SEM. Young, subjects less than 20 years old. Middle, subjects between 50 and 59 years old. Old, subjects between 80 and 100 years old

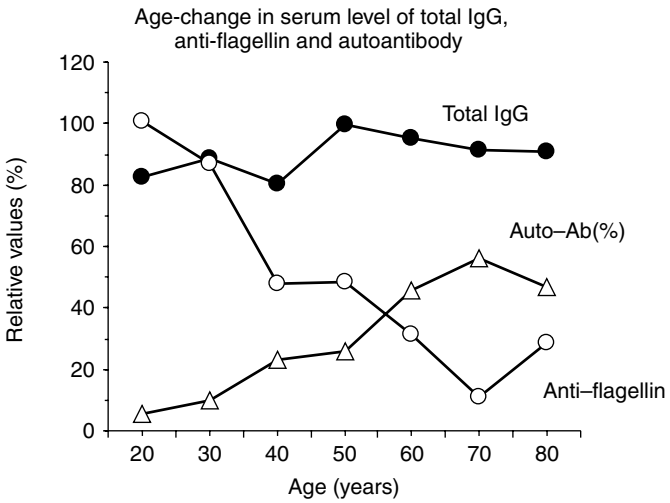


Figure 5 Age-related changes of total IgG (closed circles), relative values of anti-Flagellin (open circles) and incidence of autoantibody (auto-Ab, open triangles) in human serum (the highest level, 100%). Modified from Rowley *et al.* (1968) and Suzuki *et al.* (1984)

produced in old mice are less protective because of their low titer and affinity. The production of specific antibodies decreases with age with an increased production of autoantibodies (Figure 5), which will be discussed later. Interestingly, frequency of benign monoclonal gammopathy increases with age.

CELLS OF THE IMMUNE SYSTEM

Much information is available regarding cells in the peripheral blood, but little about cells making up the microenvironment of various lymphoid tissues, except for thymus, whose role in the aging of immune system will be discussed in the next section. Absolute number of lymphocytes, T cells, and B cells generally declines with age in association with altered composition of their subsets (Utsuyama *et al.*, 1992; Cossarizza *et al.*, 1996; Fagnoni *et al.*, 2000). It should be stressed that the decline starts during childhood or after puberty (Utsuyama *et al.*, 1992). This section will present an overview of changes of various immune cells at the cellular level.

1. *Hematopoietic stem cells (HSCs)*

The number of hematopoietic stem cells (HSCs) in the bone marrow does not change greatly with age, when assessed by the number of colonies formed in the spleen of lethally irradiated mice (CFU-s). However, when the number of cells per colony is counted, the cell counts in colonies derived from young bone marrow are apparently higher than those from old bone marrow, indicating that proliferative activity of old bone marrow cells declines with age (Albright and Makinodan, 1976). A recent review paper relates age-related functional activity of HSCs with age-related decline in replicative activity of HSCs in both murine models and human, and concludes that age-related functional decline in adult tissue HSCs limits longevity in mammals (Geiger and Van Zant, 2002). The ability of HSCs to differentiate into mature B cells also declines, and IL-7 plays an important role in the expansion of B cell precursors in bone marrow. An apparent decrease in the number of IL-7 responsive $B220^+$ B cell precursors was observed in old mice when compared with young mice (Jonsson and Phillips, 1993). Progenitors of T cells also decrease with age, when assessed by the ability of bone marrow from young and old donors to repopulate the thymus and spleen of lethally irradiated mice. However, alteration of the thymic microenvironment is much more responsible for the thymic involution than alteration of progenitors of T cells, as the size of thymus restored by bone marrow transplantation is apparently smaller in Y $\rightarrow$ O than in O $\rightarrow$ Y bone marrow chimera (Table 3).

2. *T cells*

T cells play a pivotal role in the acquired immune system and are most profoundly affected by aging. The magnitude of decrease in T cell functions *in vivo* between young and old individuals is sometimes more than 10-fold, and generally greater than the decrease observed in B cells or NK cells. Age-related changes of T cells can be ascribed to the following three types: (a) quantitative change, (b) a change in the proportion of T cell subsets, (c) a qualitative change, such as proliferative response and cytokine production.

(a) Quantitative change

The number of T cells in human peripheral blood is high in infants and young adults before 20 years of age, and a significant decrease is observed between the second and third decade. The number stays at almost the same level through the sixth decade and declines after the seventh decade (Table 4) (Figure 6) (Utsuyama *et al.*, 1992). Such a decline in T cell numbers appears to be associated with the acceleration of thymic involution. Some investigators have proposed that the thymus plays

Table 3 Comparison of regeneration of thymus, splenic T cells, and their subset among four combinations of bone marrow chimera mice constructed between young and old mice

Types of radiation bone marrow chimeras (donors → recipients)	Thymic weight (mg)	Splenic T cells ($\times 10^6$)	CD4:CD8 (ratio)	Naïve T: memory T (ratio)
Y → Y	43.9	21.1	6.5	0.91
O → Y	44.4	24.3	6.1	0.33
Y → O	14.2	9.9	8.9	0.16
O → O	13.6	8.4	7.9	0.13

Numbers indicate levels 8 weeks after the construction of bone marrow chimera mice: bone marrow cells from donor mice were grafted to sublethally irradiated mice.
Y, Young mice; O, Old mice.

Table 4 Age-related changes in cells in peripheral blood

Age	WBC	Lymphocytes	T cells	CD4/8 ratio	B cells	NK cells	Monocytes
1–19	6.8 ± 0.5	2.7 ± 0.4	1.7 ± 0.2	1.56 ± 0.09	0.27 ± 0.06	0.38 ± 0.05	0.33 ± 0.04
20–29	6.3 ± 0.3	2.2 ± 0.2	1.4 ± 0.1	1.67 ± 0.10	0.16 ± 0.02	0.38 ± 0.06	0.18 ± 0.02
30–39	6.6 ± 0.4	2.2 ± 0.2	1.3 ± 0.1	1.56 ± 0.10	0.15 ± 0.02	0.38 ± 0.06	0.23 ± 0.03
40–49	7.0 ± 0.6	2.3 ± 0.2	1.4 ± 0.1	2.31 ± 0.21	0.15 ± 0.02	0.42 ± 0.05	0.22 ± 0.02
50–59	6.6 ± 0.4	2.5 ± 0.2	1.5 ± 0.1	1.98 ± 0.13	0.16 ± 0.02	0.42 ± 0.05	0.23 ± 0.02
60–69	6.5 ± 0.4	2.2 ± 0.2	1.3 ± 0.1	2.49 ± 0.25	0.17 ± 0.03	0.52 ± 0.05	0.31 ± 0.03
70–79	5.8 ± 0.4	2.0 ± 0.2	1.1 ± 0.1	2.91 ± 0.70	0.13 ± 0.02	0.57 ± 0.12	0.39 ± 0.04
80–89	6.1 ± 0.3	1.8 ± 0.1	1.1 ± 0.1	2.13 ± 0.18	0.11 ± 0.01	0.45 ± 0.04	0.29 ± 0.02
90–	6.1 ± 0.4	1.7 ± 0.2	0.9 ± 0.1	2.21 ± 0.39	0.08 ± 0.02	0.41 ± 0.06	0.41 ± 0.06

Values $\times 10^3$ indicate cell counts per mm^3 in the peripheral blood, except for CD4/8 ratio.
Cell counts of WBC (white blood cells), lymphocytes, and monocytes were obtained by routine blood cell count. Cell counts of T cells, B cells, and NK (natural killer) cells were obtained by flow cytometric method.

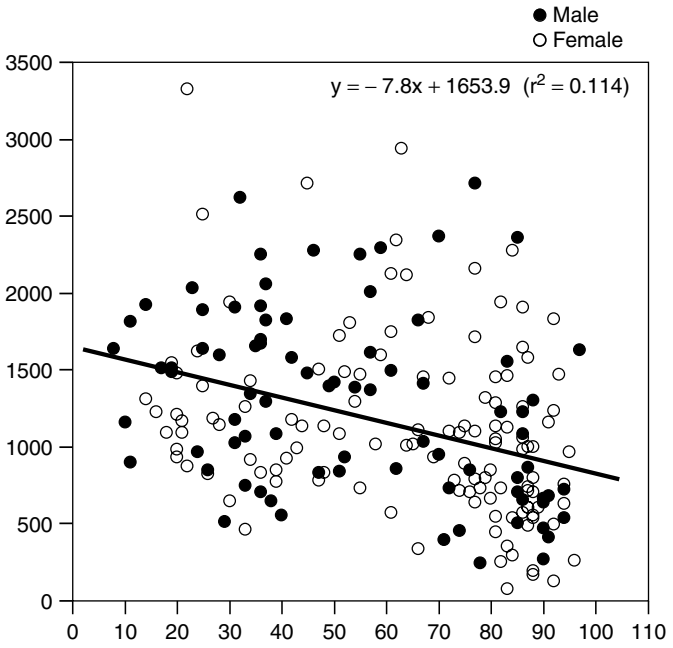


Figure 6 Number of T cells (per mm^3) in peripheral blood of male (closed circles) and female (open circles), ranging in age from 6 to 97 years. The line indicates regression

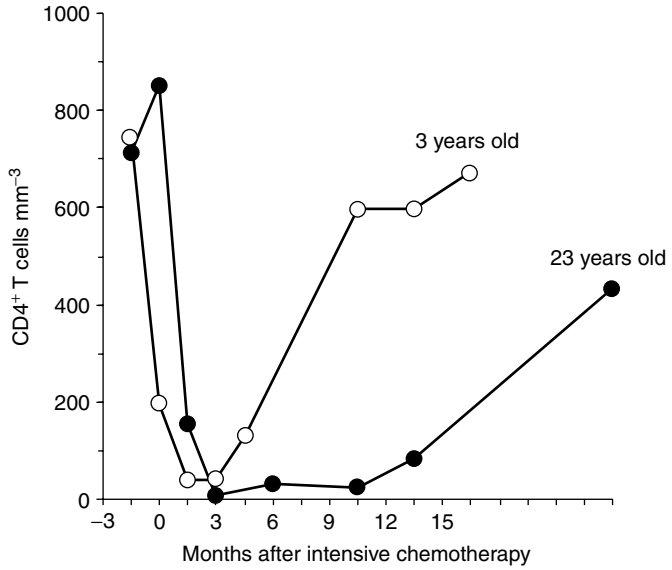


Figure 7 Regeneration of $CD4^+$ T cells in peripheral blood in patients following intensive chemotherapy. Number of $CD4^+$ T cells drastically declined after chemotherapy. In a 3-year-old patient, the number recovered nearly to the previous level in 9 months. In a 23-year-old patient, however, recovery of the number of $CD4^+$ Ta cells was significantly delayed. Modified from Mackall *et al.* (1995)

a time-keeper's role or acts as an 'aging clock'. The level of T cell numbers is easily influenced by exogenous factors, such as infection and stress, and the individual variation increases with advancing age. In this regard, the most important point is that the recovery in the T cell number after exposure to stress or drug treatment is reduced in old individuals as compared with younger ones (Mackall *et al.*, 1995; (Figure 7)).

(b) Change in T cell subsets

$CD4^+$:$CD8^+$ T cell ratio In long-lived C57BL/6 mice, the percentage of splenic T cells gradually increases after birth, peaks at around 3 months of age, stays at a constant level until 12 months of age, and then gradually declines thereafter. The number of $CD4^+$ T cells stays relatively constant in the adult and senescent stages, while that of $CD8^+$ T cells gradually declines with age. Thus, the ratio of $CD4^+$:$CD8^+$ T cell subset rises after 3 months of age. Of clinical importance is that a similar age change is observed in human peripheral blood. Thus, the ratio of $CD4^+$/$CD8^+$ T cells is low in infants and young adults, increases in middle-aged people, and again decreases in old people over 80 years of age (Table 4) (Utsuyama *et al.*, 1992). In a Swedish longitudinal Octogenarians (OCTO)-immune study, a combination of decreased $CD4^+$:$CD8^+$ T cell ratio and poor T cell proliferation was associated with higher mortality in a subgroup of very old Swedish individuals (Wikby *et al.*, 1998). In this respect, it is interesting to note that the number of $CD8^+$ T cells carrying receptors for viral epitope (cytomegalovirus (CMV) or Epstein–Barr virus (EBV)) increases with age in some cohorts (Ouyang *et al.*, 2002), which could contribute to the decrease of $CD4^+$:$CD8^+$ T cell ratio.

Naïve and memory helper T cell subsets Human $CD4^+$ and $CD8^+$ T cells can be divided into two subsets based on the expression of two markers: CD45RA and CD45RO that seem to differentiate the so-called naïve and memory T cells. At birth, most of the T cells are of naïve type and the number decreases thereafter with reciprocal increase in the number of memory type T cells (Cossarizza *et al.*, 1996). Figure 8 shows age-related changes of naïve and memory T cells in human and C57BL/6 mice (Utsuyama *et al.*, 1992). In mouse T cells, $CD4^+$ $CD45RB^{high}CD44^{low}$ and $CD4^+$ $CD45RB^{low}$ $CD44^{high}$ are referred to as *naïve* and *memory T cells*, respectively (Mossmann and Coffman, 1987). The age-related reciprocal change in the ratio between naïve and memory T cell subsets in mice (Figure 8b) is much more clear-cut than in humans (Figure 8a). In young mice, naïve and memory T cells are almost comparable to the proinflammatory Th1 and anti-inflammatory Th2 T cell ratio, in terms of cytokine production. However, the situation changes in old mice; that is, naïve T cells produce more IL-4 than IL-2 and memory T cells produce more IL-2 than IL-4.

Other T cell subsets CD28 is a costimulatory molecule that is required for optimal activation and proliferation by antigenic stimulation of T cells. T cells expressing CD28 decrease with age *in vivo*, and progressive loss of CD28 is observed in long-term T cell culture (Effros *et al.*, 1994). Thus, expansion of $CD28^-$ T cells may be one of the hallmarks of immunosenescence. CD95 is a surface molecule mediating apoptotic signal and plays an important role in immunological regulation. T cells expressing CD95 decrease with age, especially within the $CD8^+$ T cell subset (Fagnoni *et al.*, 2000).

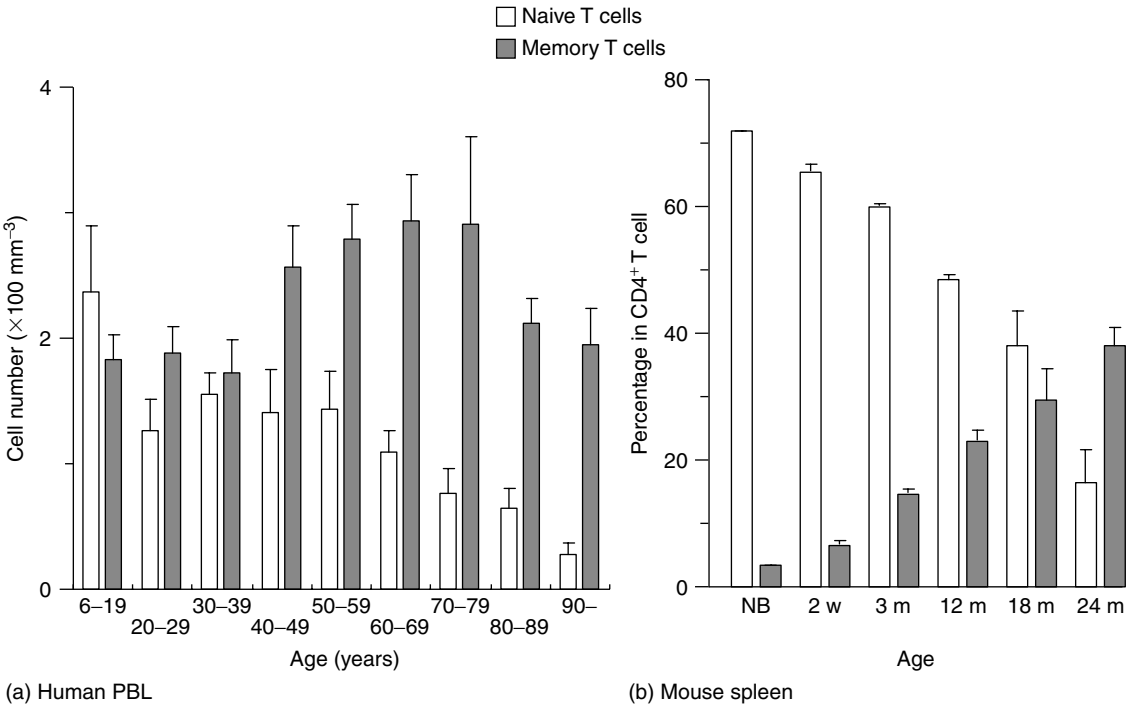


Figure 8 Age-related decrease of naïve T cells (open columns) is seen with a concomitant increase of memory T cells (cross-hatched columns) in human peripheral blood (a) and mouse spleen (b). After Utsuyama *et al.* (1992) (Reprinted from Mechanisms of Age and Development, vol 63, Utsuyama M *et al.*, pp 57–66, Copyright 1992, with permission from Elsevier)

Naturally arising $CD25^+CD4^+$ regulatory T cells contribute to the maintenance of immunologic self-tolerance and negative control of various immune responses (Sakaguchi, 2004). Suppressive activity of human $CD4^+$ $CD25^+$ T cells is reported to decline with age (Tsaknaridis *et al.*, 2003).

(c) Qualitative change

Qualitative changes in T cells are observed by their ability to proliferate and produce various cytokines following antigenic or mitogenic stimulation (Douziech *et al.*, 2002; Utsuyama *et al.*, 1993). Antigenic stimulation is received by the T cell antigen receptor (TCR), and the signal is transmitted through CD3 molecules to activate various signal transduction molecules, eventually giving rise to proliferation and cytokine production. Aging definitely influences signal transduction and cytokine production, which will be discussed later. T cells from aged humans appear to be more sensitive to TNF-α-induced apoptosis (Salvioli *et al.*, 2003).

3. *B cells*

B cells play an important role in the production of antibody. Quantitatively, the number of B cells in human peripheral blood decreases with age (Table 4) (Utsuyama *et al.*, 1992; Huppert *et al.*, 1998). Antibody forming capacity is known to decrease with age in humans and animals, and the decline is due to insufficiency of helper T cells, intrinsic changes in B cells, or both. For example, immunization with tetanus toxoid (TT) results in a significant increase in serum titers in young adults for up to 1 year, but the serum TT titers falls off to baseline by 6 months in old adults (Burns *et al.*, 1993). Stem cells in the bone marrow differentiate to pro-B cells, then to pre-B cells, and finally to B cells with sIgM. It is well known that frequencies of pre-B cells are diminished in aged mice. Age-related decrease was also observed in the number of both pro-B cells and very early B-lineage progenitors in mouse bone marrow (Miller and Allman, 2003).

Qualitatively, various age changes appear to occur in B cells. An intrinsic molecular change may occur in the aging B cells, as utilization of VH and VL genes in antibodies to a bacterial epitope (e.g. phosphorylcholine hapten) differs between young and old mice. Old mice express less diversified antibody repertoires, possibly as a consequence of reduction in the number of antibody precursors and increased peripheral selection that may be responsible for the progressive establishment of immunodeficiency.

4. *NK cells*

NK cells are a critical component of the innate immune response against various infections and tumors. The number of NK cells increases with age in humans after a certain point in old age, but contrarily, it decreases in mice (Utsuyama *et al.*, 1992; Mariani *et al.*, 1994). Despite discrepancy in the number of NK cells between humans and mice, the killer cell activity declines both in humans and mice (Mariani *et al.*, 1994). Proliferation of purified NK cells from healthy elderly donors in response to IL-2 is decreased as compared to those from young donors (Borrego *et al.*, 1999).

5. *NKT cells*

NKT cells represent a unique subset of T cells sharing some characteristics with NK cells and are found at high frequency in the liver. The number of liver NKT cells decreases in old humans and mice (DelaRosa *et al.*, 2002; Tsukahara *et al.*, 1997), in association with impaired cytotoxicity and cytokine production. It is interesting to note that liver NKT cells bearing TCR$\alpha\beta$ decrease in number with age, but those bearing TCR$\gamma\delta$ are functionally increased in very old mice (Mocchegiani and Malavolta, 2004).

6. *Macrophages*

Macrophages are one of the prototype cells of the innate immune system. Conflicting results are reported on functions of macrophages and monocytes. Phagocytosis and lysosomal enzyme activity do not change with age; however, the ability of macrophages to present antigen declines with aging. Lectin-induced proliferation of T cells is inhibited by prostaglandin (PG) E2, hydrogen peroxide (H_2O_2), and transforming growth factor (TGF) $\beta 2$, which are produced by macrophages. The inhibitory effect is significantly greater when macrophages are derived from aged rats. The production of H_2O_2 and nitric oxide (NO) in peritoneal macrophages is reduced in old mice when compared to that of young mice (Ding *et al.*, 1994). Antitumor activity of peritoneal macrophages declines with age, together with the reduced capacity to produce IL-1 and NO. Adherence of macrophages to fibronectin (FN) and type 1 collagen increases during aging, and this may be related to atherogenesis of the aorta during aging. Age-related increases in the number of monocyte/macrophage/osteoclast precursor cells could explain the increased resorptive activity seen in the elderly. Tumor necrosis factor (TNF) production by alveolar macrophages and spleen cells in response to a Streptococcus-derived factor (OK-4323) increases with age in mice (Han *et al.*, 1995). Both splenic and activated peritoneal macrophages from aged mice express significantly lower levels of all Toll-like receptors (TLRs). Secretion of IL-6 and TNF-α is decreased when stimulated with known ligands for TLRs (Renshaw *et al.*, 2002). Lipopolysaccharide (LPS) stimulated macrophages from aged animals have significantly higher levels of the inducible cycloxygenase 2 enzyme, leading to increased production of PGE_2, which is known to inhibit T cell function (Hayek *et al.*, 1997), as mentioned above.

7. *Granulocytes*

Granulocytes are a major component of natural immunity and operate as the front line of defense against various infectious agents. In healthy subjects, most functions of granulocytes do not change or even increase compared with young control. However, age-related impairment or alteration of various magnitude was detected including phagocytosis, intracellular killing, chemotaxis, proliferative response to GM-CSF, expression of CD16, production of superoxide

anion, mobilization of intracellular free calcium, apoptosis, and antibody-dependent cell-mediated cytotoxicity (ADCC) activity (Seres *et al.*, 1993; Fulop *et al.*, 1997; Schroeder and Rink, 2003; Plackett *et al.*, 2004).

8. *Antigen presenting cells (APC)*

Macrophages, B cells, and dendritic cells play an important role in presenting antigen to T cells. In senescent accelerated mice (SAMP1), B cells and dendritic cells express low level of Major Histocompatibility Complex MHC-II and intercellular adhesion molecule 1 (ICAM-1) and show a decrease in antigen presenting cells (APC) function. A decrease is also observed in accessory function of human monocytes, which is essential for T cells to proliferate in response to phytohemagglutinin (PHA) stimulation. The type of MHC should be the same between APC and T cells; however, T cells from aged, but not young, humans can be stimulated with influenza vaccine presented by allogeneic APC (Schwab *et al.*, 1992). Dendritic cells (DC) are "professional" APC, for they are most efficient in presenting antigens to T cells. Since maturation of DC subsets is suppressed by IL-10, age-related increase of IL-10 could negatively influence the maturation of DC in the elderly (Uyemura *et al.*, 2002). The number of DC is decreased in skin (Langerhans' cells) of aged mice and peripheral blood of elderly people (Shodell and Siegal, 2003).

9. *Extrathymic T cells*

It is established that T cells of various types could be developed outside of the thymus, although the number is smaller than those derived from the thymus. T cells of extrathymic origin have either $\alpha\beta$ or $\gamma\delta$ type TCR, and are found in the liver and within epithelial cells of the digestive tract. With the age-related decline of thymic function to provide T cells to the periphery, extrathymic T cells generally increase in number. They probably play a role in the local defense against pathogenic microbes as well as in the maintenance of mucosal epithelium.

ROLE OF THYMUS IN AGING OF THE IMMUNE SYSTEM

The immunological function of the thymus was first revealed by the famous brief report of Miller (Miller, 1961), indicating that neonatal but not adult thymectomy brought about immune deficiency in mice. This suggests that the thymus starts to lose its function to provide T cells to the periphery shortly after the birth. Table 5 summarizes the rate of decline in various thymic functions in long-lived mice: (a) immigration of pre-T cells into the thymus; (b) proliferative activity of thymocytes; (c) emigration of T cells to the spleen; (d) the thymic function to provide helper T cells; and (e) killer T cells (Hirokawa *et al.*, 1994). The results clearly indicate that most thymic functions decline very rapidly; that is, within 4 weeks after birth. In this respect,

Table 5 Age-related changes in thymic function in mice

Experiments	1d	1 w	2 w	4 w	17 m	24 m
Experiment 1						
Immigration of pre-T cells Into thymus	100	NT	NT	7	3	3
Experiment 2						
1. Rate of proliferation of thymocytes	100	45	15	NT	17	NT
2. Rate of emigration of T cells to spleen	100	25	15	NT	1	NT
Experiment 3						
1. Rate of proliferation of thymocytes	100	73	71	85	NT	65
2. Activity of helper T cells	100	62	41	40	NT	10
3. Activity of killer T cells	100	125	55	25	3	0.5

The numbers are percentages as compared with the value at 1-day-old mice (100%) and average of 3 mice. NT, not tested; d, days; w, weeks; m, months. Experiment 1: Bone marrow cells from young B10.Thy-1.1 mice were injected i.v. into congeneic C57BL/6.Thy-1.2 mice at various ages from day 1 to 24 months old, and the number of donor-type thymocytes was counted 4 weeks later. Experiment 2: Bone marrow cells from young B10.Thy-1.1 mice were directly injected into thymus of congeneic C57BL/6 mice at various ages from day 1 to 24 months old, and the numbers of donor-type T cells in thymus (1) and spleen (2) were counted 4 weeks later. Experiment 3: Thymus from C57BL/6 mice at various ages from 1 day to 24 months old was implanted into congenic nude mice at 6 weeks of age. Twelve weeks later, number of thymocytes (1), activity of helper T cells (2), and killer T cells (3) in spleen were assessed.

repopulation of $CD4^+$ T cells after their elimination with anti-CD4 antibody (GK1.5) is 5 times less in aged than in young mice, and there is no repopulation in thymectomized mice (Rice and Bucy, 1995). In humans, Mackall *et al.* (1995) reported that regeneration of $CD4^+$ T cells after intensive chemotherapy was seen within 6 months in a 3-year-old infant, but was significantly retarded in a young adult 23 years of age (Figure 7). Such thymic changes, which start in the early phase of life, could be determined by assessing age-related changes occurring in either pre-T cells in the bone marrow or the thymic microenvironment, or both. To address this issue, four combinations of bone marrow chimeric mice were constructed by transplantation of bone marrow cells from young (3 months old) or old (24 months old) donors into young or old irradiated recipient mice ($Y \rightarrow Y$, $Y \rightarrow O$, $O \rightarrow Y$, $O \rightarrow O$). It was shown that the thymic weight was almost comparable for those chimeric mice when the recipients are young, regardless of the age of bone marrow donors, but was distinctly reduced when the recipients are old, regardless of the age of bone marrow donors. In other words, the magnitude of *in vivo* proliferative capacity of the thymocytes was mainly dependent upon the age of thymic microenvironment (Table 3). In the experiment of intrathymic injection of bone marrow cells in mice, it was shown that the rate of emigration of T cells from the thymus greatly decreased between birth and 1 month of age (Table 5) (Hirokawa *et al.*, 1988). These findings, taken together, indicate that the

age-related alteration of thymic microenvironment is more responsible for the physiologic impairment in generating new T cells than that caused by intrinsic changes in progenitors (pre-T cells) in bone marrow (Hirokawa *et al.*, 1988).

As already described in the preceding sections, the impairment of T cell functions in the aged individuals is partly ascribed to a change in composition of T cell subsets. Such age-related change in T cell subsets can also be due to alteration in the ability of thymus to provide T cells to the periphery. It was shown that the thymus of young mice, as compared with that of old mice, produces more $CD4^+$ than $CD8^+$ splenic T cells. In case of $CD4^+$ T cell subsets, the thymus of young mice produces more naïve T cells than memory T cells, while the thymus of old mice does the opposite (Table 3). These findings are consistent with the facts that $CD8^+$ T cells are more susceptible to aging than $CD4^+$ T cells, and naïve T cells decrease with age as memory T cells increase (Utsuyama *et al.*, 1992).

CAUSES OF AGE-RELATED DECLINE IN THYMIC FUNCTION

Physiological thymic involution is considered to be under the control of both extrathymic and intrathymic factors. Since thymic involution is accelerated after puberty, sex hormone could be a possible candidate influencing thymic function. In practice, thymic involution can be delayed or reversed by castration regardless of age. Thymic hypoplasia with T cell-dependent immunodeficiencies was observed in congenitally hypopituitary Snell dwarf mice (Dorshkind *et al.*, 2003) and in rats that had undergone hypophysectomy. Conversely, thymic hyperplasia could be induced in rats by the destruction of the anterior portion of hypothalamus (AHTL, Anterior Hypothalamus Lesioning) (Utsuyama *et al.*, 1997a). AHTL gives rise to decreased secretion of somatostatin (SST) and relative increase in growth hormone releasing hormone (GHRH) in the hypothalamus. This leads to increased secretion of growth hormone (GH), causing thymic hyperplasia. As compared with young adult, high level of GH (>10 folds) is detected in the serum of newborn mice or rats, or rats treated with AHTL. In other words, size and function of thymus are partly dependent on the serum level of GH, which, in turn, is regulated by the balance between SST and GHRH in the hypothalamus (Figure 9) (Hirokawa *et al.*, 2001).

Regarding intrathymic factors influencing thymic size, most important is the thymic microenvironment composed mainly of epithelial cells. As shown in the experiment of bone marrow chimeras constructed with tissues from young and old donor mice (Table 3), the age of thymic microenvironment is crucial for the magnitude of thymopoiesis. Thus, it is important to search for genes or factors that are expressed at high level in the newborn stage and progressively decline thereafter. It has been recently reported that stromal cells expressing Notch ligand Delta-like-1 acquire the capacity to induce the differentiation of hematopoietic progenitors into CD4 CD8 double- and single-positive T cells (Schmitt

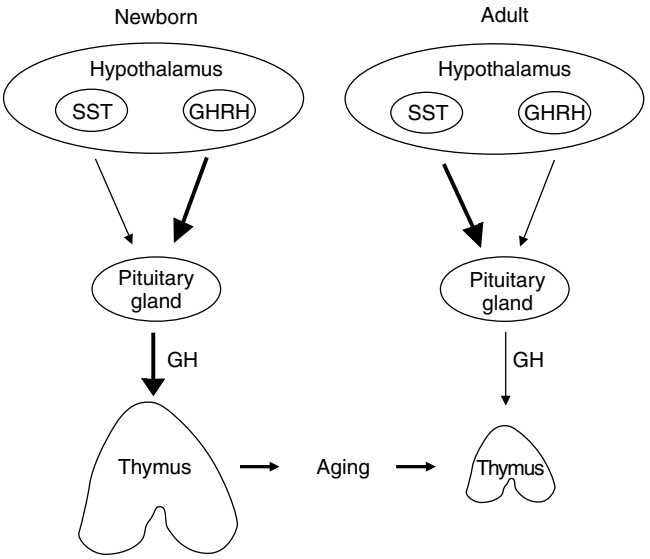


Figure 9 Control of thymic function by hypothalamus-pituitary axis. In newborn animals, positive signal of growth hormone releasing hormone (GHRH) is superior to negative signal of somatostatin (SST) in hypothalamus, leading to high secretion of growth hormone (GH). In young adult animals, negative signal (SST) exceeds positive one (GHRH) leading to a decrease in secretion of GH. A decrease in the serum level of GH in the young adult gives rise to thymic involution

and Zuniga-Pflucker, 2002). A decline in IL-7 production is another factor that is responsible for thymic involution (Andrew and Aspinall, 2002). The mRNA expression of Notch ligand Delta-like-1 and IL-7 is very high at birth and quickly declines thereafter (Hirokawa and Utsuyama, 2004). In addition, there are many other genes that are expressed at high level in the thymic stromal cells at birth and quickly decline thereafter (Hirokawa and Utsuyama, 2004). Many of them seem to participate in the process of physiological thymic involution.

CYTOKINE PRODUCTION

Among many cytokines, two types of cytokines, Th1 and Th2, are recognized. Th1 types are IL-2, IFNγ, and TNFβ, mainly responsible for cell-mediated immunity and suppressing antibody formation. Th2 types are IL-4, IL-5, IL-6, IL-10, and IL-13, responsible for antibody formation and suppressing cell-mediated immunity. It is generally accepted that production of Th1 type cytokines decreases with age, with a reciprocal increase of Th2 type cytokines, although there are some conflicting reports (Deng *et al.*, 2004; Glaser *et al.*, 2001; Neuber *et al.*, 2003). For instance, production of IL-2 and INFγ was reported to decline with age (Deng *et al.*, 2004), and such a decline is considered to be responsible for the impaired proliferation of old T cells upon antigenic stimulation. In contrast, production of IL-4, IL-5, IL-6, and 1L-10 by T cells increases with age (Castle *et al.*, 1997; Neuber *et al.*, 2003). Although INFγ belongs

to Th1 type cytokines, there are many reports indicating age-related increase in production of IFNγ or number of IFNγ^+ cells (Castle *et al.*, 1997; Neuber *et al.*, 2003; McNerlan *et al.*, 2002; Pietschmann *et al.*, 2003). The decrease in Th1 cytokines could explain a decrease in delayed type response to tuberculosis in the elderly, and increased production of Th2 cytokines would be consistent with increased frequency of autoimmune phenomena in the elderly population. IFNγ has a double edge effect in the immune system: one is antiviral effect and the other is suppressive effect on T cell function. With respect to the latter, production of TNF-α (Han *et al.*, 1995) and TGF-β also increases with age. These cytokines are known to contribute to age-related decline in immune functions. In any event, age-related change in the composition of T cell subsets is associated with an altered balance in cytokine production, and, together, they contribute to the impaired immune response capacity of old individuals.

SIGNAL TRANSDUCTION

Cells of the immune system are generally activated by stimuli such as antigens or cytokines through various receptors on the membrane. The stimulation through a receptor induces a cascade of intracellular signal transduction eventually reaching the nuclei and leading to DNA replication or generation of mRNA of some proteins.

Important receptors of T cells are TCR, costimulatory receptors, and cytokine receptors. The level of TCR expression does not change with age or, at best, only slightly (Fulop *et al.*, 1999). TCR/CD3 complex on T cells are internalized after mitogenic stimulation and reexpressed in certain interval. The level of reexpression is significantly retarded in T cells from old, as compared with young mice (Wakikawa *et al.*, 1997). CD28 is an important costimulatory receptor and the expression is known to decrease in humans (Effros *et al.*, 1994). Information is limited about the age-related change in the expression level of cytokine receptors. The expression level of IL-2R is decreased in the elderly. An increase of IL-2R after mitogenic stimulation is retarded in T cells from old mice.

Intracellular signal transduction is apparently different between cells derived from young and old individuals (Pawelec *et al.*, 2001). Pantel and Miller (Pantel and Miller, 1992) reported that quantitative and qualitative changes were observed in the pattern of protein phosphorylation between young and old T cells stimulated with mitogens. The activity of phospholipase C (PLC) acts on the phosphatidy-4,5 bisphosphate (PIP2) for liberation of inositoltrisphosphate (IP3) and diacylglycerol (DAG). The amount of PLC and PIP2 proteins extracted from T cells are comparable between young and old mice. However, phosphorylation of PLC was significantly impaired in old T cells as compared with young ones, when assessed *in vivo* after stimulation with anti-CD3 antibody (Utsuyama *et al.*, 1993). Phosphorylation of PLC is dependent upon protein tyrosine kinase (PTK) associated with CD3 molecules. Our laboratory found that

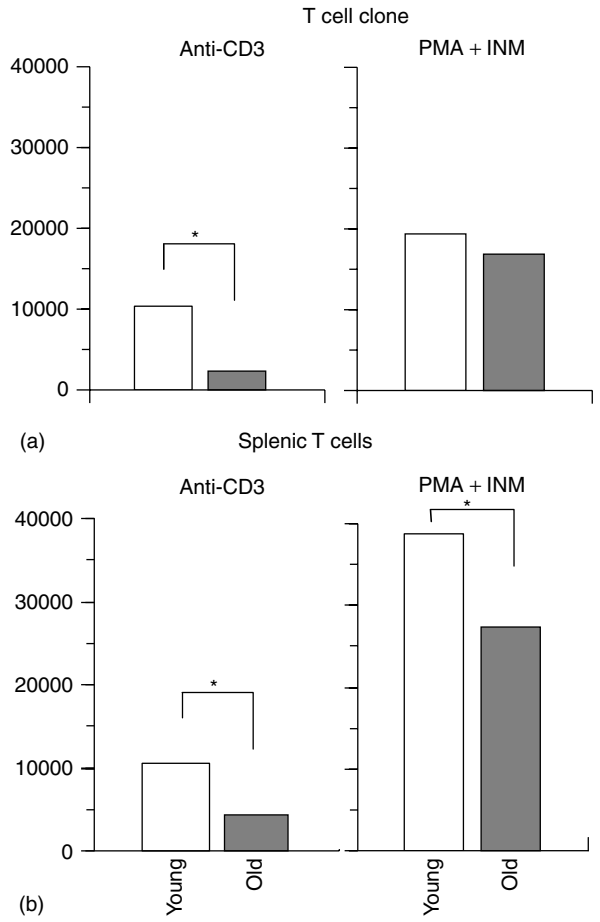


Figure 10 The proliferative response of T cell clones and splenic T cells after stimulation with anti-CD3mAb or PMA + INM. (a): [^{3}H]thymidine uptake of T cell clones established from young and old mice after stimulation with anti-CD3mAb or PMA + INM. (b): [^{3}H]thymidine uptake of splenic T cells prepared from young and old mice after stimulation with anti-CD3mAb or PMA + INM. *indicates a significant difference between young and old mice ($P < 0.001$). anti-CD3mAb: anti-CD3 monoclonal antibody (2.5μg/ml). PMA: phorbol myristate acetate (100 ng ml^{-1}). INM: ionomycin (20 ng ml^{-1})

phosphorylation of PTK such as lck, fyn, and ZAP-70 is impaired in old T cells as compared with young ones (Utsuyama *et al.*, 1997b). These findings collectively suggested that the decline in the proliferative response of old T cells could be partly ascribed to the impairment of intracellular signal transduction. Impaired phosphorylation of PTK and PLCγ1 in an old T cell clone is associated with LPS messengers and low influx of Ca^{2+}. An old T cell clone can be fully activated to the level of a young one by stimulation with phorbol myristate acetate (PMA) plus ionomycin (INM) that bypass receptor activation and directly stimulate Protein kinase C (PKC) and induce influx of Ca^{2+} (Utsuyama *et al.*, 1997b). However, when using splenic cells freshly prepared from young and old mice, the proliferative response of T cells of old mice to PMA plus INM is still lower than that of the young one (Figure 10) (Utsuyama *et al.*, 1997b). These results indicate that age changes of signal transduction

appear to be present in multiple sites within cells. The Jak-Stat pathway is one of the main signal routes under the IL-2R of T cells and is altered with age (Pawelec *et al.*, 2001). An age-related increase is observed in proportion of CD3ζ chains, associated with a FC-epsilon R instead of forming the usual ζ/ζ-homodimer in mice (Tamura *et al.*, 2000). In humans, T cells showed selective reduction in an isoform of PKC. Such a change in molecules may affect T cell function.

As regards B cells, a decreased sensitivity to the growth-promoting effects of IL-4 may be one of the mechanisms underlying defective specific antibody synthesis in aging. Such an age-related change of B cells might be related to decreased activity of PTK/PKC in human. A significant decrease of IP3 formation in granulocytes from elderly subjects was also reported.

These results suggest that alterations in signal transduction pathways occur with age in probably all cells of the immune system.

NEUROENDOCRINE-IMMUNE NETWORK

The immune system is closely related with the neuroendocrine system. Thymic involution accelerates in association with rise of sex steroids after puberty. In fact, restoration of thymic mass as well as certain immune functions is observed in the aged animals after gonadectomy. An increase of thymulin section is detected in aging rats by administration of growth hormone and thyroxine. Autonomic nerves may have influence on thymic function. An age-related decrease in noradrenergic nerves (Bellinger *et al.*, 1992) as well as dopamine-D1 like receptors (Ricci *et al.*, 1995) in the thymus may be responsible for reduced thymic mass with age. The hypothalamus plays an important role in the control of both endocrine functions and autonomic nerves; therefore, it also could be a control center regulating the rate of immunological aging. Inducing a lesion in the anterior portion of hypothalamus brings about either atrophy or hypertrophy of the thymus, depending upon the specific area of destruction (Utsuyama *et al.*, 1997a). As mentioned in the previous section, thymic function and size are partly under the control of hypothalamus (Hirokawa *et al.*, 2001). Lymphocytes can produce various hormones and neurotransmitters and express receptors for them. Figure 11 shows the expression of receptors for hormones and neurotransmitter in lymphocytes, revealed by RT-PCR. Changes of the expression level with age are variable; that is, an increase, or a decrease, or

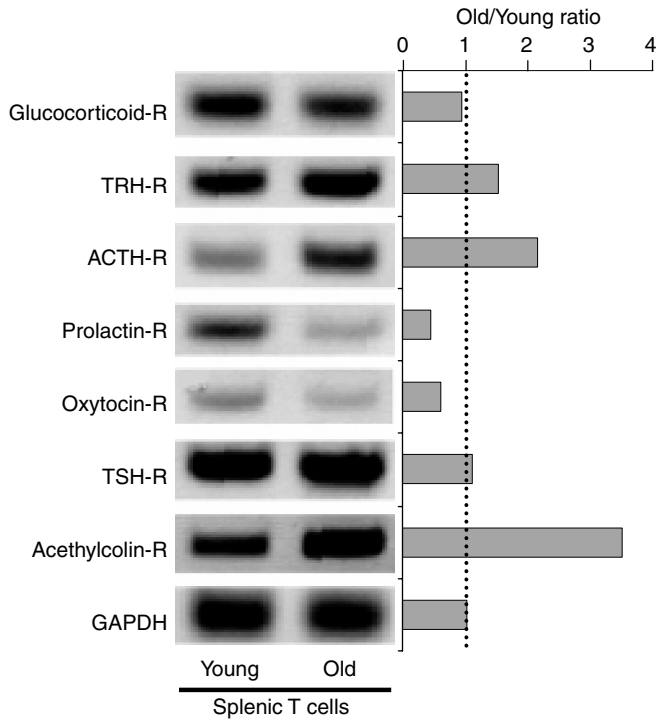


Figure 11 mRNA expression of various receptors (R) to hormones and neurotransmitters of T cells from young and old mice. Columns indicate ratio of old: young. mRNA expression of TRH-R, ACTH-R, and Acetylcholine-R are shown to increase with age

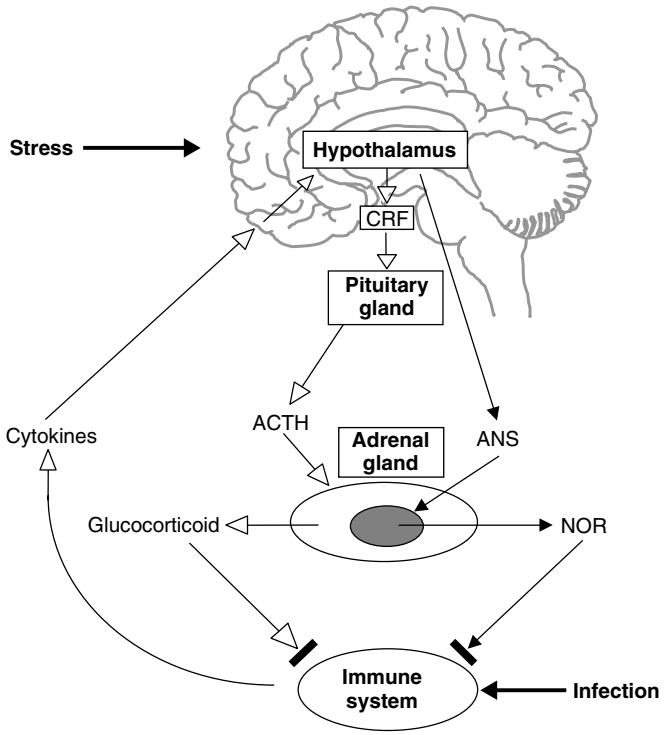


Figure 12 Stress-induced activation model of the neuroendocrine-immune network. Various types of stress from the external environment are received by the nervous system, and some signals eventually stimulate the hypothalamus to secrete Corticotropin releasing factor (CRF). CRF then stimulates the pituitary gland to secrete ACTH, which, in turn, stimulates the adrenal cortex to secrete glucocorticoid. At the same time, other stress-induced signals trigger the hypothalamus to stimulate the autonomic nervous system (ANS), eventually leading to the secretion of noradrenalin (NOR) by the adrenal medulla. Both glucocorticoid and NOR also suppress immune functions. Independently, infection stimulates the immune system to produce various types of cytokines, most of which enter the brain and stimulate the hypothalamus that eventually results in the secretion of both glucocorticoid and NOR

no change. Furthermore, cells of the nervous system can produce various cytokines and cytokine receptors. Age-related changes were reported in the levels of cytokines and their receptors in normal or pathological conditions (Utsuyama and Hirokawa, 2002; Godbout and Johnson, 2004). Another possible center for regulating immunological aging is the pineal gland, which produces melatonin for circadian rhythm. It is interesting to note that grafting of pineal gland in aged mice produces a remarkable restoration of thymic structure and cellularity. There is a growing belief that direct innervation or hardwiring of peripheral immune effector sites monitors and modulates immune homeostasis, together with the cytokine network (Downing and Miyan, 2000). More physiological studies *in vivo* are needed to further understand the significance of the neuroendocrine-immune network in aging. The data thus obtained would be helpful in understanding various diseases that are associated with immune dysfunction in the elderly population. As seen in Figure 12, the neuroendocrine-immune network acts as an integral system to combat various types of stress, including infection. As the network's function declines with age, its capacity to cope with stress declines. Thus, one physiologic characteristic of aging is the decrease in physiologic capacity of the neuroendocrine-immune network to cope with stress from the external environment.

IMMUNE RISK PHENOTYPES

As already mentioned, elderly people with elevated level of immune functions can live longer and become centenarians. Thus, the level of immune functions may predict the life span of individuals. In this respect, the longitudinal study in Baltimore (Shock *et al.*, 1984) suggests that the number of lymphocytes in the peripheral blood appeared to be a simple predictor of mortality; that is, individuals with a significant drop in the number of lymphocytes show higher rate of mortality within the next couple of years. In similar longitudinal studies of OCTO and Nonagenarian (NONA) on naturally aging population in Sweden, the concept of immune risk phenotype (IRP) was presented (Ferguson *et al.*, 1995). Parameters included in the high IRP phenotype were high CD8, low CD4, and poor T cell proliferative response that could predict two-year mortality of persons 80 years of age or older (Ferguson *et al.*, 1995). Further studies are required for the confirmation of the concept of IRP that would be helpful in understanding the importance of immune functions in morbidity and mortality of the elderly.

AUTOIMMUNE PHENOMENA INCREASING WITH AGE

Some autoimmune diseases are known to occur in young adults rather than in the elderly. For example, systemic lupus erythematosus (SLE) is an autoimmune disease that generally occurs in young females over 20 years of age. From the viewpoint of T cell immunity, however, people over 20 years of age are already in the early phase of the age-related decline of immune functions. As peak incidence of SLE, rheumatoid arthritis, and Hashimoto's thyroiditis are observed at the third, fifth, and sixth decade respectively (Figure 13), one could speculate that autoimmune diseases occur in the people whose immune functions are in the declining phase. These autoimmune diseases occur in a limited number of persons with distinct genetic background, as well as other factors such as aging of the immune system. It is important to

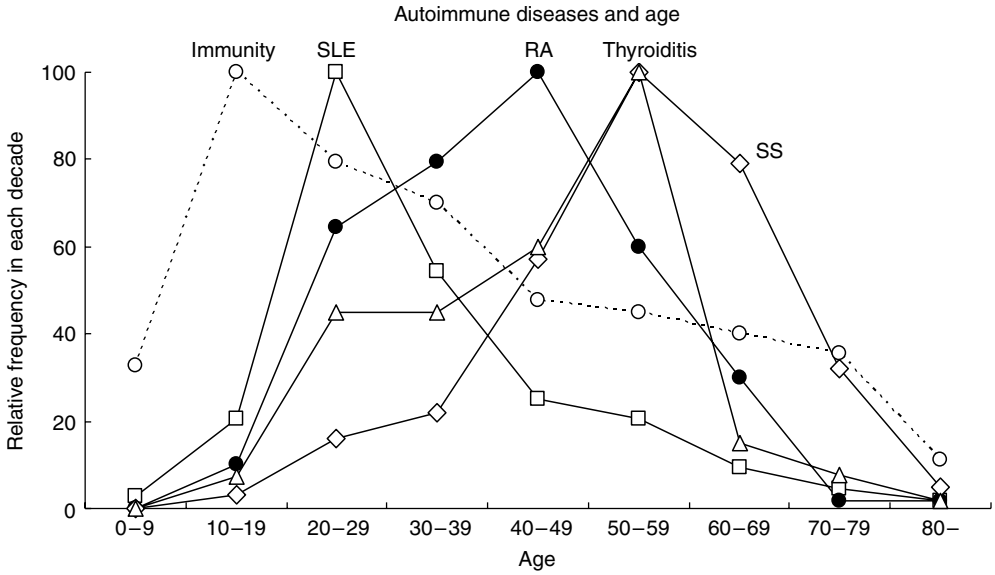


Figure 13 Age-related change of immune response and incidence of four autoimmune diseases in humans. SLE: systemic lupus erythematosus. RA: rheumatoid arthritis. Thyroiditis: Hashimoto's thyroiditis. SS: Sjögren's syndrome. Ordinate indicates relative values or frequencies, as compared with the peak level

note that autoimmune phenomena occur in most of the aged people, and they are called *age-associated autoimmune phenomena* rather than autoimmune disease, as they are generally not associated with clinical manifestations. On the other hand, the range of autoimmune disease is expanding. For instance, atherosclerosis might be an autoimmune disease due to an immune reaction against heat shock protein 60 (Wick, 2000).

Age-associated autoimmune phenomena are composed of two types of autoimmunity: one is the production of autoantibody and the other the generation of autoreactive T cells.

1. *Autoantibodies*

Accumulating data show that various kinds of autoantibodies are detectable in the sera of the elderly individuals. Both the frequency and the concentration of autoantibodies also increase with age and with a concomitant decrease of normal immune functions (Figures 1 and 5).

2. *Auto-reactive T cells*

It is very common to find focal lesions of lymphocytic infiltration in many organs of elderly autopsy cases, and most of these lymphocytes are revealed to be $CD4^+$ T cells when examined immunohistologically. The composition of the infiltrating lymphocytes in these lesions of submandibular glands was quite similar to those seen in Sjogren's disease. Focal lesions of T cell infiltration were also found in the thyroid, adrenal glands, liver, and kidney of the elderly autopsy cases as well as in aging mice. The incidence of focal T cell infiltration apparently increases with advancement in age, although the onset, incidence, and severity are different, depending on tissues and organs. In NFS/sld mouse, an animal model of human Sjogren's syndrome, α fodrin, a cytoskeletal protein, was identified as an autoantigen causing autoimmune disease (Haneji *et al.*, 1997). Interestingly, the lesion in NFS/sld mouse starts to appear as early as 1 month of age and becomes more pronounced and aggravated with age, and similar lesions develop in other sites (Kobayashi *et al.*, 2004).

RESTORATION OF IMMUNE FUNCTIONS

The development of methods to restore impaired immune functions of elderly people is urgently needed (Hirokawa and Utsuyama, 2002). Most of the methods reported are still at the level of animal models. Broadly speaking, there are two ways for immunological restoration: one is activation or functional enhancement of existing immune cells in individuals, and the other is transplantation or infusion of active or functional immune cells from young donors.

1. *Enhancement of immune cell functions*

(a) Caloric restriction

The effects of caloric restriction (CR) in rodents are pronounced in terms of elongation of life span and restoration of immunological functions (MaCay *et al.*, 1935). There has been accumulating evidence that similar observations are found not only in rodents but also in many other animal species, and CR influences various physiological systems, including the immune system (Longo and Finch, 2003; Heilbronn and Ravussin 2003; Pahlavani, 2004). Two important outcomes of CR are reduction of oxidative stress and improved glucoregulation. Studies are now ongoing to see the effect of CR on various physiological parameters in monkeys (Roth *et al.*, 2002), and they suggest several beneficial effects. Although data are limited, CR in humans could bring about similar physiological changes resembling those of rodents and monkeys. Thus, for example, there is a study reporting that long-term calorie restriction is highly effective in reducing the risk of atherosclerosis in humans (Fontana *et al.*, 2004). Animals under CR have decreased fat mass and alterations in insulin/insulin-like growth factor 1 (IGF-1). Mice with a fat-specific insulin receptor knockout (FIRKO) have reduced fat mass and show an increase in mean life span, although intake of calorie is normal (Blüher *et al.*, 2003).

(b) Antioxidants

Harman (Harman, 1969) hypothesized that degenerative changes associated with aging could be produced by the accumulation of deleterious side reactions of free radicals produced during cellular metabolism. Free radicals or reactive oxygen species (ROS) are harmful to immune cells, gradually attenuating their activities with increase in age. For instance, oxidative inactivation of CD45 protein tyrosine phosphatase may contribute to T lymphocyte dysfunction in the elderly (Rider *et al.*, 2003). Thus, vitamin E and other dietary antioxidants may play an important role in reducing ROS-initiated decline of immune functions with age. In animal models, vitamin E supplementation has been shown to increase immunological function and enhance survival against infection (Adolfsson *et al.*, 2001). Dietary supplementation with thioproline, a free radical scavenger, can significantly increase phagocytosis, NK activity, and proliferative response of lymphocytes in old mice (De La Fuente *et al.*, 2002). In humans, restoration of immune functions has been observed in some, but not all individuals (Ravaglia *et al.*, 2000; Gardner *et al.*, 2000). It is interesting to note that age-related physiological zinc deficiency induces deleterious changes in thymus structure and function, which can be partially corrected by a mild oral zinc supplementation (Mocchegiani and Muzzioli, 2000).

(c) Endocrine hormones

Age-related changes in the production of several hormones may be closely related with immunosenescence (Arlt *et al.*, 2002). Sex steroid hormones are inhibitory for lymphoid cells. Therefore, their withdrawal generally gives rise to enhanced immunological functions, as already described in gonadectomy. In contrast,

pituitary hormones, such as growth hormone and thyroid stimulating hormone, are stimulatory for the thymus and T cells. Concentration of dehyroepiandrosteron (DHEA) declines with age in humans. *In vivo* treatment of old rats with DHEA results in the restoration of age-associated defects in the protein kinase C signal transduction pathway with enhancement of mitogenic response of spleen cells (Corsini *et al.*, 2002). Melatonin is a hormone secreted by the pineal gland, and it plays an important role in the regulation of circadian rhythm. Melatonin was shown to act as a free radical scavenger; therefore, it could chemically correct immunodeficiencies of the elderly (Pierpaloi *et al.*, 1994). However, data reported on its effect on immunity are conflicting; some are positive (Atre and Blumenthal, 1998) and others are negative (Pahlavani *et al.*, 2002).

(d) Thymic peptides
Peptides isolated from the thymus are thymosin, thymic humoral factor (THF), thymopoietin, and FTS or thymulin, and they used to be called *thymic hormones*, but not any more. It is now generally accepted that they are not directly involved in T cell differentiation. Both successful and unsuccessful restoration of T cell function by thymic peptides, based on *in vivo* and *in vitro* experiments, have been reported by many investigators.

2. *Grafting of cells and tissues*

In animal experiments, transfusion of T and B cells from young mice into old mice did not give rise to a significant effect, probably due to inhibitory effects of preexisting cells in old individuals (Makinodan and Kay, 1980). In humans, the treatment of AIDS patients by transfusion of autologous T cells, expanded *ex vivo* in large scale, has been successful; that is, T cells were expanded 100–1000-fold by *ex vivo* culture for 2 weeks with recombinant interleukin-2 and immobilized monoclonal antibody to CD3 (Shimizu *et al.*, 2000). This model of large scale *ex vivo* expansion of T cells could be applied for the restoration of immune functions of the elderly.

The level of immune functions of aged mice can be restored to a level approaching that of young adult mice by grafting both newborn thymus and bone marrow cells of young donor animals (Hirokawa and Utsuyama, 2002). The results suggest that intrinsic cellular change of the immune system is more responsible for immune deficiencies of aged individuals than the environmental or structural tissue change, including connective tissues and humoral factors. Table 6 shows relative levels of anti-SRBC antibody response in eight combinations of chimeras, constructed by young or old recipients, young or old bone marrow cells, and newborn or old thymus. The relative magnitude of antibody response is always high or medium, regardless of the age of recipients and bone marrow cell donors. Thymic stromal tissues, rather than bone marrow cells, are important for restoration of the T cell-dependent immune system. In practice, aged mice treated with multiple newborn thymus grafting can survive significantly longer than control mice (Hirokawa and Utsuyama, 2002). For human application, MHC type should be the same or very close between donors and recipients. Therefore, a new method needs to be developed for the reconstruction of the thymic microenvironment using appropriate cells and genes of the individual (Hirokawa and Utsuyama, 2004).

Table 6 Eight combinations of chimeras constructed by young/old recipients, young/old bone marrow, and newborn/old thymus

Recipients	Bone marrow	Thymus	anti-SRBC antibody response
Young	Young	Newborn	High
Young	Young	Old	Low
Young	Old	Newborn	High
Young	Old	Old	Low
Old	Young	Newborn	High
Old	Young	Old	Low
Old	Old	Newborn	Medium
Old	Old	Old	Low

Young (2 months) and old (23 months) C57BL/6 male mice were irradiated (8.5Gy) and transplanted with bone marrow cells (5×10^5) from young (3 months) or old (24 months) C57BL/6 male mice. One month later, thymus from newborn or old (24 months) mice was transplanted under kidney capsule of recipient mice. One month after the last treatment, anti-SRBC antibody response was assessed.

CONCLUDING REMARKS

The immune system not only functions as the body's defense system against infections from the external environment but also as the body's regulatory system, maintaining homeostasis of the internal environment. In the latter case, the immune system operates together with the endocrine and nervous systems using many common mediators among themselves. In other words, the neuroendocrine-immune network combats various kinds of stresses from the outer environment, and its age-related decline in functional capacity is causally related to the increase in occurrence of various age-associated diseases and decline in quality of life (QOL) in the elderly population. Thus, the restoration of immune capacity is necessary not only for protection against infection but also for the improvement of QOL in the elderly.

Age-related functional decline is observed in many kinds of cells and tissues composing the immune system, but the most pronounced decline occurs in those involved in T cell-dependent immune functions that are due mainly to thymic involution starting in the early phase of life. Accordingly, the restoration of T cell-dependent immune functions is becoming an important issue in combating infectious diseases and improving the QOL of the elderly population. Various methods to restore T cell-dependent immune functions in the frail elderly population are now under investigation in many laboratories. Among them, the reconstruction of thymic microenvironment using modern tissue and gene technology appears to be one of the most exciting and challenging tasks.

KEY POINTS

- Infection, a major cause of death in the elderly population, is primarily due to age-related decline in T cell-dependent immune functions.
- Age-related decline of T cell-dependent immune functions, caused by thymic involution that occurs early in life, is manifested quantitatively by a decrease in the number of T cells and a shift in the proportion of T cell subsets, and qualitatively by changes in proliferative activity and cytokine production that are caused by alteration of molecules involved in intracellular signal transduction.
- The immune system collaborates with the neuroendocrine system, and the neuroendocrine-immune network combats various kinds of environmental stress, including infections.
- Age-related decline in immune functions is causally related to increase in occurrence of various age-associated diseases, including infections, autoimmune diseases, and autoimmune phenomena against internal antigens, and, as a consequence, to decrease in quality of life (QOL).
- Restoration of impaired immunological functions in the elderly is an urgent need, and therefore, various restorative methods are discussed, including caloric restriction, antioxidant dietary supplements, hormone supplement, and grafting of limiting immune cells and tissues.

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4

Physiology of Aging

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THE HUMAN BODY EVOLVING, CHANGING, AND AGING

In the last century, we have seen a near doubling of life expectancy in humans. Modern medicine has left us with a vast knowledge of information toward the aging process. A multitude of changes have been known to occur consistently in humans. This chapter will examine and focus on these changes. The organ systems will be highlighted with a brief synopsis of each and how they age. The aging process affects all organ systems and, as such, understanding these changes will allow us to better understand the functional impact they have on the aged individual.

A multitude of changes occur in each organ. These changes are irrespective of diseases modifying aging. The rate of age-related decline in organ function varies greatly. Aging has been defined as a failure to maintain homeostasis under conditions of physiological stress. All species show aging. Within a normal cell, oxidative stress (free radical theory of aging) chronically leads to changes in gene expression. This leads to alteration in the phenotype and aging of tissue. In a different model, "wear and tear" (somatic mutation, error catastrophe, protein glycosylation) of cells leads to necrosis or apoptosis. This leads to an increase in cell turnover causing an alteration in the phenotype leading to an aged cell. Senescence is defined as the permanent exit from the cell cycle of cells that would normally be able to undertake division. This may also lead to aging because it leads to a decline in the growth potential of cell populations, which have undergone turnover. These cells display biochemical features that are distinct from their growing counterparts. The expression of some genes (intrinsic mutagenesis, programmed death) goes up, while others go down or are unaffected. Olovnikov proposed that cells might count divisions through the progressive shortening of chromosome ends (telomeres). Telomerases are enzymes that prevent shortening of telomeres. The consequence of this is that a small amount of terminal DNA is not replicated with repeated cell divisions. This may contribute to senescence. It has been shown by Zglinicki that mild oxidative stress may increase the rate of telomere shortening. DNA helicases unwind damaged DNA to allow for repair. Organisms that have greater resistance to DNA damage have conferred longevity (Von Zglinki *et al.*, 2000). The neuroendocrine theory of aging stresses the need to regulate the biological clock to maintain homeostasis. The hypothalamo–pituitary–adrenal axis acts as the master regulator to adjust to the physiological needs of the organism during stress. The neuroendocrine-immuno theory of aging stresses the relation of the endocrine system as it regulates the immune system to fight off infection. As the immune system wanes, the organism becomes susceptible to death due to higher chance for infection. Aging then would result from a "decreasing ability to survive stress". Thus, a multitude of factors can lead to aging.

AGING OF ORGANS

Aging of the Skin

The skin is the largest organ of the body. It has many important functions. It functions as a mechanical barrier, regulates temperature, initiates immunological functions, communicates external stimuli to the body, and protects against the effects of ultraviolet light. The skin is composed of three major layers. The outermost layer is the epidermis, followed by the dermis, which leads to the hypodermis. In the epidermis, a multitude of cells exist such as keratinocytes, melanocytes, Langerhans cells, and Merkel cells. The basement membrane separates the epidermis from the dermis. The dermis is composed of connective tissue, consisting mainly of collagen fibers, and elastin. The fibroblasts are the major cell type. The hypodermis is composed of the adipocytes, as well as the intravascular bundle. The typical signs of aging include wrinkling and sagging of the skin. Extrinsic aging is more prominent in the hands, neck, and the face and is attributed to sun exposure (Gilchrest, 1989).

Principles and Practice of Geriatric Medicine, 4th Edition. Edited by M.S. John Pathy, Alan J. Sinclair and John E. Morley.
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Intrinsically aged skin is thin, pale, and finely wrinkled. Histological staining shows flattening of the dermo-epidermal junction. This form of aging is felt to be secondary to superoxide free radical formation. Aged skin demonstrates a reduced keratinocyte proliferative capacity. The number of epidermal cell layers remains unaltered during aging (Table 1). A decrease in melanocytes contributes to the paling of the skin.

The dermo-epidermal junction flattens with age due to the retraction of the epidermal papillae (Table 2). This leads to a skin structural unit, which is less resistant to shear forces than younger skin is. Skin thickness tends to decrease after the seventh decade (de Rigal *et al.*, 1989). Within aging skin, increased vasoconstrictor responses and decreases in both vasodilators and vasoprotective agents have been demonstrated. Atrophy and hypertrophy of the subcutaneous tissue are common in aged individuals.

The repair of physical damage is an essential day-to-day function of skin. Alteration in wound healing may lead to chronic ulceration and nonhealing. The dysfunction of dendritic cells leads to the formation of skin neoplasms. The decrease in the protective effect of the skin leads to further loss of protection from UV light. Sunlight is also felt to lead to the generation of oxygen radicals leading to aging. It has been shown *in vitro* that Keratinocytes and dermal fibroblasts from habitual sun exposed sites have shorter life spans (Glichrest, 1979; Gilchrest, 1980; Gilchrest *et al.*, 1983).

In summary, the skin is the major barrier for our body to protect us within the environment (Table 3). As the aging process ensues, cellular functions are altered leading to problems with wound healing, immunosurveillance, temperature regulation, and general barrier functions.

Table 1 General effects of aging on the cell types resident within the skin

Cell type	Effect of aging
Keratinocytes	↓ proliferation, ↓ differentiation
Melanocytes	↓ density, ↓ proliferation, ↓ biochemical activity
Epidermal lymphocytes	↓ antigen presentation, ↓ response to activating factors
Fibroblasts	↓ proliferation, ↓ ECM production, ↑ ECM turnover
Endothelial cells	↓ proliferation, ↓ response to vasodilators
Inflammatory cells	↓ proliferation, ↓ response to mitogens

ECM, extracellular matrix

Table 2 General effects of aging on the function of individual components of the skin

Skin structure	General effects of aging
Epidermis	Little change in overall structure and function
Basement membrane	Flattening (loss of rete ridges)
Dermis	↓ thickness, ↑ stiffness
Vasculature	↓ number of blood vessels, ↓ blood flow
Sebaceous glands	↓ secretion of sebum in women
Hypodermis	↓ or ↑ dependent on body location
Hair	Graying, hair loss
Nails	↓ growth and change in appearance

Table 3 Summary of age-associated changes in skin function

Skin function	General effects of aging
Wound healing	
a. Inflammatory response	Dysfunctional and protracted
b. Re-epithelialization	Slowed and sometimes inhibited
c. Dermal repair	Impaired granulation tissue formation
d. Angiogensis	Reduced
Immunoregulation	Dysfunctional and impaired leading to neoplasm
Thermoregulation	Impaired ability to perceive the cold, decreased sweat response
Barrier function	Decreased with respect to UV protection

Skeletal Muscle Aging

Skeletal muscle comprises 40–50% of the human body. It is composed of muscle tissue, nerve tissue, blood vessels, and connective tissue. Myoblasts are precursor cells, which fuse together forming bundles of muscle fibers. There are two types of individual muscle fibers: type I or slow twitch and type II or fast twitch. Type two has two components: type A are called *fast-oxidative fibers*, and type B are known as *fast-glycolytic fibers*. There are several types of muscle contractions: shortening contractions, isometric contractions, and lengthening contractions. Skeletal muscles have developed adaptive responses to the generation of reactive oxygen species to protect themselves from oxidative damage.

These age-related changes in muscle mass are termed *sarcopenia* (*see* **Chapter 80, Sarcopenia and Sarcopenic-Obesity**). This leads to an age-related decrease in muscle strength and power. The basal metabolic rate of muscle decreases by 4% per year after the age of 50. The synthesis of myosin heavy chains declines with age, whereas the sarcoplasmic protein pool is unchanged (Balagopal *et al.*, 1997; Rooyackers *et al.*, 1996; Welle *et al.*, 1993; Short *et al.*, 1999). The regenerative potential of skeletal muscle, and overall muscle mass, declines with age. Several cytokines (Cannon, 1998), including Interleukin-1, tumor necrosis factor (TNF), Interleukin-15, ciliary neurotrophic factor, as well as growth hormone and insulin-like growth factor-I (IGF-I) (Welle, 1998) have strong influence on the balance between muscle protein synthesis and breakdown. Glucocorticoids have catabolic effects, reducing protein synthesis and stimulating protein degradation in muscle. In older rats, muscle wasting occurred more rapidly and the recovery of muscle mass was impaired (Dardevet *et al.*, 1995). Testosterone declines with age in men and a concomitant change in body composition occurs with a lower percentage of muscle mass and a redistribution of body fat (Baumgartner *et al.*, 1995). Thyroid hormone (T3) acts on nuclear receptor proteins, which, in skeletal muscle cells, regulate the gene expression of myofibrillar protein isoforms (Yu *et al.*, 1999). As circulating T3 levels decrease with aging, there is an associated fiber shift from fast to slow (Sonntag, 1987). Insulin-mediated skeletal muscle cell glucose uptake declines with advancing age (Paolisso *et al.*, 1995; Ferrannin *et al.*, 1996).

Table 4 Summary of changes in muscle

Age-related changes of muscle
Reduction in muscle mass (30–40%)
Decreased myosin heavy chain synthesis
Decrease in force
Infiltration of fat into muscle tissue
Increased fatigability
Decrease in basal metabolic rate
Decreased innervations
Increased number of myofibril per motor unit
Loss or reduced proliferation of satellite cells

During senescence, there is a loss of motor neurons and muscle fibers. The loss of motor neurons is of primary importance because it is likely to be the main reason for loss of muscle fibers. Electrophysiological studies have demonstrated a reduced number of motor units in old muscle (Dohert and Brown, 1993). The size of the average motor unit increases with age. The loss of strength does not result from failure of the central nervous system to activate motor nerves. However, a reduced rate of firing of motor nerves during maximal voluntary contraction in older subjects may limit the maximal force production in some muscles (Kamen *et al.*, 1995). During a sustained contraction, central fatigue may be more common in older adults than in younger persons. Age-related fiber atrophy generally is restricted to type II fibers, at least in the muscles of the leg. This selective atrophy is important functionally because type II fibers can generate more power than type I fibers. It is unclear whether there is impairment in the release of calcium affecting the rate of relaxation and contraction. Welle *et al.* have shown that older human muscle has reduced expression of several mRNA's encoding proteins involved in mitochondrial electron transport and ATP synthesis (Welle *et al.*, 2000). An accumulation of DNA deletions is seen in mitochondria of skeletal muscle with age (De flora *et al.*, 1996).

In summary, a multitude of changes occur with skeletal muscle and aging, affecting size, strength, endurance, and functionality in the elderly (Table 4).

The Aging Eye

Multiple population-based studies have shown a significant increase in the prevalence of impaired vision with advancing age (Tielsh *et al.*, 1990; Klaver *et al.*, 1998; Klein *et al.*, 1991; Attebo *et al.*, 1996). As such, visual impairment is negatively associated with the independence and functional status of elderly people (Wang *et al.*, 1999; Klein *et al.*, 1998). In addition, impaired vision may negatively affect cognitive functions among the elderly (Uhlmann *et al.*, 1991; Lin denberger and Baltes, 1994). The eye suffers age-related disease and is affected by many systemic illnesses (*see* **Chapter 103, Disorders of the Eye**). The eye consists of the retina, lens, cornea, and a neurovasculature.

The lens is a transparent, avascular tissue contained within a capsule. The lens cells divide, but are not shed. As a result, the lens continues to grow throughout life. It has defense mechanisms from reducing compounds that can cause damage. Aggregation of proteins are thought to be responsible for the yellowing of the lens as well as the increase in light scattering. Glutathione, a key-protecting molecule in the lens, tends to decrease with aging. Crystallins are proteins that provide the high refractive index of the lens. Alterations in structure and increased aggregation of these proteins are noted with aging. Cataract formation increases with aging. A multitude of enzymes have lowered activity in a cataract.

Table 5 Changes in vision with aging

Vision
Impaired dark adaptation
Yellowing of lens
Inability to focus on near items (presbyopia)
Decreased contrast sensitivity
Decreased lacrimation
Minimal decrease in static acuity
Profound decrease in dynamic acuity (moving target)

The retina is the light-responsive part of the eye. It is highly vascular unlike the lens, and it has 6 neural cell types organized in 10 layers. The photoreceptor cells (rods and cones), and the retinal pigment epithelium (RPE) are most affected with aging. Photoreceptor density decreases with aging. There is also loss of ganglion cells and RPE. Lipofuscin is a protein that is formed through many mechanisms. Its accumulation can cause cell death in cell culture (Davies *et al.*, 2001; Shamsi and boulton, 2001). Age-related macular degeneration (AMD) is the major cause of nonpreventable blindness in Western countries. Prevalence increases with aging. The molecular pathway leading to AMD has not been elucidated yet. There are also age-related changes to the sclera where it is thinner, yellower, and less elastic. Light scattering appears to increase through the cornea with aging. The vitreous body tends to liquefy with age, and collagen fibers concentrate.

In summary, a multitude of changes occur with aging affecting the functionality and cognitive capabilities of elders (Table 5).

The Aging Cardiovascular System

Aging is associated with complex and diversified changes of cardiovascular structure and function. Changes occur at the structural/functional levels, as well as the molecular/cellular level. The heart becomes slightly hypertrophic and hyperesponsive to sympathetic (but not parasympathetic) stimuli, so that the exercise induced increases in heart rate and myocardial contractility are blunted in older hearts. The aorta and major elastic arteries become elongated and stiffer, with increased pulse wave velocity, evidence of endothelial dysfunction, and biochemical patterns resembling atherosclerosis. The arterial baroreflex is altered in aging, with the baroreceptor of the heart showing greater impairment than the baroreceptor control of peripheral vascular resistance. No

Table 6 Effects of normal aging on the cardiovascular system

Structural/functional level
Systolic function
1. No change in maximum capacity of the coronary flow bed
2. Moderate left ventricular hypertrophy
3. Maintenance of ability to generate wall tension
4. Decreased velocity of myocardial shortening
5. Increased myocardial stiffness
6. Prolonged duration of (systolic) contraction
7. Increased left ventricular cavity diameter
8. No change in stroke volumes, heart rate, cardiac output, or ejection fraction at rest
9. Greater use of the Frank–Starling mechanism
10. Decline in maximum heart rate and maximum oxygen uptake with exercise
11. Increased ventricular stiffness
12. Decreased ventricular relaxation
Diastolic function
1. Delayed relaxation
2. Diastolic peak filling rate deceases with age
3. Decreased peak velocity of early filling while atrial fraction increase with age
4. Ratio of early peak to atrial peak (E/A ratio) flow velocity decrease with age
Arterial function
1. Increased arterial stiffness
2. Decreased endothelial function
3. Increased blood pressure
Molecular/cellular level
1. Increased catecholamine levels
2. Decrease in β-adrenoceptor-mediated responses
3. Preservation of β-adrenoceptor number/density but decreased sensitivity
4. Maintenance of peak amplitude of force generation
5. Increased duration of the myoplasmic calcium transient during excitation-contraction coupling (in rats)
6. Prolongation of the ventricular transmembrane action potential (in rats)
7. Cell dropout and compensatory cellular hypertrophy

conclusive evidence has been shown that alterations in afferent, central neural, efferent, and effector organ portions of the reflex arch are altered with aging. Reflexes arising from cardiopulmonary vagal afferents are blunted in aged individuals.

In summary, a multitude of changes occur in the aged heart (Table 6). It is important to clarify that all these changes in cardiovascular function do not imply failure of the system, and in the absence of overt cardiovascular disease, do not result in symptoms.

The Aging Immune System

The function of the immune system declines with age (Table 7). This leads to an increased frequency of infections, increased prevalence of neoplasms, and autoimmune disorders. Thymic involution is a hallmark of aging although there are thymic independent pathways for the development of the immune system. Response to vaccines is also decreased. The ability of hematopoetic stem cells to replicate decrease with aging (Geiger and Van Zant, 2002).

There is an age-dependent alteration to antigen presenting cells. Certain cytokines increase with aging such as: (1) interferon γ, (2) TGF-β, (3) TNF, (4) IL-6, and (5) IL-1, which can lead to dysregulation of hematopoiesis. Most tests of T-cell function is depressed in elderly individuals (Thoman and Weigle, 1989). They tend to secrete less IL-2 after being stimulated by antigen presenting cells. Several studies have suggested a positive association between good T-cell function *in vitro* and individual longevity (Roberts-Thomson *et al.*, 1974; Murasko *et al.*, 1988; Wayne *et al.*, 1990), and between absolute lymphocyte counts and longevity (Bender *et al.*, 1986). A high proportion of centenarians have relatively well preserved immune functions compared to the less elderly (Franceschi *et al.*, 1995).

Monocytes have also been shown to have decreased function with aging (Table 8, 9). Natural killer cells have been shown not to have altered function with aging (Kutza *et al.*, 1991).

Table 7 Changes in immune system function

Immune system
1. Decreased cell-mediated immunity
2. Lower affinity antibody production
3. Increased autoantibodies
4. Decreased delayed-type hypersensitivity
5. Decreased cell proliferative response to mitogens
6. Atrophy of thymus and loss of thymic hormones
7. Increased interleukin IL-6
8. Decreased IL-2 and IL-2 responsiveness
9. Decreased production of B cells by bone marrow
10. Accumulation of memory T cells (CD-45)
11. Impaired macrophage function
12. Facilitated production of anti-idiotype antibodies

Table 8 Changes in T cells with age

Decreased	Increased
Number of reactive T cells	Number of memory cells
Number of mitogen-responsive cells	T-cell help for nonspecific-antibody production
Proliferative response	
Expression of early activation genes	
Sensitivity to activating signals	
Cytotoxic cell target	
T-cell help for specific antibody production	
Help for generation of cytotoxic cells	

Table 9 B cell changes with aging

B cells
↓ surface MHC class II molecule expression
↓ proportion of cells capable of clonal expansion
↓ number of bone marrow precursors
↓ number of T cell-dependent antibody-forming cells
↓ potency
↓ antibody efficacy

MHC, major compatibility complex

In summary, a multitude of changes occur in the immune system that affects function and survival in the elderly.

The Aging Pulmonary System

The aging lung mimics closely changes in lung tissue that are associated with disease process such as emphysema. There is stiffening of the chest wall, loss of respiratory muscle strength, a decrease in intervertebral spaces and a decrease in elastic recoil of the lung tissue. These changes result in age-related declines in the lung volumes and flow rates affecting the forced expiratory volume (FEV1) and the forced vital capacity (FVC) (Johnson and Dempsey, 1991). The PaO_2 decreases progressively and linearly, falling from approximately 95 Torr at age 20 to about 75 torr at age 70 (Sorbini *et al.*, 1968). The alveolar dead space increases while the pulmonary diffusing capacity decreases progressively and linearly with age, falling approximately 20% over the course of adult life. The ventilatory responses to both hypoxia and hypercapnia have also been shown to decrease with age.

The ability to exercise, as indicated by the maximal oxygen uptake (Vo_2 max) also decreases linearly and progressively, falling about 35% between the ages of 20 and 70. The alveolar ducts also enlarge resulting in decreased surface area.

In summary, a multitude of changes occur in the lung with aging that affect the exercise potential of the aged (Table 10).

The Aging Nervous System

The nervous system is composed of a multitude of cells, and layers which control many aspects of function such as memory, speech, verbal, and visual function, as well as sensory and motor functions. There is great variation between individuals (Table 11).

Both normal senescent age-related changes and late onset diseases of the brain produce decline in performance. The number of contacts and the total surface area of the synapses decrease significantly and their average synaptic size increases at a different extent according to the brain area taken into account. Pre- and postsynaptic elements thicken with age, while vesicle size decreases (Table 12). There is failure of the chemical transmission process with aging (Agnati *et al.*, 1990).

The regulation of calcium influx is essential to presynaptic and postsynaptic events. Tannaka *et al.* (1996) showed that reduced calcium influx with aging might cause the reduced acetylcholine release by aged synapses. Brain aging is also associated with oxidative damage and low energy metabolism (Cotman and Su, 1990), and nitric oxide has cytotoxic action on neurons (Nomura, 1996). Adrenal glucocorticoids have been shown to accelerate age-related damage in the hippocampus, because of their ability to compromise energy metabolism and make neurons more vulnerable to glutamate excitoxicity (Maines *et al.*, 1998).

Autonomic dysfunction increases with aging. Age-associated changes have been reported in some, but not all regions of the autonomic nervous system. There is greater age-related changes in the sympathetic system than in the parasympathetic system.

Table 10 Changes with aging of the lung

Pulmonary system
1. Decreased FEV1 and FVC
2. Increased residual volume
3. Cough less effective
4. Ciliary action less effective
5. Ventilation–perfusion mismatching causes PaO_2 to decrease with age
6. Trachea and central airways increase in diameter
7. Decreased lung mass
8. Decreased respiratory muscle strength
9. Diffusion of carbon monoxide decreased
10. Maximal inspiratory and expiratory pressures decrease
11. Chest wall stiffens

Table 11 Changes in the aging nervous system

Central nervous system
1. Small decrease in brain mass
2. Decreased brain flow and impaired autoregulation of perfusion
3. Proliferation of astrocytes
4. Decreased density of dendritic connections
5. Increased numbers of scattered senile plaques and neurofibrillary tangles
6. Decreased myelin and total brain lipid
7. Altered neurotransmitters including dopamine and serotonin
8. Nonrandom loss of neurons to modest extent
9. Increased monoamine oxidase activity
10. Decrease in hippocampal glucocorticoids receptors
11. Slowed central processing and reaction time (Belli and Wilber, 2001)

Table 12 Age-related changes in the pre- and postsynaptic markers of the striatal dopamine synapse (Agnati *et al.*, 1990)

Presynaptic markers	
Tyrosine hyrdroxylase - IR	↓
TH-activity	↓
Dopamine	→ / ↓
DA turnover	→ / ↑
Cold stress-induced DA turnover increase	↓
Reserpine-induced DA turnover increase	↓
DA turnover increase induced by training in reaction time	↓
Postsynaptic markers	
D1 receptor levels	↓ / →
D2 receptor levels	↓
D1 receptor turnover	↓
D2 receptor turnover	↓
Adenylate cyclase activity	↓
cAMP-induced phosphorylation	↓
DA/cholecystokinin receptor interaction	↓
D2 denervation supersensitivity	↓

TH, tyrosine hyrdroxylase; DA, dopamine; IR, immunoreactive.

Table 13 Age-related changes in the Peripheral Nervous System

Peripheral nervous system
1. Loss of spinal motor neurons
2. Decreased vibratory sensation, especially in feet
3. Decreased thermal sensitivity
4. Decreased sensory nerve action potential amplitude
5. Decreased size of large myelinated fibers
6. Increased heterogeneity of axon myelin sheaths

In summary, the aging nervous system has many features that affect individuals in a wide variety of ways (Table 13).

The Aging Skeleton

Almost everyone loses bone with aging (Table 14). Women have acceleration of bone loss with onset of menopause. Men lose bone more slowly, and lose cortical bone only as they lose tissue in general, not preferentially, as is the case in women. Both men and women lose trabecular and cortical bone. Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue. This increases the susceptibility to fracture. Remodeling of both cortical and trabecular bone takes place through sequences of activation, resorption (by osteoclasts), and formation (by osteoblasts). A multitude of hormones regulate bone remodeling; (a) calcitriol, (b) parathyroid hormone (PTH), (c) sex steroids, (d) calcitonin, (e) Insulin-like growth factors (IGF-1, IGF-2). Vitamin D and PTH maintain serum calcium. Serum calcium levels do not change with age, but the way in which they are maintained changes dramatically.

With increasing age, serum calcium levels are increasingly maintained by resorption of calcium from bone rather than resorption from the diet. The decreased sensitivity of the parathyroids to calcium, decreased responsiveness of the kidney to PTH, and decreased responsiveness of the intestine to $1,25(OH)_2D$ all work together to increase serum PTH levels with age. Calcium supplementation is effective in lowering PTH levels and reducing bone loss in the elderly (Dawson-Hughes *et al.*, 1990)

The Aging Gastrointestinal Tract

The digestive tract maintains much of its normal physiological function during the aging process. There are a number of physiological changes that occur with aging that have the potential to influence drug deposition and metabolism, and may influence gastrointestinal (GI) function.

Table 14 Changes in calcium homeostasis with age

Parameter	Age-related change
Serum calcium	No change
Intestinal calcium absorption	↓
Serum parathyroid hormone	↑
Serum $1,25(OH)_2D$	↓ or no change
Resorption of calcium from bone	↑
Net calcium balance	↓

Table 15 Changes of aging in the GI tract

System	Change
General	Reduced total body mass Reduced basal metabolic rate Reduced proportion of body fat
Gastrointestinal	Increased gastric acid production Reduced gastric emptying rate Reduced gut motility Reduced gut blood flow Reduced absorption surface Decrease in gut-associated lymphoid tissue
Hepatic–biliary	Reduced liver mass Reduced liver blood flow Reduced albumin synthesis Impaired clearance of drugs that require phase I metabolism

Pharyngoesophageal function changes with age, but the clinical significance is unclear. In elderly individuals, a decrease in the number of myenteric ganglion cells per unit area along with a thickening of the smooth muscle layer has been described. In a study by Sonies (1992), age had no effect on peristaltic velocity, basal lower esophageal sphincter (LES) pressures, or frequency of "abnormal" double and triple peaked waveforms. Moore *et al.* (1983) and Horowitz *et al.* (1984) have both shown that gastric emptying is reduced in the elderly. Goldschmiedt *et al.* (1991) showed that gastric acid levels are increased with aging. The incidence of peptic ulcer disease is known to increase with age. Gastroduodenal mucosal prostaglandin levels have been shown to decline in aging (Cryer *et al.*, 1992). Changes in small bowel motor patterns are described with aging. This includes relatively minor effects on small bowel manometric patterns with decreased frequency of contractions after eating, reduction in the frequency of the migrating motor complex, and reduced frequency of propagated clustered contractions (Anuras and Sutherland, 1984). The physiologic and clinical consequences of these changes are uncertain. The absorption of nutrients by the intestinal tract depends on a multitude of factors. Highly lipid soluble compounds such as vitamin A show increased absorption whereas vitamin D is decreased. Fat absorption is decreased whereas cholesterol is increased. Carbohydrate absorption has been shown to decrease in rats. Numerous studies have assessed sigmoid functioning and colonic transit, and there is little evidence of any alteration in these measures in older adults (Orr and Chen, 2002).

In summary, physiologic changes of the GI tract are primarily preserved although changes do occur that have clinical consequences (Table 15).

The Aging Kidney

The aging kidney maintains its ability to regulate body fluid homeostasis under general conditions (Table 16). It becomes progressively limited in its ability to respond to stresses.

Table 16 Changes in the renal system with aging

Renal system
1. Decreased creatinine clearance and GFR 10 ml/decade (Hoolensberg *et al.*, 1974)
2. Decrease of 25% in renal mass
3. Decrease in sodium and potassium excretion and conservation
4. Decreased concentrating and diluting capacity
5. Decreased serum renin and aldosterone
6. Accentuated ADH release in response to dehydration
7. Decreased nitric oxide production
8. Increased dependence of renal prostaglandins to maintain perfusion
9. Decreased vitamin D activation
10. Impaired secretion of acid load

GFR, glomelular filtration rate; ADH, antidiuretic hormone.

Table 17 Morphologic changes in aged kidneys

Morphologic changes	Reduced size and weight Relative cortical atrophy
Vascular changes	Hyalinosis of arterial walls
Glomerular changes	Increased number of sclerosed glomeruli Hypertrophy of the remnant glomeruli Increased thickness of basal membrane Mesangial matrix expansion Irregular fusion of foot processes
Tubular changes	Reduction in the number of tubules Atrophy of the tubular epithelium Increased thickness of basal membrane
Interstitial changes	Interstitial fibrosis

These changes result from anatomic changes as well as from alterations in tubular cell function and responsiveness to hormonal and hemodynamic factors.

The loss of renal mass is mainly due to progressive atrophy of the renal cortex, with relative sparing of the medulla. By age 80, between 10 and 30% of the glomeruli are completely sclerosed. The glomeruli of the outer cortex are affected the most (Table 17).

There are also functional changes in aged kidneys. Renal blood flow decreases about 10% per decade after a peak in young adulthood, and the renal plasma flow is reduced by 50%.

The cause of age-related changes in the kidney remain unknown (Viig and Wie, 1995). One hypothesis, the hyperfiltration theory due to reduced nephron mass, proposes that a kidney with reduced number of glomeruli, has increased capillary blood flow through each Glomerular bed and a corresponding high intracapillary pressure (Neuringer, 1993). This high pressure results in local endothelial damage, platelet aggregation, and thrombin production. This leads to the release of growth factors from platelets such as (1) platelet-derived growth factor, (2) epidermal growth factor, (3) fibroblast growth factor, and (4) tumor necrosis factor α (Neuringer, 1993; Hostetter *et al.*, 1981; Brenner, 1985). These factors increase fibroblast collagen production and mesangial cell sclerosis (Wardle, 1992). Angiotensin II secretion is then increased due to the disruption of vascular hemodynamics. As glomeruli become sclerosed, the amount of blood flow to each remaining nephron increases, further potentiating the damage. The other hypothesis describes an imbalance between synthesis and degradation of matrix proteins leading to glomerulosclerosis. There is limited data for this hypothesis.

In summary, a multitude of functional and morphologic changes occur in the aged that affect homeostasis (Table 18).

The Aging of the Endocrine System

Aging is associated with hormonal changes. Aging is associated with anatomic changes of the endocrine glands as a result of programmed cell death, autoimmune destruction of the gland, or neoplastic transformation of glandular tissue. Age-related changes could also occur in hormonal secretion secondary to physiologic changes due to circadian and seasonal rhythm, or in frequency or height of hormonal pulses. Other changes with aging include (1) altered bioactivity of hormones, (2) altered transport of hormones to binding receptor sites, (3) altered hormone–receptor interactions, or (4) postreceptor changes. Aging is associated with alterations in plasma membrane properties and intrinsic changes in cellular enzyme activity, and changes in calcium mobilization and gene expression. Aging is associated with important structural changes (Table 19).

Changes in hormone secretion are noted with aging. They are related to altered endocrine cell physiology than cellular

Table 18 Functional changes in aged kidneys

Renal blood flow	Decreased Relative increase of medullary blood flow
Glomerulus	Decreased glomelular filtration rate Increased filtration fraction Increased permeability to macromolecules
Tubule	Impaired ability for sodium and potassium handling Deranged tubular transport Impaired concentration and dilution Impaired acidification
Other	Decreased synthesis of rennin Decreased 1-α-hydroxylase activity

Table 19 Anatomic changes of endocrine glands with aging

Endocrine gland	Structural changes
Pituitary	Increased occurrence of adenomas and empty sellae, proportional decrease in eosinophil cells, increased nonparenchymal cells
Thyroid	Lymphocytic and plasma cell infiltration, fibrosis, and increased nodularity
Parathyroid	Increase in oxyphil cells, large oxyphil nodules
Adrenal glands	Fibrotic changes in cortex, accumulation of lipofuscin, mitochondrial fragmentation, increased adenomas and vascular hemorrhage, cellular depletion of zona reticularis
Testis	Germ cell arrest, thinning of germinal epithelium
Ovary	Depletion of oocytes, papilomatous outgrowths, sclerosis of medulla
Pancreas	Loss of compact structure of islet cells, amyloid deposition

Table 20 Age-related changes in the degradation of hormones

Increased	Decreased	Probably no change
Epinephrine	Aldosterone	FSH, LH
PTH	Testosterone	GnRH in rats
Cortisol	Dihydrotestosterone	ACTH
	Estradiol	AVP
	Noradrenaline	Glucagon
	Insulin	Calcitriol
	GH	T4, T3
		TSH

FSH, follicle stimulating hormone; LH, luteinizing hormone; PTH, parathyroid hormone; GnRH, gonadotropin-releasing hormone; ACTH, adenocorticotropic hormone; AVP, arginine vasopressin; GH, growth hormone; TSH, thyroid stimulating hormone.

depletion. Age-related changes in the pituitary gland are attributed to altered pulsatile pattern of hormone secretion. Desynchronization of various biological rhythms occurs with aging. Glandular sensitivity to secretagogs are also affected with some glands having reduced, increased, inhibited, or no alteration in response. Finally, clearance of hormones is also altered with aging.

In summary, a multitude of changes occur in the aged endocrine glands affecting homeostasis greatly (Table 20).

Aging of Other Systems

A multitude of changes occur in other systems of the body (Table 21). The dysregulation of these systems affect homeostasis in a multitude of ways.

In summary, the aged body, complex yet intricate, adaptive yet reactive, has shown a resolute progression and preservation of function. Although many changes occur leading to decreased reserves, the successful aging process that some seniors possess proves the will of humanity to strive for longevity.

Table 21 Changes of organ systems with aging

System	Change
Hematopoeisis	Decreased bone marrow reserves in response to high demand
Temperature	Impaired shivering
Regulation	Decreased cutaneous vasoconstriction and vasodilatation
	Increased core temperature to start sweating
Smell	Detection decreased by 50%
Thirst	Decreased thirst drive
Balance	Reduced number of organ of Corti hair cells
	Increased threshold vestibular responses
Audition	Bilateral loss of high-frequency tones
	Central processing deficit
Adipose	Decrease in expression and activity of lipoprotein lipase
	Decreased leptin levels in females and increased in males
Genitourinary	Incomplete bladder emptying and increased residuals
	Reduced intensity for orgasm for men and women
	Prolonged refractory period for erections for men

KEY POINTS

- A multitude of theories have been proposed to explain how the body ages.
- Cytokines play a major role in the aging process.
- Modulation of cytokines can slow the aging process.
- The aging of certain organ systems compound the aging affects of other organs.
- The rate of decline among organs varies greatly.

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5

Aging of the Brain

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In a single review, it is obviously impossible to comprehensively address the neurobiology of aging. One book on the subject (Hof and Mobbs, 2001) is almost 1000 pages long but is still not comprehensive. Numerous reviews examining various specific aspects of brain aging have also been published (Grady and Craik, 2000; Toescu *et al.*, 2000; Barnes, 2001; Brandt, 2001; Farkas and Luiten, 2001; Mattson *et al.*, 2001; Finch, 2003). Therefore, the present review focuses on two major functions, motor systems and cognitive systems, that are most susceptible to age-related pathologies.

MOTOR SYSTEMS

Motor functions are among the most vulnerable to age-related disease. These impairments in humans may be associated with the development of several age-related diseases of motor systems (including Huntington's disease and Parkinson's disease) superimposed on universal but gradual impairments in neuromuscular functions, especially due largely to decrease in muscle mass. The incidence of each disease peaks at a characteristic age (for Huntington's disease around age 40, for Parkinson's disease around age 70), then begins to decline, but the relative contribution of the universal age-related declines in neuromuscular function continues to increase with age. As the incidence of disease increases, the contribution of disease to individual variation in motor function also increases, and to the extent that risk of disease is primarily genetic, genotype contributes substantially to phenotype during this time. However, as the incidence of motor diseases decreases (after about age 70) there is also a decline in the relative contribution of motor disease genes to age-related impairments in motor function.

Huntington's Disease

Huntingtons' disease is an autosomal dominant neurodegenerative disease associated with profound movement disorders whose age-specific incidence peaks around the age of 40 (Greenamyre and Shoulson, 1994). Monozygotic twins are essentially 100% concordant in the development of Huntington's disease, demonstrating the primary contribution of genotype to the risk of developing Huntington's disease (Sudarsky *et al.*, 1983). Huntington's disease is caused by a variable expansion of a CAG repeat producing a polyglutamine stretch in the gene product, huntingtin (Lunkes *et al.*, 1998). Using this genetic marker, Kremer *et al.*, (1994) demonstrated that by late middle age the concordance between genotype and Huntington's phenotype is essentially 100%.

Nevertheless, at relatively young ages (under 20), there is little concordance between genotype and Huntington's phenotype, since at these young ages only about 10% of individuals who express CAG repeats in the huntingtin gene exhibit Huntington's phenotype. Therefore, with respect to incidence, Huntington's disease represents an extreme coupling between genotype and age-related phenotype, in which the coupling increases from very low (below the age of 20, where a great majority of individuals bearing the CAG repeat do not exhibit the Huntington phenotype) to essentially 100% concordance by age 70 (at which age almost every individual who bears the CAG repeat would have developed the disease). By the same token, however, the relative contribution of the CAG repeat to phenotypic variation in the whole population increases with age as the incidence of the disease peaks at about 40 years of age, but then begins to decline as the incidence of Huntington's disease decreases.

Parkinson's Disease

Parkinson's disease is about 10-fold more prevalent than Huntington's disease, and the incidence rate of Parkinson's disease peaks later than that of Huntington's disease, at about 75 years of age, after which incidence rate begins

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to decline (Martilla, 1987). In contrast to the perfect concordance for Huntington's disease in identical twins, several studies have failed to observe any concordance for Parkinson's disease in identical twins (Lilienfeld, 1994). This observation demonstrates a much lower overall contribution of genotype to Parkinson's phenotype than for Huntington's phenotype. On the other hand, several families have been studied where Parkinson's disease follows an autosomal dominant pattern of inheritance (Golbe *et al.*, 1996), and in several different families this led to the identification of an allele of α-synuclein as the genetic basis of the disease in these families. (Polymeropoulos *et al.*, 1997). In another group of families where Parkinson's disease is inherited in an autosomal recessive pattern, mutations in the gene coding for parkin account for the appearance of the Parkinson's phenotype (Hattori *et al.*, 1998; Kitada *et al.*, 1998). Nevertheless, mutations in α-synuclein and parkin only account for a small subset of all cases of familial Parkinson's disease (Vaughan *et al.*, 1998), and thus, of an even smaller subset of all cases of Parkinson's disease.

These observations demonstrate that the coupling of genotype to phenotype is much lower, and the genetic basis much more complex in Parkinson's disease, than in Huntington's disease. On the other hand, Parkinson's disease is not only much more common than Huntington's disease, it is a much more heterogeneous syndrome, and thus plausibly involves a more heterogeneous set of pathophysiological processes. Thus, for those forms of Parkinson's disease for which a single gene defect has been defined, the coupling between genotype and phenotype behaves as it does in Huntington's. Thus, within kindreds in whom α-synuclein mutations are common, at young ages, there is no concordance between mutations in α-synuclein and Parkinson's phenotype, whereas by age 70, there is a very high concordance between genotype and phenotype. On the other hand, in the population as a whole, this relationship is less evident since α-synuclein mutations only account for a small proportion of all cases of Parkinson's disease, in contrast to Huntington's disease, where all cases are accounted for by mutations in a single gene.

It should be noted that the incidence rate of familial forms of Parkinson's disease peaks earlier than nonfamilial forms than in sporadic or nonfamilial forms. Thus, mutations in parkin lead to juvenile-onset Parkinson's disease, whose incidence peaks at around 20 years of age and the incidence of Parkinson's disease due to mutations in α-synuclein peaks at around 50 years of age. In contrast, the incidence rate of Parkinson's disease in the population as a whole peaks around 70 years. Since twin studies indicated that genotype makes little contribution to the late-onset (and most common) form of the disease, taken together, these data imply that the contribution of genotype to Parkinson's phenotype increases with age until about age 50, then begins to decline, such that, by age 70 and over, there is little contribution of genotype to phenotype (Langston, 1998).

Nonpathological Age-related Changes in Motor Function

For age-related diseases, the effect of genotype generally increases with age until about age 70 (in humans), then begins to decline as the incidence of age-related diseases declines. However, as the incidence of disease decreases in later life, relative contribution of disease to the variance in age-related phenotype also begins to decline. Thus, a major question is the extent to which genotype accounts for nondisease phenotype during aging. While it might be assumed that the effect of life-long environmental effects would increasingly dominate genetic effects, there is little evidence to support this as a general phenomenon. For example, twin studies have indicated that although psychomotor speed declines with age, the effect of genotype and possibly early environment continues to dominate this phenotype during aging (at least until age 67), whereas in contrast, effects of exercise were minimal (Simonen *et al.*, 1998).

COGNITIVE FUNCTION

Although genetic effects on motor diseases increase with age before they decrease, it might be hypothesized that cognitive functions are more likely to reflect cumulative experience during aging, and thus the contribution of genotype might be less for cognitive functions. However, as described below, effects of genotype are probably at least as great on cognitive functions during aging as for motor functions.

Alzheimer's Disease

Twin studies have demonstrated a much greater significant genetic contribution to the risk of developing Alzheimer's disease than for Parkinson's disease, with most studies indicating that about 50% of the variance in vulnerability to Alzheimer's disease is genetic (Pedersen *et al.*, 2004). Conclusions from twin studies have been corroborated by family studies. For example, offspring whose parents had both been diagnosed with Alzheimer's disease had a 47% chance of developing Alzheimer's disease by age 65, far higher than the risk of the general population at that age (Bird *et al.*, 1993). Similarly, analysis of 70 families with evidence of the hereditary forms of Alzheimer's disease indicated that offspring whose parents had Alzheimer's disease had a lifetime risk of developing the disease (by age 87) of 64% (compared to a risk of less than 10% in the general population by that age). Interestingly, the risk for offspring in families with early-onset Alzheimer's disease was only 53%, compared to 86% for offspring in families with late-onset Alzheimer's disease (Farrer *et al.*, 1990). Thus, at least within these families, there is evidence of increased penetrance of genotype during aging. On the other hand, the incidence rate of Alzheimer's disease appears to decrease

after age 90 (Lautenschlager *et al.*, 1996). Because of the relatively small number of individuals alive at these very advanced ages, it is not yet known if the effect of genotype on the risk of Alzheimer's disease may decline after age 90.

Allelic variations in several specific genes (presenilin 1, presenilin 2, β-amyloid precursor, and Apolipoprotein E (ApoE)) have been implicated in the etiology of Alzheimer's disease (Cruts and Van Broeckhoven, 1998). How aging influences the penetrance of these genes is of great interest. Campion *et al.*, (1999) addressed this question in a study which examined the genetic basis of early-onset autosomal dominant Alzheimer's disease in the whole population of a single city in France. In this study, early-onset autosomal dominant Alzheimer's disease was defined by the occurrence of Alzheimer's disease before the age of 61 in three generations of a family. Thirty-four such families were observed in the city examined, with a population of almost 5 00 000. In 56% of such families, allelic variations in presenilin 1 were observed, and in 15% of such families, allelic variations of the β-amyloid precursor were observed. In contrast, in nine families which did not exhibit an early-onset form of the Alzheimer's disease, such allelic variations were not observed. These data suggest that the penetrance of presenilin 1 and β-amyloid precursor mutations reaches 100% at relatively young ages (around age 60). However, since the incidence of Alzheimer's disease before the age of 60 is less than 5% of the incidence at age 80–90, this demonstrates that the coupling between presenilin 1 (or β-amyloid precursor) and Alzheimer's disease phenotype peaks at around age 60, then returns to being negligible by age 80. In contrast to the (eventual) complete penetrance of the presenilin and β-amyloid alleles, alleles of the ApoE gene are never completely penetrant, but nevertheless account for a much larger proportion (possibly 20%) of cases of Alzheimer's disease (Slooter *et al.*, 1998). Nevertheless, the effect of ApoE genotype peaks at around age 70, then declines (but is significant even at 90 years of age) (Farrer *et al.*, 1997; Slooter *et al.*, 1998). Thus, taken together, the evidence indicates that the coupling between genotype and Alzheimer's disease phenotype peaks at about 70 years of age, then, as with other age-related diseases, the role of genotype begins to decline.

Nonpathological Age-related Impairments in Cognitive Functions

Several studies have examined the effects of aging and genotype on performance in standardized intelligence tests (Swan *et al.*, 1992; Plomin *et al.*, 1994; Finkel *et al.*, 1995; McClearn *et al.*, 1997; Emery *et al.*, 1998; Finkel *et al.*, 1998). For example, Plomin *et al.*, (1994), as part of the Swedish Adoption/Twin Study of Aging examined cognitive functions in 112 pairs of twins (both monozygotic and dizygotic) reared apart and in 111 matched pairs of twins reared together. The age of the twins was 64.1 ± 7.5 (mean $\pm$ SD) years. At this age, the average heritability of general cognitive function (a composite of spatial, verbal, memory, and speed of processing performances, after removal of effects of age and gender) was 80%. In a review of studies from both the Swedish Adoption/Twin Study of Aging and the Minnesota Twin Study of Adult Development and Aging, Finkel *et al.*, (1995) concluded that both sets of studies suggested that heritability of general cognitive function is about 80% throughout adulthood (though this estimate is higher than has been observed in other studies), but evidence suggested a possible decrease in heritability after age 70. A further analysis of the Swedish Twin study appeared to corroborate this result, since in Swedish twins over the age of 80, heritability of general cognitive function was estimated to be about 62% (McClearn *et al.*, 1997). Although direct comparisons are not conclusive, other studies have suggested that heritability of general cognitive function increases from about 50% in childhood and adolescence to about 80% in adulthood (McCartney *et al.*, 1990; MaGue *et al.*, 1993). Although aging influences the heritability of general cognitive function, the effect of age on cognitive function itself is more specific to certain subsystems. In general, functions reflecting knowledge improve with age, whereas functions reflecting speed of processing and memory are impaired with age. Thus, aspects of cognition reflected by the Wechsler subscales of Information, Vocabulary, and Comprehension are relatively unimpaired or even improve with age in nondemented individuals, whereas cognitive functions reflected by the subscales of Block Design, Picture Arrangement, and Digit Symbol, tend to deteriorate robustly with age (Botwinick, 1978). Interestingly, the heritability of general cognitive function during aging is greater than the heritability of any of the functions reflected by subscales, which has been interpreted to indicate that the "nature of the genetic influence in the cognitive domain appears to be more general than specific" (Plomin *et al.*, 1994). Thus, in contrast to the effect of age on the heritability of general cognitive function, heritability on memory function alone appears to be stable with age (Finkel and McGue, 1998).

Since cognitive function is defined by experience, it may seem surprising that heritability of cognitive function can increase with age at all (although decreasing after the age of 70). One resolution of this apparent paradox is that the influence of experience may greatly depend on genotype; that is, the effect of experience may be enhanced by genotype. For example, in a twin study examining the effect of genotype on the acquisition of a motor skill, Fox *et al.*, (1996) reported that while genotype influenced the initial performance of the skill, the effect of genotype on the enhancement of the skill by practice was even greater. These investigators concluded that "the effect of practice is to decrease the effect of environmental variation (previous learning) and increase the relative strength of genetic influences on motor performance". Similarly, it seems plausible that genotype may influence the cumulative effect of experience on general cognitive functions. On the other hand, after the age of 70, it appears that these genetic effects have reached their peak, and the effects of unique experiences come to dominate.

KEY POINTS

- Pathological and nonpathological age-related impairments are quantitatively and qualitatively distinct: pathological impairments involve substantial neuronal loss, whereas, nonpathological impairments do not involve such loss.
- Pathological impairments in motor functions include Parkinson's disease and Huntington's disease, the former entailing very little genetic effects while the latter is almost entirely genetic.
- Nonpathological impairments in motor functions include loss of muscle mass.
- About half the vulnerability to Alzheimer's disease is due to genetic effects.
- The importance of heredity in determining age-related impairments increases with age until about age 70, after which environmental influences become increasingly important.

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6

Psychological Aspects of Aging

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INTRODUCTION

This chapter will address how adults psychologically adapt as they age. Psychological theories of adult development have been extensively written about in the scientific literature. Several approaches addressing life stage perspective will be presented as it relates to mental vitality in late life.

Psychology is the study of behavior and the facts and factors that influence behavior. Psychology of aging studies behavior that is organized or disorganized as the adult ages, that is, how the adult adapts or does not adapt to life stresses. These behaviors may be constant throughout life as the person experiences tasks and challenges.

Generally, psychology is viewed as a broad field encompassing personality development, intelligence, memory, motivation, neuropsychological changes, creativity, and sensory and motor functioning. Important for the aging person are information processing, cognition, life satisfaction, and personal control. As with all fields, psychology of aging interrelates with the biological and social aspects of aging. Psychological processes are constantly intertwined with biological, social, and environmental factors. Understanding the psychology of aging helps the practitioner assess the person's ability to adapt to change, understand, and cope with aging, illness, and loss. Furthermore, understanding the older adult's previous or lack of coping and adaptive skills, the practitioner may be able to predict and understand potential problems.

Successful psychological aging is dependent upon mental vitality. Mental vitality can be described as psychological or intellectual energy. That is, given life's choices, how does the aging adult face the challenge? What is the individual's mental vigor to cope with changing biopsychosocial changes? What has been their history of adapting and coping throughout life? Studies have found that ill health is related to problems with cognition, learning, and motivation, thus challenging the elder's ability to cope (Havighurst, 1968; Botwinick, 1977). As Kermis (l986) so aptly put, aging is the greatest challenge.

Mental vitality encompasses present life-style choices, as well as one's history of choices. These choices include reducing stress, establishing rest and relaxation, challenging the mind, cultivating satisfying relationships and activities, and avoiding known risk factors such as smoking, poor nutrition, weight problems, and excessive alcohol consumption. Equally important are the attitudes and beliefs that the older adult has about aging that reflect how successfully one ages. A mentally vigorous older adult with a positive attitude will be able to better cope with life's challenges and make informed choices. While cognitive deficits have been extensively written about, it is the positive changes and adaptive abilities that may be more important in daily living skills.

LIFE STAGE PERSPECTIVE

In this chapter, the focus will be on the emphasis of mental vitality as a life stage approach. This developmental-stage theory emphasizes integration of life experiences. The developmental theorists attempt to describe human development as a sequence of stages or steps. Developmental-stage models hold that changes in the adult personality are results of interaction of the social and biological environment. How the individual interacts with others and integrates that interaction into his/her personality is determined by the developmental tasks that the person performs. These tasks are markers of the individual's movement through the life cycle. Each task combines some aspects of the person's biological, psychological, and social functioning. Developmental tasks combine the drive toward growth of the person with the demands, constraints, and opportunities of the social environment. These tasks occur for all people in approximately the same sequence, which may overlap each other without a particular onset or termination. Failure and delay in resolving these tasks may affect how successful one will be in resolving future tasks, adjustment, and overall mental health. All of these tasks act to move the individual toward optimal psychological function and personal integrity if they are

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successfully accomplished. Erikson (1963), the most familiar of the developmental-stage theorists, applied his approach to the aged. In his eight stages of development, the person has a conflict with two possible outcomes, adaptive or maladaptive solutions. If an early stage is resolved with a low degree of adaptation, resolving later stages will be more difficult. Erikson's last two stages directly apply to adults and aging adults. These two stages are broad and cover many years, resulting in other theorists defining more definitive age-specific conflicts.

Havighurst and Peck postulated theories that have particular significance for the elderly. Both authors elaborate on Erikson's psychosocial tasks with consideration of tasks of the older adult (Havighurst, 1968; 1972; Peck, l968; Erikson, l963). Havighurst (1968) describes the six tasks of old age as follows:

1. adjusting to declining physical strength and health;
2. adjusting to retirement and its reduced income;
3. adjusting to changes in the health of one's spouse or partner;
4. establishing an explicit affiliation with one's age group;
5. adopting and adapting social roles in a flexible way;
6. establishing satisfactory physical living arrangements.

Aging adults experience a variety of physical, social, and psychological losses. These losses can affect mobility both physically and socially, resulting in increasing isolation. There is a chance that the environment will continue to diminish unless the individual takes action. Havighurst's (1968) focus is on reorganizing functions and expectations. For example, older adults who do not accept their changing physical and health limitations and adapt may become maladjusted. Partner roles may change if one partner becomes ill. The partner who nurtured may need nurturing care; the healthy partner may have to assume new roles of banker, handyman, and decision maker. Old age is a time of almost constant change. Older adults who do not adapt or adjust flexibly may find themselves increasingly stressed and maladjusted. According to Havighurst (1968), the continued refining roles and expectations to meet environmental demands accomplish the maintenance of identity.

Peck's (1968) tasks are summarized into three areas of conflict. The first is ego differentiation versus work-role preoccupation, and finding a way to identify and appreciate self without the job or one's career as the marker of success. This includes satisfaction with retirement and children leaving home. The task is to find new ways, activities, and passions to define one's self. The second is body transcendence versus body preoccupation, which is understanding the changes in the body and illnesses without being preoccupied with symptoms or illness concerns. The question is, can one live successfully despite age-related changes and disease states? Many older adults cope with illness and live successful lives despite pain or infirmity. Others are preoccupied with their illness, by constantly talking about their symptoms, medication requests, and frequent doctor appointments or "shopping". Lastly, the third area of conflict is ego transcendence versus ego preoccupation. This process is the coming to terms with the reality of death, putting closure on the past, ensuring the welfare of children and others, and leaving a legacy. There is a need to share one's wisdom, knowledge, and experience. Conversely, if maladaptive, there is a tendency to treat the world as if it will end with their death. This person may not make wills or plans for the future, or for anything that would go on after their death (Peck, 1968).

In summary, the personality is constantly changing in response to the individual's adaptation throughout life. Life challenges can occur at any time in the life cycle, but older people are more likely to have to confront more challenges simultaneously. Losses, physical and functional changes, and cultural expectations stress older adults when their psychological reserves are low and their social supports are diminishing (Kermis, 1986).

WHAT DO WE KNOW?

Aging is not uniform or static. There is differentiation among the aging commonly divided into four groupings of the young-old (60–70 years of age), the old (71–74 years of age), the old-old (75–84 years of age), and the frail-old (85 years of age and over) (Neugarten, 1977; Neugarten, 1979; Riley and Suzman, 1985). Each grouping has different tasks, abilities, and issues. For example, the 60–70-year-old groups may still be employed and more active. They may be dealing with retirement, considering housing options, developing leisure activities, and relationship issues. The 71–74-year-old group may be adjusting to retirement, loss or changes in work-role identity, income changes, friends moving or ill, widowhood, and readjusting time management. Neugarten (1974, 1979) noted that chronic illness and role losses were more characteristic of those over the age of 75. She, further, contended that the 55–74-year olds are more like the middle-aged with fairly good health and as active as they wish.

Riley and Suzman (1985) further divided the old-old into the old-old and the frail-old. The old-old group may have more medical conditions, more medications on board, and may require more support services either by family or agencies or both. There are more losses, more issues with dependency and those related to assisted living situations. For couples, one partner may need more care and placement, resulting in the couple being separated.

As a group, the frail elderly is growing the fastest, with estimates of over 3 million in the United States (Aging Demographics, NIA, 2004). Worldwide, the World Health Organization (WHO) estimates 4 million elders over the age of 85 (Aging Demographics, AAHSA, 2004). This group is primarily female, widowed, and more likely to face declining functional ability without a spousal caregiver. The old-old and particularly the frail-old group experience more physiological changes, more comorbid medical conditions, more

frailties, higher rates of dementia, and loss of connectedness. Connectedness is the desire to feel connected to others, their homes, and community. This sense of connectedness is threatened when there are limitations in functioning, necessitating moves to a more secure and assisted living environment, removing the elder form the security of their neighborhood, their home (Kropf, 1992).

Overall, the frail elder is more likely to be in a supported living setting with more health problems, is more dependent upon others to meet their daily needs, and generally takes longer to recover from acute illnesses (Blazer, 1980; Beckett and Schneider, 1992). Many of this population, primarily women, may outlive their financial and health care resources (Beckett and Schneider, 1992; Mercer and Garner, 1989).

With each group, there may be a wide range of health or illness states varying from healthy, chronic but stable, acute, and acute superimposed with chronic illnesses. Rather than relying totally on age categories alone, it is also important to address health status, adaptive abilities, and social characteristics.

AGE-RELATED PSYCHOLOGICAL CHANGES

Intelligence

Intelligence is composed of crystallized and fluid intelligence. Crystallized intelligence is the ability to apply past learning to new situations. Crystallized intelligence increases with age, experience and knowledge. Examples of crystallized intelligence are problem-solving activities, mechanical skills, word meanings, and understanding social relationships. Fluid intelligence is the ability to improve organization of information and to generate new hypotheses. Fluid intelligence decreases with age. Fluid intelligence consists of reasoning and abstraction, relationships between objects, acquiring new ideas, and adapting to change.

IQ increases until the 20s, then levels off and generally remains stable throughout the life cycle. With aging, there is decreased speed on timed tests. Poor health represents an adverse factor in the older adult's performance. If given more time, the older adult is as accurate as a younger adult is. In general, older adults perform better on everyday practical tasks over laboratory-based tests. Performance on Wechler Adult Intelligence Scale (WAIS) demonstrates that older adults have an increase in verbal skills, while there is a decrease in tests of performance. Results show that intelligence is stable until the 70 s, when there is a decrease in performance countered by an increase in verbal skills (Botwinick, 1977). These verbal skills reflect the knowledge and skills acquired over a lifetime.

Aging does influence intellectual functioning. Changes in motor skills and slower decision-making time affect reaction time. Performance is also affected by changes in cerebral cortex functioning and cardiovascular deterioration. When decision making, older adults have been found to sacrifice speed for accuracy and to reject quick, simplistic solutions to problems, preferring to work slowly and to examine issues from a variety of perspectives before responding. Older persons are more likely to make errors of omission rather than errors of commission, which suggests cautiousness, deliberateness, and anxiety (Poon, 1985). As a compensatory strategy and to avoid embarrassment, many older persons avoid unfamiliar activities and places. This cautiousness may be mistaken for resistance or obstreperousness.

A word of caution is advised to many older adults who do not have the advantage of many years of formal education as compared to younger persons and have been many years away from the classroom environment (Botwinick, 1977). Deliberateness, slower response time, and time away from traditional school activities impact tests of intellectual abilities.

Clinicians need to clearly evaluate the impact of physical infirmities, compensatory skills, and the older adult's social environment before coming to any conclusions regarding intellectual decline. The impact of the living situation, lack of stimulation, and isolation may constrain intellectual functioning and should not be ignored (Botwinick, 1977). If healthy and fit, the older adult's response time is no different from that of less healthy younger people.

MEMORY

The capacity to learn continues throughout life. Optimal learning involves reading or following instructions on how to organize information, finding tasks meaningful and rewarding, and being able to link visual memory with auditory information. There are three phases of information processing – encoding, storage, and retrieval. With aging, more time and effort is required to encode information. Sensory changes can reduce memory efficiency. Because sensory memory lasts less than a second and with aging sensory changes, the older adult is less able to encode as well. Short-term memory lasts a few seconds and declines with age.

Recall involves search and retrieval of information from storage. Recognition requires matching information in storage with information obtained in the environment. Recognition abilities remain stable over time (Poon, 1985). All ages do well in recognition tasks, but recall diminishes over time. It is easier for older adults to do tasks of recognition than recall information.

Long-term memory includes storage of information, a fact learned earlier in life, and day-to-day experiences, and is relatively permanent. Long-term memory increases from age 20 to 50 and then is constant into the 70s. Older adults require more time to encode new information. This encoding process is affected not only by sensory losses but also by changes in the environment, such as moves and deaths. These events contribute to memory deficits.

Many older adults adapt fairly well, and deficits may not be evident until a traumatic event occurs or is uncovered by a skilled clinician. Using compensatory strategies to augment

memory, such as use of calendars and notes and taking time and practicing new material, is indicated. Structure and familiarity also help in improving memory and retention. With slowed recall and physical decline, there is a slower response, which can be misconstrued as more significant memory deficits or resistance.

In summary, older adults do retain well-practiced and adaptive skills. Less-practiced tasks and recall requiring a timed response declines.

SENSORY

The nervous system is important in receiving, processing, and storing information. The senses provide contact to the environment. Changes or decline in senses affects one's participation in their environment and their quality of life. Losses or changes in vision, hearing, taste, smell, and touch influence the individual's functioning, activities, stimuli response, and perceptions. Sensory losses can produce alterations in behavior, independence, confidence, and self-esteem. On the other hand, assumptions are made that sensory-impaired elders are senile, stubborn, or manipulative. Careful assessment of sensory loss is indicated before assumptions can be made concerning self-care and adaptive capabilities. Glasses and hearing aides help compensate for sensory losses and allow more independence.

CREATIVITY

Even though creativity is generally not considered a component of psychological functioning, it is an area that is a part of mental vitality and quality of life. There have been many debates that creativity is limited to a few and it declines with age (Adams-Price, 1998). Research shows that creative thinking is a universal ability that helps adults manage satisfying lives. Creativity is a complex of traits, skills, and capacities, including the ability to work independently, curiosity, unconventional thinking, openness to experience, and tolerance of ambiguity (Adams-Price, 1998; Generations, 1991). Cognitive psychologists define creativity as a mental process like imagination and intuition. The newer definition is particularly apropos to the older adult. It is the integration of cognitive processes, knowledge, thinking style, personality, motivation, and environment over a lifetime. Creativity is a way to address and resolve dissatisfactions, improve quality of life, and can be a response to limits and an uncertain future (Generations, 1991; Adams-Price, 1998). Older adults do appear to experience a decrease in divergent thinking, the ability to generate novel ideas, but this is a qualitative change in the creative process. In contrast, there is an increase in crystallized intelligence and integrative or convergent thinking (Sasser-Coen, 1993). Later life may afford more time for reflection, life review, and creative pursuits aimed at the development of one's life story and the filling in of gaps and discontinuities. This creative process, which is similar to Butler's (1963) *Life Review*, is a positive therapeutic process. Adams-Price (1998) concludes that late-life creativity reflects aspects of late-life thinking: synthesis, reflection, and wisdom.

IMPLICATIONS FOR PRACTICE

Aging is an adaptive challenge. Mental vitality is the vigor needed to meet this task. As clinicians, continual evaluation of the older person's understanding of the implication of age-related changes and losses is required. Identifying coping skills and adaptive strategies is paramount as well to an effective relationship and treatment planning. To incorporate the aforementioned psychological changes into practice, recommendations are outlined.

1. Face-to-face education should occur, presenting the information in small increments and supplemented with one-page practical handouts to carry home.
2. Helpful teaching techniques include teaching time, with practice and episodic spot checks to reinforce or to correct, and phone number and contact person to call if they have questions or concerns.
3. Allow time to complete forms in a setting conducive to writing.
4. Printed materials need to be in larger boldface type and simplified to adjust for sensory changes. The guidelines of the Americans with Disabilities Act recommend that print be at least 18-point font. Signs should be in large print or symbols with contrasting background of eggshell, matte, or nonglare paper for easier reading and to clarify directions (ADA, 1990).
5. Observe accessibility and visibility issues in the physical environment. Are the directions and locations easy to follow? Lighting should be 100 to 300 lux to ensure adequate vision and easy reading (ADA, 1990).
6. Encourage the older person to take notes or write their concerns before their appointment.
7. If necessary or beneficial, suggest that the older person bring someone to assist or take notes.
8. Encourage the older adult's participation in the treatment planning.
9. Allow the older person the opportunity to present concerns, fears, or objections to the plan.
10. Allow time to process information and study their options.
11. Ask how they are coping and what coping strategies they use. For example, "How do you handle this?" "You have a lot to deal with," "How are you holding up?" or "What helps you?"
12. Encourage innovative or creative solutions. Ask how they would solve.
13. Referral to support group, if exists, for their medical condition.

14. Referral to geriatric/gerontology professional for counseling and environmental options.

CONCLUSION

Not all cognitive changes are negative. The positive cognitive changes include greater experience-based knowledge, increased accuracy, better judgment concerning their abilities, and generally an improved ability to handle familiar tasks as compared to their younger counterparts.

Aging presents psychological and cognitive challenges requiring mental vitality to adapt. An older person who ages "successfully" has been able to use their accumulated knowledge and wisdom to accomplish most day-to-day living activities well. Rigidity and exaggerated and maladaptive behaviors may represent psychological and neurological problems and are not normal aging, and a referral to a specialist is warranted. As with any treatment planning, the older adult's problems may be obvious but treatment interventions are based upon what the person can do.

KEY POINTS

- Mental vitality or energy is needed for older adults to cope with life changes.
- Intelligence changes with age. Older persons have increased verbal skills and they demonstrate slowed performance skills. Life-long experience and knowledge is reflected in verbal skills.
- Older adults tend to be more cautious in decision-making activities, pondering their options before responding. This deliberateness should not be mistaken for resistance.
- Memory changes with age. Long-term memory remains fairly constant. It is easier to do tasks of recognition over recall activities.
- Illness, social, and environmental changes affect learning, memory, and creativity. These changes need to be incorporated in treatment planning.
- Creativity is a positive therapeutic process that encourages reflection and development of the older adult's life story.

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7

Neurochemistry of Aging

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Based in part on the chapter 'Neurochemistry' by Alan M. Palmer and Steven T. DeKosky, which appeared in *Principles and Practice of Geriatric Medicine*, 3rd Edition.

INTRODUCTION

The world's population is getting older. During the first 50 years of this millennium, the worldwide population aged over 65 years is projected to increase from 6.9% of the total population to 15.9%, which constitutes an extra billion people (Table 1). This is attributable to a combination of a progressive increase in life expectancy (Table 1) and elevated fertility in many countries during the two decades after World War II (i.e. the "Baby Boom" effect; Figure 1) (*see also* **Chapter 9, The Demography of Aging**). This growing number of older adults increases demands on the public health system and on medical and social services, particularly for chronic neurological diseases such as stroke, Alzheimer's disease (AD), and Parkinson's disease (*see* **Chapter 9, The Demography of Aging**). Such disorders affect older adults disproportionately and contribute to disability, diminish quality of life, and increased healthcare costs. Thus, stroke afflicts 30% of persons aged over 65 years (fatally in 10%), and its incidence doubles during successive decades. AD affects 10% of the population aged over 65 years and is rising to 49% of those aged 80 years or more, and Parkinson's disease affects 1% of persons aged 60 or older and 2.6% of those over the age of 85 years (Palmer and DeKosky, 1998). Both age-associated neurological deficits and the increased risk to ischemic stroke and neurodegenerative disease with advancing age can be attributed to neurobiological deterioration. In many cases, the changes in degenerative diseases are qualitatively the same, but quantitatively more severe, than those of normal aging.

Aging itself causes more modest changes in overall function. Thus, there is a mild slowing of both motor speed and reaction time and a decline of complex cognitive skills, particularly memory. Memory is a complex function, encompassing the encoding, storage, and retrieval of diverse types of information. There are multiple memory systems in the brain. For example, there are dissociable systems underlying such memory functions as new learning of verbal information, acquisition of a procedural skill, and retrieval of semantic knowledge from long-term storage. Age does not affect all domains of cognition equally. For some functions, such as speed of visual-motor processing, slight decline often can be detected as people enter their 40s and 50s. However, for most cognitive abilities, no measurable decline is evident until age 65 or older. For example, the average expected number of words recalled from a 15-word list after a 30-minute delay is approximately 10 for people aged 55–65, nine for those aged 66–70, and eight for those up to age 85. These changes, while noticeable, are not disabling. Furthermore, some aspects of cognition, such as an individual's general fund of information, can actually continue to improve throughout their lifetime. There is considerable current interest in distinguishing age-related changes in cognition from "mild cognitive impairment" (MCI) (*see also* **Chapter 94, Mild Cognitive Impairment**), which may be a prodrome of various forms of dementia (Figure 2). Noncognitive changes in behavior are also important in aging since there is often an increase in psychiatric symptoms, including major depression, and a profound disruption of the sleep-wake cycle (*see* **Chapter 63, Sleep Disorders in Elderly People**; **Chapter 98, Geriatric Psychiatry** and **Chapter 100, Depression in Late Life: Etiology, Diagnosis and Treatment**).

This chapter will consider the neurochemical pathology of aging and, where appropriate, relate this to the changes associated with stroke, vascular dementia, AD, and Parkinson's disease (*see also* **Chapter 66, Parkinson's Disease and Parkinsonism in the Elderly**; **Chapter 71, Acute Stroke**; **Chapter 92, Cellular Changes in Alzheimer's Disease** and **Chapter 95, Vascular Dementia**).

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Table 1 Trends in world population

Year	1950	2000	2050
Total population (thousand persons)	2 518 629	6 070 581	8 918 724
Population aged >65 (thousand persons)	130 865	419 197	1 418 742
Percentage of those aged >65	5.2	6.9	15.9
Male life expectancy at birth (years)	45.2	63.3	72.0
Female life expectancy at birth (years)	47.9	67.6	76.7

Data derived from the 2002 revision of the UN "World Population Prospects" (www.un.org).

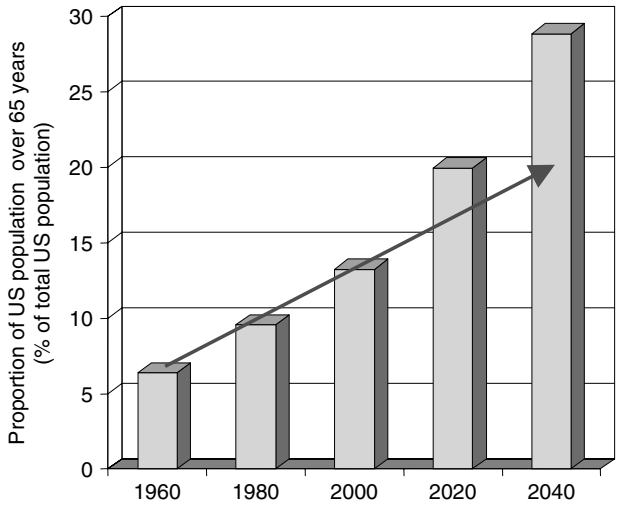

Figure 1 The proportion of adults aged over 65 as a proportion of the total US population (Data from the US Census, Middle Series Projections)

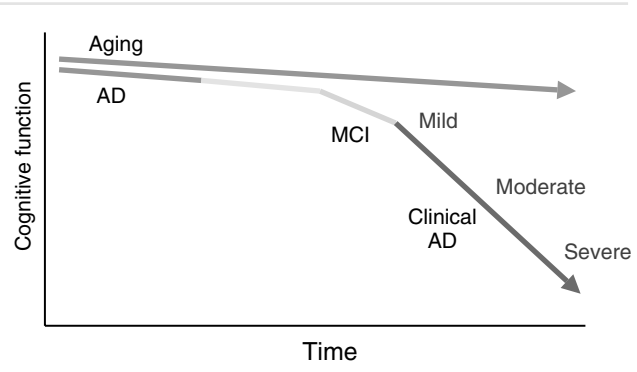

Figure 2 The decline in cognitive function in aging and Alzheimer's disease (*see also* **Chapter 93, Clinical Aspects of Alzheimer's Disease** and **Chapter 95, Vascular Dementia**)

THE AGING BRAIN

Brain weight and volume decrease with age. On average, the brain loses 5–10% of its weight between the ages of 20 and 90. In the older brain, tissue loss is most obvious on the surface and is seen as shrinkage of the brain gyri and sulci, which reflects a loss of neurons – from 10 to 60% – in different cortical areas. Neuronal loss is particularly evident in the hippocampus, but is also seen in the cerebellum, locus ceruleus, nucleus basalis of Meynert and the raphe nucleus. Besides neuronal loss, there also appears to be diminished dendritic arborization with age, although the number of synapses appears not to decline with age, which contrasts with AD, where there is clear evidence of synapse loss (Palmer and DeKosky, 1998) (*see also* **Chapter 8, Neuropathology of Aging** and **Chapter 5, Aging of the Brain**).

NEUROCHEMICAL CHANGES IN THE AGING BRAIN

Cholinergic Neurons

The cholinergic hypothesis of memory posits that the deterioration in cognitive function associated with age or AD is attributable to decreased cholinergic neurotransmission. The major success of this hypothesis is that it has led to the rational development of new medicines, principally acetylcholinesterase (AChE) inhibitors which inhibit ACh catabolism, together with numerous other cholinomimetics that are currently undergoing clinical development (Palmer, 2002; Wilkinson *et al.*, 2004). Although the first AChE inhibitors (e.g. tacrine) were associated with significant side effects and short plasma half-lives, second-generation compounds (e.g. donepezil, rivastigmine, and galantamine) have superior safety and efficacy profiles. Other cholinomimetic approaches to therapy include selective muscarinic M_1 receptor agonists, M_2 receptor antagonists, and nicotinic receptor agonists. Despite the apparent clinical utility of cholinomimetic approaches to the treatment of cognitive dysfunction, the evidence to support this hypothesis does have a number of shortcomings. In addition, recent data suggest a greater role of cholinergic neurons in mediating some of the noncognitive behavioral symptoms associated with AD (Francis *et al.*, 1999). The utility of AChE inhibitors in the treatment of MCI is currently under investigation, but clear efficacy has not yet been established.

Dopaminergic Neurons

There is a steady decline in dopaminergic cells in the substantia nigra with age in humans. The number of dopaminergic neurons in each substantia nigra declines from 400 000 at birth to 250 000 at age 60. In Parkinson's disease, cell counts range from 60 000 to 120 000. Dopaminergic cells in the substantia nigra innervate the neostriatum and corresponding changes in the concentration of dopamine in the neostriatum have also been observed (Table 2). It has been

Table 2 Summary of neurochemical changes in aging

Neuron type	Cortex	Hippocampus	Striatum
Cholinergic	Reduced in most studies	No change in most studies	Reduced in most studies
Noradrenergic	No change in most studies	No change in most studies	No change
Serotonergic	No change in some studies but reductions in others	No change	No change in most studies
Dopaminergic	No change	No change	Reduced in most studies
GABAergic	Reduced in all studies	Reduced in all studies	Reduced in one study
EAAergic	No change	No change	No change

The table is largely derived from Palmer and DeKosky (1998).

suggested that Parkinson's disease is related to a combination of environmentally induced subclinical damage to the substantia nigra pars compacta and the age-related loss of additional nigra neurons. Essential to this hypothesis is the existence of deteriorated function of the nigrostriatal pathway with advancing age. However, the hypothesis that Parkinson's disease is simply the additive effects of aging and cumulative neurotoxicity has been challenged by data indicating that the pattern of striatal cell loss in normal aging differs substantially from the pattern typically observed in Parkinson's disease. Nonetheless, before frank Parkinsonian symptoms emerge it is necessary that there is more than an 85% loss of dopamine from the striatum. The age-related loss of dopamine from the striatum therefore contributes to emergence of symptoms in Parkinson's disease and to the shuffling gait and stooped posture often seen in the very elderly. Age-related changes in dopaminergic neurons were largely restricted to the neostriatum since neither the cerebral cortex nor the hippocampus displayed marked age-related changes (Palmer and DeKosky, 1998).

The age-associated loss of nigrostriatal neurons may also underlie the striking increase in choreic symptoms seen midlife in patients with Huntington's disease. In addition to changes in dopamine (DA), a number of studies have consistently demonstrated elevation in the activity of the DA catabolic enzyme monoamine oxidase-B (MAO-B). This may serve to reduce synaptic concentration of DA with age and this will exacerbate the functional consequences of age-related loss of DA neurons. In contrast to MAO-B, the activity of MAO-A is relatively spared in Parkinson's (Palmer and DeKosky, 1998). Dopamine receptors have not yet been extensively studied in the aging human brain, but evidence indicates increased binding to D-1 receptors and reduced binding to D-2 receptors in the neostriatum. This age-related loss of D-2 receptors with age has been suggested to underlie the increasing incidence and severity of tardive dyskinesia with aging (Palmer and DeKosky, 1998).

Noradrenergic Neurons

Marked loss of locus ceruleus neurons has been reported, as a function of age, from approximately 19 000 cells in youth to about 10 000 cells for people in their ninth decade (Palmer and DeKosky, 1998). In contrast to morphometric studies, neurochemical studies have indicated a general sparing of noradrenergic indices in aging, with the possible exception of the hippocampus (Table 2). This is probably a reflection of the assessment in neurochemical studies of only transmitter and metabolite concentration and the postmortem instability, which in turn leads to increased variability, in these markers (Palmer and DeKosky, 1998). This is supported by studies of experimental animals, where postmortem influence is small and pronounced age-related reductions in noradrenergic activity have been reported, particularly in hypothalamic regions (Palmer and DeKosky, 1998). Noradrenaline is catabolized largely by MAO-A; about one-third is catabolized by MAO-B. Therefore, noradrenergic function may also be affected by the age-related increase in MAO activity, albeit to a lesser extent than dopamine. The two general types of adrenergic receptors, α and β, have been further subdivided into $\alpha 1$ and $\alpha 2$ and $\beta 1$ and $\beta 2$. $\beta 2$ receptors have been found to decline with age in the cerebral cortex whereas, $\beta 1$ receptors were unaffected (Palmer and DeKosky, 1998). Disturbances of the noradrenergic system are considered to play a role in depressive illness, so age-associated changes may contribute to the increased incidence in depression in the elderly.

Reduced concentration of noradrenaline (NA) have generally been reported in postmortem AD brain together with marked atrophy and cell loss from the locus ceruleus. This has been corroborated by data obtained from tissue removed antemortem where both the concentration of noradrenaline was reduced in both temporal and frontal cortex. In addition, high affinity uptake of [^{3}H]noradrenaline was reduced in the temporal cortex (Palmer, 1996).

Evidence suggests that these changes may contribute to some of the noncognitive changes in behavior associated with AD (Palmer, 2002).

Serotonergic Neurons

There are reports indicating loss of 5-hydroxytryptamine (serotonin, 5-HT) nerve terminals in the cerebral cortex but not in the hippocampus or neostriatum (Table 2). 5-HT is principally catabolized by the MAO-A and so is not likely to be affected by the age-related increase in MAO-B activity.

The 5-HT content in the neocortex from AD subjects has, in general, been found to be reduced. Neurofibrillary tangles and neuronal loss occur in the dorsal raphe nucleus, but it is unclear what proportion of cells are affected and whether the affected cells relate topographically to areas of pronounced neocortical damage (Palmer and DeKosky, 1998). Postmortem data indicating and serotonergic denervation has been corroborated by antemortem studies in which the release and uptake of 5-HT have been measured in addition to the

concentration of both 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) (Palmer, 1996).

Dysfunction of serotonergic (and noradrenergic) neurons probably relate more to noncognitive changes in behavior, such as aggression and depression that often accompany AD. In addition, the activity of serotonergic (and noradrenergic) neurons has been shown to closely reflect the state of behavioral arousal (maximal during periods of vigilance and absent during rapid-eye-movement sleep), so loss of these neurons may be responsible for the disturbance of sleep (and selective attention) associated with aging and AD (Palmer and DeKosky, 1998).

Cortical Interneurons

γ-Aminobutyric acid (GABA) constitutes a major inhibitory transmitter system in the cortex, accounting for as many as 30% of all cortical neurons. A number of markers of GABA metabolism have been examined in human brain and all have been shown to decline with aging (Table 2). A large number of peptides have been described in the cerebral cortex that are localized to neurons and are released upon depolarization. These are believed to play a role in slow chemical signaling. It appears that virtually all such peptides are colocalized with GABA in a GABAergic interneurons. Although neuropeptides have not been extensively examined in the aging human brain, it can be expected that they will change in concert with GABAergic neurons (Palmer and DeKosky, 1998).

In AD, reduced concentrations of both GABA and somatostatin-like immune reactivity have been reported. By contrast, studies of tissue obtained antemortem have indicated that the concentration of GABA and somatostatin-like immunoreactivity (SLIR), the potassium-evoked release of GABA and SLIR and glutamic acid decarboxylase (GAD) activity were unaltered in AD (Palmer, 1996). This suggests that GABAergic neurons are not affected until a relatively late stage of the disease. In such a case, it is likely that loss of cortical interneurons contributes to the final stages of the syndrome of dementia, but it is difficult to predict the consequences (if any) of the small losses associated with aging.

Excitatory Amino Acid–releasing Neurons

Pyramidal cells are the largest and most abundant neuron type in the cerebral cortex and play a key role in all aspects of higher mental and sensorimotor function. The neurotransmitter(s) associated with these neurons is considered to be an excitatory amino acid (EAA), principally L-glutamate and L-aspartate (Francis, 2003). Age-related loss of pyramidal neurons from the hippocampus and cortex have been demonstrated (Morrison and Hoff, 1997). Corresponding neurochemical data to support these changes is equivocal (Palmer and DeKosky, 1998). In experimental animals, EAA neurotransmission is, in at least a functional sense, preserved with normal aging since EAA uptake in cortex, hippocampus, and striatum and EAA release in cortex are preserved with age in a study using long-lived Fischer 344/Norwegian brown strain of rat aged 3, 12, 24, and 37 months (Palmer *et al.*, 1994). This corresponds with data from most other studies. The exceptions (Segovia *et al.*, 2001) may be attributable to comparisons between immature and mature animals since brain maturation may not be complete until 12 months. Thus "aging" changes may simply reflect changes occurring as a result of brain maturation rather than senescence. Other complicating factors include the common use of animals that do not achieve senescence (most inbred strains die before "old age" is achieved), along with the practice of comparing just two age points.

Tissue from the same animals used in Palmer *et al.* (1994) was used in a detailed study of the integrity of N-methyl-D-aspartate (NMDA) receptors. Both coagonist sites (for glutamate and glycine) were examined along with polyamine and zinc modulatory sites (Palmer, 2000). No age-related changes were observed, which largely corresponds with data from other studies (Segovia *et al.*, 2001), particularly if the caveats mentioned above are taken into account. Thus, it appears that both EAA terminals and NMDA receptors are preserved with aging; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors also appear to be unchanged with aging (Segovia *et al.*, 2001). However, there may be losses in distinct brain regions. This is supported by an immuonhistochemical study showing an age-related loss of human AMPA receptors from cholinergic neurons in the basal forebrain. What's more, since these alterations increase cation permeability, they may well contribute to the age-related loss of cholinergic neurons and contribute to the vulnerability of these neurons in AD (Ikonomovic *et al.*, 2000).

The relative preservation of EAA nerve terminals in aging contrast to the status of these neurons in AD (Francis, 2003). Some of the symptoms of AD, particularly aphasia, agnosia, and apraxia, are often similar to those associated with cortical disconnection syndromes (Pearson, 1996). This has led to the hypothesis that AD represents a global cortical disconnection syndrome in which each cortical region functions in isolation. Support has derived from correlations between the loss of pyramidal neurons from layers III and V of Alzheimer's patients with the severity of dementia and scores on five psychometric tests (Mann, 1996).

STRUCTURAL MARKERS OF BRAIN MEMBRANES

Markers of Neuronal Membrane and Connectivity

Neuron membrane–specific protein and lipid membrane markers have been utilized in human as well as experimental animal studies to quantify "axodendritic expanse", the amount of a neuronal (as opposed to glial) membrane present in a given volume of tissue (or expressed per mg wet weight

or per mg protein). Lipid sialoganglioside is enriched in neuronal membranes, and has been used as a neuronal marker. This relative stability is in contrast to the marked loss of gangliosides in AD, in which massive neuronal and axodendritic loss occurs (Palmer and DeKosky, 1998).

A more specific marker of neuronal connections is synaptophysin, a protein present at the synapse itself. Increases in synaptophysin occur in animal brains during the period of developmental synaptogenesis. In respect to normal aging, little data is available but studies in monkeys show no reduction. This may reflect the fact that synapses take up a small proportion of the neuropil or that synapse loss occurs at a similar rate to brain atrophy (Geinisman *et al.*, 1995). However, synaptophysin decreases in the target zone after lesion-induced denervation and increases with regeneration of synapses (Palmer and DeKosky, 1998). Therefore, as expected in AD, synaptophysin is decreased in areas of known synapse loss which are affected by the disease (cortex and hippocampus) but not in regions that are behaviorally or neuropathologically uninvolved, such as the cerebellum (Palmer and DeKosky, 1998). Actual synapse loss in AD compared to age equivalent controls has been shown in electron microscopic studies, which directly quantify synapses (Palmer and DeKosky, 1998). The severity of dementia of AD patients has been shown to correlate with synapse counts in biopsy tissue and synaptophysin concentration in postmortem tissue (Palmer and DeKosky, 1998).

White Matter

White matter represents axons, their insulating sheath, and the supporting cell. Age-related white matter changes are a frequent finding in CT/MRI of older subjects. The evidence points toward an association between white matter changes and cognitive impairment, with speed of mental processes, attention, concentration, executive functions, and visual spatial skills being the cognitive domains more commonly affected (Ferro and Madureira, 2002).

PROTEIN SYNTHESIS AND GENE EXPRESSION

Overall, the data suggest that there is a reduction in the capacity to synthesis proteins during aging, which is related to changes in the nucleus. Studies of the aging rodent brain indicate diminished rates of protein synthesis, but such studies have not been performed on the human brain, although the shrinkage of neurons and decreases in specific proteins (e.g. neurotransmitter receptor enzymes) may stem from such declines. In AD, the capacity for protein synthesis is reduced, which in pyramidal cells may be associated with the formation of neurofibrillary tangles. This, along with impaired cytoskeletal transport of proteins, will substantially disrupt normal function.

POSSIBLE CAUSES OF AGE-ASSOCIATED NEURODEGENERATION

The cause of age-associated neurodegeneration is not yet known. However, there are a number of mechanisms of neurodegeneration that may play a role in senescent brain dysfunction. These include the triumvirate of excitotoxicity, oxidative stress, and impaired energy metabolism, along with neurotrophic factors, and are considered below.

Excitotoxicity

The excitotoxic hypothesis of brain injury posits that elevated interstitial concentrations of EAAs cause cell death by overactivation of EAA receptors. EAAs could accumulate because of a disruption of energy metabolism leading to increased EAA release or impairment or reversal of EAA uptake (or a combination of both). Another possibility is that the number of EAA receptors or their selectivity for particular ions change and thus cause cell death. For example, loss of basal forebrain cholinergic neurons in AD may be linked to the numbers of calcium-permeable AMPA/kainate receptors present on such cells. By whatever mechanism a major consequence of these changes is depolarization of the postsynaptic membrane, which removes the depolarization block to the NMDA receptor channel complex, thus permitting a large influx of Ca^{2+} ions over the period that it is in the open state. Toxicity is then determined by both the magnitude and duration of the rise in cytosolic Ca^{2+} concentrations.

It is now well established that excitotoxic mechanism contribute to the neurodegenerative changes associated with stroke and motor neuron disease, while for AD the extent of such involvement remains to be established clearly. In aging, there is increased vulnerability of selected populations of neurons to excitotoxicity and oxidative stress. Environmental stress can also contribute to hippocampal cell death. These neurons have endogenous glucocorticoid receptors, which interact with glucocorticoids secreted from adrenal glands in response to stress reduce glucose uptake (Behl, 1998). This increases vulnerability to cell death and may provide the basis to stress-induced neurodegeneration, which has been observed in experimental animals. The hippocampus is particularly vulnerable to both age- and Alzheimer-associated degeneration and is selectively vulnerable to the effect of metabolic poisons (Palmer *et al.*, 1994).

Oxidative Stress

The brain is particularly vulnerable to free radical damage because of its high requirement for both energy and oxygen, along with particularly high concentrations of polyunsaturated fatty (which are major substrates for free radicals) acids and transition metals (which often catalyze radical-generating reactions). This situation is exacerbated by a lower antioxidant capacity than that in most other organs. Oxidative stress

occurs when pro-oxidant activity exceeds the capacity of the tissue's antioxidant capacity. Oxidative stress increases with age because of increased pro-oxidant activity rather than any diminution of antioxidant capacity (Palmer *et al.*, 1994). This elevated pro-oxidant activity causes oxidative damage to DNA, protein, and lipids in the brain, which leads to neuronal dysfunction and ultimately to neuron loss. Nerve terminals are particularly vulnerable because of the high number of mitochondria, which is the source of most free radicals. This is supported by age-related increases in a marker of DNA damage (8-hydroxydeoxyguanosine concentration) and elevated lipid peroxidation in synaptosomes (pinched off nerve endings). The oxidative polymerization of lipids leads to the formation of lipofuscin and increases in a linear fashion with age in humans. Its formation occurs as a result of free radical formation, so accumulation with age may reflect the cumulative consequence of free radical reaction over the lifespan. Lipofuscin has been shown to accumulate in both the cholinergic nucleus basalis of Meynert and the serotonergic raphe nucleus and may therefore be associated with the age-associated loss of these cells. Similarly, neuromelanin accumulation, also thought to occur in response to free radical reactions, increases with aging in the noradrenergic locus coeruleus and the dopaminergic substantia nigra, and there is good evidence for free radical involvement in the etiology of Parkinson's disease (Beal, 2003).

In addition to oxidative damage to DNA and lipids, there is also evidence for an age-related increase of oxidized protein (assessed by measuring the concentration of protein carbonyls) in brain tissue from both humans and experimental animals. The full significance of oxidative stress increasing with age is not yet clear, but the fact that damage to DNA, lipids, and proteins is also evident in AD and Parkinson's disease (Floyd, 1999) suggests that these age-related changes increase vulnerability to the pathogenic process associated with neurodegenerative diseases.

There is evidence of free radical damage to all classes of macromolecules (protein, DNA, RNA, lipids, and sugars) in brains of patients with AD, although great care must be taken to control for the effects of postmortem delay and brain acidosis occurring as a consequence of terminal coma. Taking this into account, there is evidence of damage to specific proteins such as the glial glutamate transporter GLT-1, glutamine synthase and β-actin as well as the lipids arachidonic acid and docosahexaenoic acid (Butterfield *et al.*, 2001). The oxidative damage to GLT-1 has been attributed to the action of an aldehydic product of lipid peroxidation, 4-Hydroxynonenal (Lauderback *et al.*, 2001). The functional consequences of this modification are as yet unknown but may explain the functional reduction in glutamate uptake seen in AD (Procter, 1996) in the presence of stable amounts of GLT-1 protein (Beckstrom *et al.*, 1999).

Reduced Energy Availability/Mitochondrial Function

There remains some uncertainty as to whether the cerebral metabolic rate as determined by positron emission tomography (PET) declines with aging but the most closely controlled studies indicate that at least some brain regions are affected. The complication is that brain atrophy as well as functional decline can both contribute to reductions. Only when studies using full coregistration of PET with MRI become more frequent will it be possible to resolve this issue. Cerebral metabolic rate for glucose and for oxygen and cerebral blood flow are all reduced in AD and the pattern of reductions tends to mirror neuropathology. Again the complication is atrophy and cell loss. However, evidence energy levels appear to be reduced in AD, probably because of impaired mitochondrial function (Beal, 1998; Francis *et al.*, 1993). The likely cause is not known, but it may be related to reductions in the activity of key enzymes in the Kreb's cycle. Thus, there have been consistent reports of reduced activity of pyruvate dehydrogenase α-ketoglutarate dehydrogenase and cytochrome oxidase (Blass, 2003). Other evidence points to the possibility of uncoupling of oxidative phosphorylation and oxidation (Francis *et al.*, 1993), which would reduce energy availability; it is also likely to increase free radical production.

Neurotrophic Factors

Over the past decade, there has been much interest in the possible role of neurotrophic factors in neurological disorders. In particular, nerve growth factor (NGF), the founding member of the neurotrophin family, has generated great interest in relation to AD. This interest is based on the observation that cholinergic basal forebrain are dependent upon NGF and its receptors for their survival. In fact, NGF transduces its effects by binding two classes of cell surface neurotrophin receptors: TrkA and p75, both of which are produced by cholinergic neurons. Recent findings indicate an early defect in NGF receptor expression in CBF neurons; therefore, treatments aimed at facilitating NGF actions may prove highly beneficial in counteracting the cholinergic dysfunction found in end-stage AD and attenuating the rate of degeneration of these cholinergic neurons (Lad *et al.*, 2003). There are no quantitative data on changes in NGF receptor density over the lifespan or in aging.

Amyloid (Aβ)

Aβ, a 40–42 amino acid peptide derived from amyloid precursor protein, is considered to play a central role in the pathophysiology of AD since it forms the core of senile plaques. In some cases, (autosomal dominant AD and Down's syndrome (*see* **Chapter 92, Cellular Changes in Alzheimer's Disease** and **Chapter 101, The Older Patient with Down's Syndrome**)) this occurs because of increased production of Aβ, whereas in sporadic AD it may be linked to altered Aβ processing or impaired clearance of Aβ. Both Aβ deposition and plaque formation increase with aging, although the mechanism is not yet clear, it may be linked to oxidative stress since amyloidoisis is blocked by antioxidants.

APPROACHES TO THERAPY

Aging is a highly complex multifactorial process characterized by the progressive loss of the ability of organs and cells to maintain normal function. Thus, there is no unitary neurochemistry of aging and age-associated brain dysfunction manifests in a variety of way and increases the likelihood of coincidence neurological disease. It is therefore unlikely that there will ever be a single pharmacotherapy for brain aging, but, rather, specific therapies will be used for particular symptoms, as is now being realized in neurological disorders such as AD (Palmer, 2002). Understanding the underlying neurochemistry thus provides an essential framework for rational therapy, which may be categorized as either neuroprotective or palliative (*see also* **Chapter 97, Treatment of Behavioral Disorders**).

Neuroprotective Therapy

Antiexcitotoxic Agents

Excitotoxicity clearly plays an important role in mediating neurodegenerative changes in stroke, severe hypoglycemia, severe epilepsy, and severe head injury. Although the involvement of excitotoxic mechanism in chronic brain injury is less clear-cut, evidence is emerging for a critical role in mediating the neurodegenerative changes associated with motor neuron disease and AIDS. Excitotoxicity coupled with oxidative stress may also be central to the neuropathology associated with the diseases of Huntington, Parkinson, and Alzheimer. Since most of these diseases are age-related, disease-induced changes are probably potentiated by the neurodegeneration associated with normal aging, which itself may be caused by excitotoxic injury, probably in conjunction with oxidative stress (Palmer *et al.*, 1994). Thus, there is great potential for drugs that block the cascade of destruction associated with excitotoxic injury. Preclinical studies have now established the utility of NMDA and AMPA/kainate receptor antagonists in the treatment of acute brain injury. However, none of these compounds showed clear efficacy in clinical trials (Dawson *et al.*, 2001). However, one well tolerated NMDA receptor antagonist (memantine) has recently been launched as a palliative for AD (Palmer and Stephenson, 2005). Whether it is also able to alter the course of this disease remains to be established (Tariot *et al.*, 2004).

Antioxidants

The proposed involvement of oxidative damage in aging has prompted studies to examine the neuroprotective efficacy of various antioxidants. However, the results so far are encouraging but variable (Floyd, 1999). The nitrone-based free radical trap PBN (α-phenyl-*N*-*tert*-butyl nitrone) has been investigated extensively. Chronic low-level administration to old experimental animals appears to reverse their age-enhanced susceptibility to stroke. In addition to its radical scavenging activity, it has also been shown to block inflammation-induced neurodegeneration, suggesting there that the senescent brain may be an enhanced neuroinflammatory state as well as at an increased level of oxidative stress (Floyd and Hensley, 2000).

Palliative Therapy

Of the behavioral changes seen in apparently normal elderly, relatively few have a significant impact on function. Those changes that affect function relate primarily to motor slowness, difficulty with complex cognitive complexity, visual and auditory alterations, depression, and sleep disturbance. The most successful example of palliative therapy is the use of levodopa to treat Parkinson's disease. The effect of levodopa on age-associated motor dysfunction is not yet clearly established. The age-associated impairments in cognitive function may well respond to therapies aimed and improving cognitive function in Alzheimer patients. Some of the symptoms of AD, particularly aphasia, agnosia, and apraxia, are often similar to those associated with cortical disconnection syndromes. Quantitative data on the distribution of senile plaques and neurofibrillary tangles further suggest that corticocortical projection fibers are selectively affected within association areas of the cortex. This has led to the hypothesis that AD represents a global cortical disconnection syndrome in which each cortical region functions in isolation. Support for this hypothesis has come from an antemortem study of AD, in which loss of the perikarya of pyramidal neurons from layers III and V of the midtemporal gyrus of Alzheimer's patients was found to correlate significantly with an assessment of the severity of dementia and scores on five psychometric tests (Mann, 1996). As pyramidal neurons use EAA as a neurotransmitter and receive prominent excitatory inputs, the cortical disconnection hypothesis of AD predicts that changes in EAA neurons and receptors make a substantial contribution to the progressive impairments of memory, personality, and intellect that characterize AD (Francis, 2003). Studies have demonstrated that the NMDA receptor antagonist Memantine improves global functioning and activities of daily living, cognitive function, and caregiver burden (Tariot *et al.*, 2004). Another approach is to target 5-HT_{1A} receptors, which in the cerebral cortex are entirely located on pyramidal cells. 5-HT_{1A} receptor antagonists have been shown to increase EAA release; it has been suggested that such compound will be effective in the treatment of AD (Schechter *et al.*, 2002). Cholinergic mechanisms have also been linked to memory dysfunction, although recent evidence suggests that the cholinergic system may play a greater role in attentional processing. There are a number of approaches to the treatment of the cholinergic deficit in AD, most of which have focused on ACh replacement with precursor (choline or lecithin) the AChE inhibitor physostigmine or the muscarinic agonist are coline. More recent studies have used M_2 muscarinic antagonists, M_1 muscarinic

agonists, nicotinic agonist, or improved AChE inhibitors (Palmer, 2003).

Again in AD, dysfunction of noradrenergic and serotonergic neurons probably relate more to noncognitive changes in behavior, such as aggression, depression, and sleep disturbances, that often accompany AD (Palmer and DeKosky, 1993; Procter, 1996). Thus, there is now a theoretical basis for treating subsets of elderly persons and patients with AD who display overt noncognitive changes in behavior with drugs that act upon noradrenergic and serotonergic systems (Palmer and DeKosky, 1998). Thus, for example, 20–30% of elderly persons with concurrent mental illness are depressed. Similarly, depression affects a similar proportion of Alzheimer patients and anti-antidepressant therapy appears to be effective, although there have been no double blind yet (Palmer and DeKosky, 1998).

CONCLUSIONS AND FUTURE DIRECTIONS

Neurochemical changes in the aging brain are varied and for many markers they are qualitatively the same, but quantitatively less severe than those occurring in neurodegenerative disease. Impairments in dopamine transmission probably contribute to the gait and movement disorders in the elderly and contribute to the age-associated increase in the prevalence of Parkinson's disease. Similarly, alterations in EAA and cholinergic transmission probably contribute to the impairments in cognition and attention seen in the elderly whereas the age-related decline in noradrenergic and serotonergic transmission are likely to contribute to the age-associated changes in noncognitive behavior, such as depression, aggression, and sleep disturbance. This lays the conceptual framework for palliative therapy for the behavioral abnormalities associated with old age. Similarly, the development of preventative therapy depends on a clear understanding of the mechanisms responsible for age-associated neurodegeneration. The most plausible mechanism at present is that it occurs as a result of oxidative stress, which causes damage to DNA, lipid, and protein, which contribute to cell dysfunction. If this is sufficient to impair the production of ATP (which is required for neurons to maintain their high level of activity), then the membrane potential will not be maintained. This inability to maintain neuronal membrane potential (because of diminished activity of the Na^+ /K^+ ATPase) eases the Mg^{2+} blockade of the NMDA receptor and facilitates activation by EAAs, leading to increase influx of Ca^{2+} and, if sustained at a high level, will lead to cell death.

Given the major implications of cognitive competency for personal independence and quality of life, together with growing evidence that how an individual lives in earlier stages of life affects cognitive aging, greater attention to memory and the aging brain is likely to have significant public health benefits. It is now clear that significant cognitive decline is not an inevitable consequence of advanced age. Furthermore, AD and related disorders, which in the past have been approached with a sense of therapeutic nihilism, are increasingly being seen as targets for active intervention. But what of "age-associated memory impairment"? New research that offers to attain the ancient goal of improving our cognitive ability raises an important issue – the use, by healthy people, since aging is not considered a disease. There is a long history of "cognitive enhancers" but the effectiveness of such supposed "nootropics" is far from clear (Rose, 2002). Although pharmaceutical companies race to provide treatments for memory loss in AD, there is much less enthusiasm to treat "age-associated memory impairment".

Long term, however, it is clear that there is likely to be an increased need for drugs to improve cognitive function in both the demented and nondemented elderly. With the projected growth in the elderly (Figure 1), there will be a corresponding decline in the number of working taxpayers relative to the number of older persons. This means that there is likely to be inadequate public resources and fewer adults available to provide informal care to older, less able family members and friends. Having drugs available to improve brain function (for both cognitive and noncognitive aspects) would clearly be a positive contribution. However, CNS drug discovery is associated with significant challenges (Palmer and Stephenson, 2005) and the pharmacotherapy of aging remains an embryonic science.

KEY POINTS

- The number of people in the world aged over 65 years is projected to increase sharply in the next 2–3 decades.
- Aging is associated with loss of brain cells, but this loss is much less pronounced than that seen in neurodegenerative disorders such as Alzheimer's dementia and Parkinson's disease.
- Aging is associated with modest changes in cognitive function and mild changes in noncognitive changes in behavior.
- Aging is a major risk factor for neurodegenerative diseases and psychiatric disorders such as depression.
- Our understanding of the neuronal basis of aging is becoming more sophisticated, but the pharmacotherapy aging remains an emerging science.

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8

Neuropathology of Aging

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INTRODUCTION

The effects of age on the nervous system, and the nature of the association between senescence and senility have long exercised us and been subjected to detailed clinical, electrophysiological, biochemical, morphologic and molecular genetic study. This chapter includes a detailed description of the gross and microscopic alterations in the nervous system that occur with increasing age. Inevitably, this involves some consideration of the histological overlap between the alterations of "normal" aging and those due to degenerative neurological diseases, particularly Alzheimer's disease. The pathological findings in Alzheimer's disease and other neurological diseases are, however, described in more detail elsewhere in this book.

GROSS CHANGES

External Appearance

External examination is relatively insensitive to the effects of age on the adult brain but some changes are usually evident by about the 7th decade. The sulci are slightly wider and the gyri narrower than in younger individuals and there is often some thickening and opacity of the leptomeninges over the cerebral convexities, particularly toward the vertex. The dura mater may become firmly adherent to the skull vault.

Brain Weight

Several studies have documented an approximately inverse linear relationship between age and brain weight in later years. In a series of over 7000 autopsies, Peress *et al.* (1973) found that a decline in brain weight was evident from as early as 30 years of age and affected the supratentorial and infratentorial parts of the brain proportionately. Hartmann *et al.* (1994) calculated that the weight of the brain decreases from mean values of 1336 g in young adult males and 1198 g in young adult females by about 2.7 g per year in males and 2.2 g per year in females. Similar figures can be derived from data based on magnetic resonance imaging (MRI). In the MRI series of Coffey *et al.* (1992), the volume of the cerebral hemispheres was found to fall by an average of 0.23% per year in healthy adults; the reduction in volume was greater than average in the frontal lobes (0.55% per year), the temporal lobes (0.28% per year) and the amygdala-hippocampal complex (0.30% per year). Resnick *et al.* (2003) reported that the mean annual rates of tissue loss in adults aged between 59 and 85 years were 5.4, 2.4, and 3.1 ml per year for total brain, gray, and white volumes, respectively. Thus, although there is some shrinkage of gray matter, the greater part of the reduction in brain weight is due to atrophy of the white matter.

Ventricular Size

Not surprisingly, as brain weight declines, ventricular size tends to increase. The effects of aging on the volume of ventricular and sulcal cerebrospinal fluid (CSF) have been the subject of several CT and MRI studies. In an MRI study of 76 healthy adults, Coffey *et al.* (1992) found the volume of the lateral ventricles to increase by an average of 3.2% per year and of the third ventricle by 2.8% per year. Pfefferbaum *et al.* (1994) reported that the ventricular volume increased between 21 and 70 years by approximately 0.3 ml per year but the volume of sulcal CSF increased more rapidly, at 0.6 ml per year. Resnick *et al.* (2003) found mean ventricular volume to increase by 1.4 cm^3 per year over a 4-year period in his cohort of normal 59–85 year olds.

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MICROSCOPIC CHANGES IN THE GRAY MATTER

Neuronal Loss and Neuronal Shrinkage in Cerebral Cortex and Hippocampus

There is marked regional variation in the pattern of neuronal loss in the central nervous system. Several studies have been made of the distribution and extent of neuronal loss in the neocortex. The earliest of these were based on relatively time-consuming manual counting methods and, of necessity therefore, included fewer cases and smaller samples of cortex than later studies in which counts were obtained by means of automated image-analyzers. Variations in the methodology and results of these studies were discussed in detail by Terry *et al.* (1987). Early studies (see Love, 1998) indicated a variable but substantial depletion of neurons from the cerebral cortex during adult life in many regions, amounting to 40–50%. In contrast, both Haug *et al.* (1984) and Terry *et al.* (1987) found no correlation between age and neuronal density in several regions of cerebral cortex, the "loss" of large neurons being largely attributable to shrinkage and associated, therefore, with an "increase" in the number of smaller neurons. Terry *et al.* (1987) suggested that the fully automated acquisition and analysis of some earlier morphometric data, with no manual editing of the digitized images, may have been inaccurate. It is worth noting that most of these investigators have found a two- to threefold variation between the numbers of neurons in any given region of cortex even in neurologically normal individuals of similar age, so that the relatively small early series should be interpreted with circumspection. Using stereological methods that avoid artifacts due to gray matter atrophy, processing, or sectioning, Pakkenberg *et al.* (2003) calculated that the number of neocortical neurons in women was 19.3 billion and in men, 22.8 billion, a difference of 16%. The number of neurons declined by less than 10% between 20 and 90 years. In summary, the evidence is of some, but only mild, loss of neurons from the neocortex of neurologically normal individuals during adult life, and shrinkage of many of the larger neurons that remain. The gender-related difference in the number of neocortical neurons probably exceeds the loss of neurons that is attributable to aging.

Several recent studies have shown that neuronal populations in the entorhinal cortex of cognitively normal subjects remain stable well into old age (Trillo and Gonzalo, 1992; Lippa *et al.*, 1992; Gómez-Isla *et al.*, 1996). This contrasts with findings in Alzheimer's disease, in which severe loss of neurons from laminae II and IV is an early manifestation (Lippa *et al.*, 1992; Gómez-Isla *et al.*, 1996).

Studies differ as to the extent and distribution of neuronal loss from the aging hippocampus. Miller *et al.* (1984) recorded a loss of neurons from the CA1 field, of approximately 3.6% per decade. Devaney and Johnson (1984) made a rather confusing study of neuronal density in the hippocampus. They counted dispersed cells in a hemocytometer and related their numbers to the weight of the whole of the hippocampus. The density of neurons as determined in this way increased slightly between 20 and 87 years but this is probably attributable to senescent shrinkage of the molecular layer of the dentate fascia and hippocampal white matter. Probably the most accurate quantification of neurons in different parts of the hippocampus has been that of West and colleagues (West, 1993; West *et al.*, 1994) employing modern stereological methods. They found an age-related decline in the numbers of neurons in the subiculum and hilus of the dentate gyrus, at about 0.7% per annum and 0.4% per annum respectively, but no significant change in the number of neurons in the CA1 field (which shows most marked loss of neurons in Alzheimer's disease). Although the number of CA1 neurons is probably well preserved during normal aging, Dickson *et al.* (1994) found hippocampal sclerosis, characterized by marked focal loss of neurons and gliosis predominantly involving the CA1 field, to be a surprisingly common finding in demented patients over 80 years of age, usually in the absence of other neurodegenerative diseases to account for the dementia.

Cholinergic and Peptidergic Input to Cerebral Cortex and Changes in the Nucleus Basalis of Meynert

Most investigators have found that there is only mild or no reduction in the number of neurons in the nucleus basalis of Meynert complex, which provides the cholinergic input to the cerebral cortex (Chui *et al.*, 1984; Mann *et al.*, 1984; Bigl *et al.*, 1987; Lowes-Hummel *et al.*, 1989). However, substantial age-related reductions, of 50% or more, were reported by McGeer *et al.* (1984) and de Lacalle *et al.* (1991). These last authors found the neuronal loss to be greatest in the posterior subdivision (64.5% by 90 years), where there was also 10% shrinkage of the remaining neurons. The loss from the intermediate subdivision was 42% and no significant change in the number of neurons occurred in the anterior subdivision, where the cell size actually increased by an average of 15%. According to Baloyannis *et al.* (1994), it is principally the small spiny GABA-ergic neurons in the nucleus basalis that decrease in number in normal aging, the large cholinergic neurons being spared. In keeping with this observation, the density of cholinergic fibers in the neocortex, entorhinal cortex, and amygdaloid complex declines only slightly in normal aging, compared with the dramatic loss in Alzheimer's disease (Geula and Mesulam, 1989; Benzing *et al.*, 1993; Emre *et al.*, 1993). The density of somatostatin-, neurotensin- and substance P-containing nerve fibers in the cerebral cortex, amygdaloid complex, and subcortical white matter seems to be preserved well into old age (Benzing *et al.*, 1993; Emre *et al.*, 1993; Ang and Shul, 1995).

Other Subcortical Nuclei

The numbers of neurons in many of the subcortical nuclei that have been studied are relatively stable throughout adulthood. The density of neurons in the striatum remains constant

(Pesce and Reale, 1987), although there is some shrinkage of the large, strongly calbindin-positive neurons (Selden *et al.*, 1994). No significant loss of neurons occurs from the supraoptic or paraventricular nuclei of the hypothalamus (Goudsmit *et al.*, 1990; Wierda *et al.*, 1991). There is loss of neurons from the suprachiasmatic nucleus, although less so than in Alzheimer's disease (Swaab *et al.*, 1993). Swaab *et al.* (1993) documented hypertrophy of neurons containing estrogen receptors in the infundibular/arcuate nucleus of the hypothalamus in postmenopausal women and speculated that this may be related to the development of hot flushes. Similar observations were made by Abel and Rance (2000).

With increasing age, there is a mild loss of pigmented neurons from the substantia nigra and locus ceruleus (Perry *et al.*, 1990; Fearnley and Lees, 1991). This loss is not related to coexistent Alzheimer-type or Lewy body pathology (Perry *et al.*, 1990; Love *et al.*, 1996) and has not been demonstrated in all series (Kubis *et al.*, 2000). In the substantia nigra, the fallout of neurons with age is largely confined to the medial ventral and dorsal tiers of the pars compacta, whereas Parkinson's disease affects the lateral ventral tier most severely (Fearnley and Lees, 1991). The number of neurons remains constant with age in the roof nuclei of the cerebellum (Heidary and Tomasch, 1969), the ventral cochlear nucleus (Konigsmark and Murphy, 1970), the nucleus of the facial nerve (van Busirk, 1945) and the inferior olivary complex (Moatamed, 1966). With aging, there is a significant decrease in the number of neurons in the vestibular nuclear complex (Tang *et al.*, 2001). Alvarez *et al.* (2000) found that aging does not affect the size of the complex, and that the neuronal loss affects the descending, medial and lateral vestibular nuclei but not the superior nucleus. Tomlinson *et al.* (1981) counted neurons in the locus ceruleus in brains from 25 neurologically normal adults and noted that the counts gradually declined after middle age. The number of cholinergic neurons in the pedunculopontine nucleus was reported to decrease with age between the third and tenth decades (Ransmayr *et al.*, 2000); however, four centenarians had neuronal cell counts comparable to those in much younger adults, leading the authors to speculate that centenarians may start out with greater numbers of neurons in the pedunculopontine nucleus or may experience slower loss of neurons with aging.

Dendritic Changes

There is accumulating evidence that the dendrites in several regions of the adult brain are capable of considerable growth and plasticity, resulting in expansion of the dendritic tree. This may be a compensatory response to loss of adjacent neurons. This phenomenon is best documented for dendrites in the molecular layer of the hippocampal dentate gyrus (Flood *et al.*, 1987; de Ruiter and Uylings, 1987) and in lamina II of the parahippocampal cortex (Buell and Coleman, 1979; Flood and Coleman, 1990). In contrast, the extent of the dendritic trees decreases in both of these regions in patients with Alzheimer's disease. Whereas the expansion of the dendritic tree in the parahippocampal cortex seems to continue well into old age, that in the molecular layer of the dentate gyrus peaks in middle age and subsequently regresses (Flood *et al.*, 1987). The dendritic trees of neurons in the subiculum (Flood, 1991) and the pyramidal cell layer of the hippocampus remain relatively constant during normal aging (Flood and Coleman, 1990; Hanks and Flood, 1991) but regress in Alzheimer's disease.

Outside of the hippocampus and parahippocampal gyrus, only relatively minor dendritic alterations have been observed in the cerebral cortex. Jacobs and Scheibel (1993) found that the number of dendritic segments in pyramidal cells in the superior temporal gyrus remained relatively stable with age although the length of the dendrites tended to decrease. A decrease in the number of basal dendrites with advancing age was noted by Nakamura *et al.* (1985) in pyramidal neurons in the motor cortex (Brodmann area 4).

Limited information is available concerning changes to dendrites in the subcortical nuclei. Arendt *et al.* (1994) found that the dendritic field of neurons in the nucleus basalis increased in size during normal aging. In contrast, the growth of dendrites that occurred in Alzheimer's disease tended to increase their density without enlarging the dendritic field. Significant loss of dendrites was observed in neurons in the substantia nigra of elderly subjects (Cruz-Sanchez *et al.*, 1995)

Synaptic Density

With increasing age, there is a mild decline in the density of synapses in the hippocampus and in parts of the cerebral neocortex, whether assessed by electron microscopy (Adams, 1987; Bertoni-Freddari *et al.*, 1990) or synaptophysin immunohistochemistry (Masliah *et al.*, 1993; Eastwood *et al.*, 1994). A possible exception is the postcentral (primary somatosensory) cortex, in which Adams (1987) found the density of synapses to remain constant. Masliah *et al.* (1993) calculated that the density of synaptic terminals in the frontal cortex of subjects over 60 years was approximately 20% below that of younger subjects. The loss synapses in the hippocampus and at least some regions of the neocortex is probably accompanied by an increase in the mean area of contact at each synapse (Adams, 1987; Bertoni-Freddari *et al.*, 1990).

Love *et al.* (2005) found that the concentration of synaptic proteins in the superior temporal cortex was related to the apolipoprotein E (*APOE*) genotype. In superior temporal cortex from normal brain, the concentration of the postsynaptic protein PSD95 (postsynaptic density-95) was significantly higher in cortex from people with than without an *APOE* $\varepsilon 2$ allele. In contrast, possession of the *APOE* $\varepsilon 4$ allele was associated with lower concentrations of two presynaptic proteins, synaptophysin and syntaxin. A positron emission tomographic investigation showed that people who possess an $\varepsilon 4$ allele have lower rates of cerebral glucose metabolism in the posterior cingulate, parietal, temporal, and prefrontal cortex (Reiman *et al.*, 2004), and in another study,

morphometry revealed that neurons in nucleus basalis of Meynert from people with $\varepsilon 4$ have smaller Golgi apparatus (Dubelaar *et al.*, 2004), another measure of metabolic activity. These *APOE*-related premorbid differences in synapses and metabolic activity may influence the capacity of the brain to respond to injury and may thereby account for the association between *APOE* and clinical outcome in a range of neurological diseases, such as head injury (Chiang *et al.*, 2003; Teasdale *et al.*, 1997), hemorrhagic stroke (McCarron *et al.*, 2003), and multiple sclerosis (Chapman *et al.*, 2001; Fazekas *et al.*, 2001).

Dystrophic Axons and Ubiquitinated Deposits

During normal aging, axons in certain parts of the central nervous system tend to undergo dystrophic changes: they develop focal argyrophilic swellings within which lysosomes, mitochondria, membranous bodies, and neurofilaments accumulate. Sites of predilection include the gracile and cuneate nuclei, the substantia nigra, the globus pallidus, and the anterior horns of the spinal cord. These dystrophic axons react strongly with antibodies to ubiquitin, which also label smaller, dotlike structures in the white matter and cerebral cortex. Ubiquitin is an 8-kDa polypeptide involved in the degradation of many abnormal or short-lived proteins. The density of the dotlike structures increases with age and they are particularly prominent after about 60 years (Dickson *et al.*, 1990). These small ubiquitinated bodies correspond to dystrophic neurites (Dickson *et al.*, 1990; Dickson *et al.*, 1992; Migheli *et al.*, 1992; Yasuhara *et al.*, 1994) and foci of granular degeneration of myelin sheaths in the white matter (Dickson *et al.*, 1990, 1992; Migheli *et al.*, 1992).

Lipofuscin

Lipofuscin, a pigment produced by oxidation of lipids and lipoproteins, accumulates with age in the form of irregularly shaped, brown cytoplasmic granules that are acid-fast, sudanophilic, and autofluorescent under ultraviolet light. Electron microscopy shows the granules to contain both highly electron-dense, and homogeneous, moderately electron-lucent material, aggregated together within a unit membrane. Lipofuscin accumulates to a varying extent in most neurons and glia (Wisniewski and Wen, 1988). Neurons of the inferior olivary nuclei tend to amass large amounts of lipofuscin from early adulthood. With increasing age, relatively large amounts of lipofuscin also accumulate in the dentate nucleus of the cerebellum, pyramidal neurons in the cerebral cortex and hippocampus, large neurons in the amygdala, thalamus and hypothalamus, and motor neurons in brain stem and spinal cord.

Hirano Bodies

Hirano bodies are brightly eosinophilic rod-shaped or oval cytoplasmic inclusions (Figure 1). They contain actin, actin-associated proteins, tau, low and middle molecular weight neurofilament subunits, and C-terminal β-amyloid precursor protein epitopes, and consist of a regular lattice of multiple layers of parallel 10–12-nm filaments, a 12-nm gap separating adjacent layers (Hirano, 1994). Filaments in one layer are transversely or diagonally orientated with respect to those in the adjacent layers. Hirano bodies are most numerous in the CA1 field of the hippocampus, particularly in the stratum lacunosum, but can occur elsewhere in the central nervous system (and are occasionally seen in Schwann cells in the peripheral nervous system). In the stratum lacunosum, their density increases until middle age and declines gradually thereafter. There is an increased density of Hirano bodies in the stratum lacunosum in chronic alcoholics (Laas and Hagel, 1994). In normal elderly subjects, Hirano bodies also occur in the stratum pyramidale, where their number continues to increase well into old age, but they are particularly numerous in this region in patients with Alzheimer's disease.

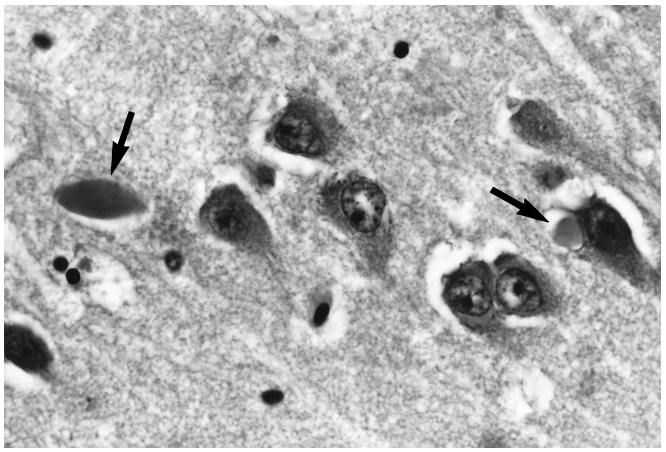


Figure 1 Hirano bodies (arrows) in the pyramidal cell layer of the hippocampus

Granulovacuolar Degeneration

The term "granulovacuolar degeneration" describes the accumulation of small, round, dense bodies, more or less in the center of clear vacuoles, in the neuronal cytoplasm (Figure 2). The dense bodies are ubiquitinated (Love *et al.*, 1988; Dickson *et al.*, 1993) and react with antibodies to some, but not all, epitopes of the microtubule-associated protein, tau (Dickson *et al.*, 1993). These data have been interpreted as suggesting that the dense bodies are a product of partial degradation of tau, which is the main constituent of neurofibrillary tangles. In the absence of Alzheimer's disease, granulovacuolar degeneration rarely occurs to any noticeable extent before the 7th decade but becomes increasingly prominent thereafter (Peress *et al.*, 1973; Xu *et al.*, 1992). Neurons in the CA1 field are most severely affected and, in descending order of severity, those in the prosubiculum, CA2, CA3, and CA4 fields less so (Xu *et al.*, 1992). In normal aging, granulovacuolar degeneration is virtually confined

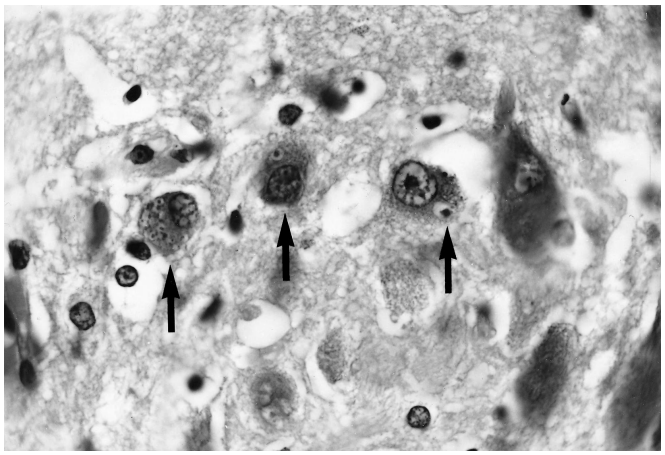


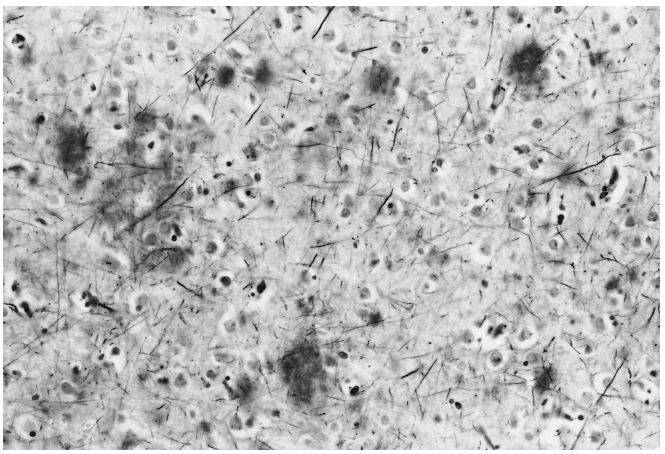
Figure 2 Granulovacuolar generation of several neurons (arrows) in the CA1 field of the hippocampus

to the hippocampal formation. Granulovacuolar degeneration is more severe in patients with Alzheimer's disease and may involve other neurons in a wide range of subcortical nuclei in addition to those in the hippocampus (Xu *et al.*, 1992).

Plaques

The nature and composition of plaques are considered in detail in **Chapter 92, Cellular Changes in Alzheimer's Disease**. The plaques that develop during normal aging, after 55–60 years, are predominantly diffuse (nonneuritic) (Mann *et al.*, 1990; Crystal *et al.*, 1993). They consist largely of nonfibrillar extracellular Aβ peptide, predominantly Aβ_{1-42}. They are readily visualized by silver impregnation or immunohistochemistry for Aβ (Figure 3). Despite the absence or marked paucity of amyloid fibrils in these plaques, they are usually faintly autofluorescent under ultraviolet light in thioflavin-S preparations (although much less so than neuritic plaques).

The diffuse plaques of aging resemble those of Alzheimer's disease in both their chemical composition (see, for example, Fukumoto *et al.*, 1996) and widespread neocortical distribution. They are usually much less abundant than in Alzheimer's disease, but there is overlap in the density of diffuse plaques in patients and cognitively normal elderly people. In the latter group, the plaques rarely involve the striatum or cerebellum, which are often affected in Alzheimer's disease, but plaques can occur in the lateral inferior pulvinar and superior colliculus (Leuba *et al.*, 2001). Although diffuse plaques are a common finding in older age, their accumulation does not seem to be consistent or progressive (Crystal *et al.*, 1993; Mackenzie, 1994). Delaere *et al.* (1993) reported that Aβ deposits were a constant finding in the brains of the "oldest old", based on a study of 20 centenarians. However, even in very old subjects, diffuse plaques may be very scanty or even absent (e.g, Giannakopoulos *et al.*, 1993; Morris *et al.*, 1996).



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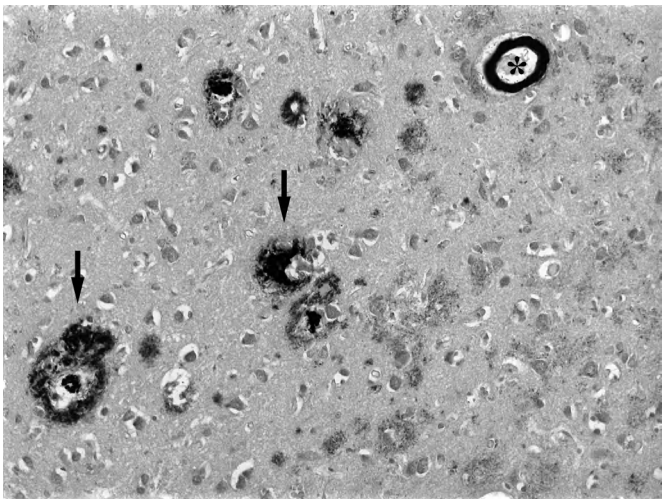
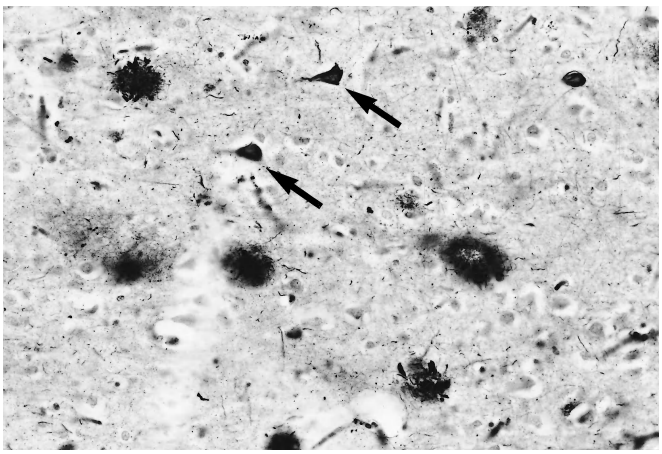


(b)

Figure 3 (a) Diffuse plaques in the superficial cortex (modified Bielschowsky silver impregnation). (b) Immunohistochemistry for Aβ reveals several diffuse plaques (toward right of figure) as well as some densely labeled neuritic plaques (arrows) and a blood vessel with changes of amyloid angiopathy (asterisk)

Neuritic plaques can also occur in cognitively normal elderly subjects, predominantly in the CA1 field, subiculum and entorhinal cortex, and also, in small numbers, in the neocortex. Neuritic plaques are usually much more numerous in the context of Alzheimer's disease (*see* **Chapter 92, Cellular Changes in Alzheimer's Disease**), but the distinction is not clear cut and reports differ as to the extent of overlap (Davis *et al.*, 1999; Leuba *et al.*, 2001; Neuropathology Group. MRC CFAS, 2001). Neuritic plaques contain extracellular Aβ in the form of amyloid fibrils, and irregularly swollen dystrophic neurites, which are strongly argyrophilic (Figure 4). Microglia and astrocyte processes may also be present. Within the dystrophic neurites are accumulations of lysosomes, degenerating mitochondria and membranous bodies. Some dystrophic neurites also contain paired helical filaments, composed of modified tau proteins (see *Neurofibrillary tangles* in following text). Neuritic



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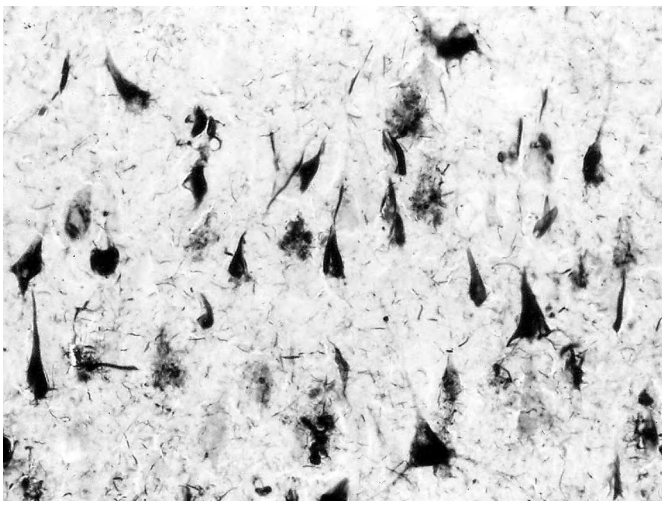


(b)

Figure 4 (a) Neuritic plaques and neurofibrillary tangles (arrows) in the temporal cortex (modified Bielschowsky silver impregnation). Note the swollen, darkly impregnated dystrophic neurites within the plaques (modified Bielschowsky silver impregnation). (b) Neurofibrillary tangles are strongly immunopositive for tau. In this section of hippocampus from a patient with Alzheimer's disease, the antibody also labels many neuropil threads, nerve cell processes that contain abnormal filaments similar to those in the tangles

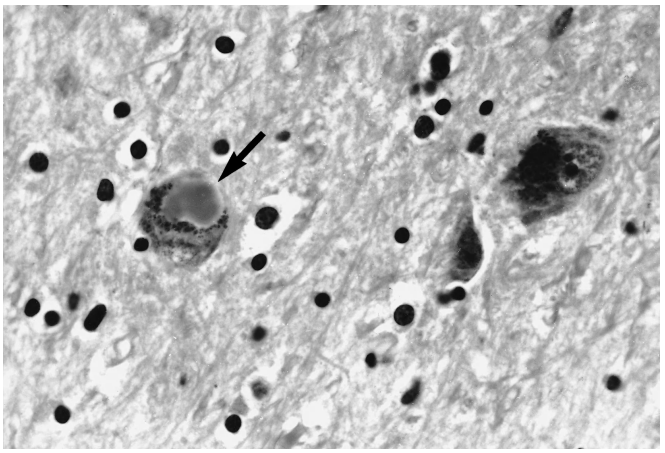
plaques in Alzheimer's disease probably include at least two, usually distinct, types of dystrophic neurite: those containing tau proteins and those that contain the synaptic protein, chromogranin A (Yasuhara *et al.*, 1994; Wang and Munoz, 1995). It has been reported that the tau-positive dystrophic neurites tend to be more elongated, less globular in shape, than those containing chromogranin A, but that the latter predominate in the neuritic plaques that may occur in cognitively normal subjects (Yasuhara *et al.*, 1994).

Neurofibrillary Tangles

Neurofibrillary tangles consist of hyperphosphorylated tau proteins that are variably ubiquitinated and glycated (Brion *et al.*, 1985; Mori *et al.*, 1987; Love *et al.*, 1988; Yan *et al.*, 1995; Yen *et al.*, 1995). These form filaments measuring up to 10 nm in diameter, paired in right-handed helices with a period of approximately 80 nm and a maximum width of approximately 20 nm (Terry, 1963; Kidd, 1964; Ruben *et al.*, 1993). The filaments are aggregated together in the cytoplasm in looped or twisted skeins that are faintly basophilic, appear autofluorescent when stained with thioflavin-S and viewed under ultraviolet light, and can be impregnated with silver or immunostained for tau to facilitate their light microscopic detection (Figure 4). Although the frequency of neurofibrillary tangles tends to increase with age after 55–60 years (Tomlinson *et al.*, 1968; Peress *et al.*, 1973; Price *et al.*, 1991; Arriagada *et al.*, 1992; Hof *et al.*, 1995; Davis *et al.*, 1999), they are not a consistent feature of normal aging and are much more numerous and widely distributed in Alzheimer's disease and certain other neurological disorders (e.g. Wisniewski *et al.*, 1979; Love *et al.*, 1995; Spillantini *et al.*, 1999). When present in cognitively normal elderly individuals, tangles may be confined to the transentorhinal cortex or may also involve the subiculum and CA1 field of the hippocampus, lamina II and, to a lesser extent IV, of the entorhinal cortex (in the anterior part of the parahippocampal gyrus) and the anterior olfactory nucleus (Price *et al.*, 1991; Braak and Braak, 1991; Arriagada *et al.*, 1992; Hof *et al.*, 1995; Braak and Braak, 1996). In the absence of dementia, the neocortex and subcortical nuclei contain few, if any, neurofibrillary tangles (although in one study, some degree of neocortical neurofibrillary pathology was found in as many as one-third of nondemented elderly individuals (Neuropathology Group, MRC CFAS, 2001)). The involvement of different populations of neurons by neurofibrillary tangles seems to follow a consistent, predictable topographic sequence during "normal" aging that is indistinguishable from the earliest, presymptomatic stages of Alzheimer's disease (Braak and Braak, 1991; Arriagada *et al.*, 1992; Braak and Braak, 1996). It is arguable that the asymptomatic accumulation of neurofibrillary tangles in the transentorhinal cortex and limbic region should be regarded as a preclinical manifestation of Alzheimer's disease (for further discussion, see Braak and Braak (1996)).

Lewy Bodies

The structure and patterns of distribution of these neuronal inclusions are described in the context of Parkinson's disease and other Lewy body diseases in **Chapter 66, Parkinson's Disease and Parkinsonism in the Elderly** and **Chapter 96, Other Dementias**. Lewy bodies are an incidental finding in the substantia nigra and locus ceruleus in a small proportion of neurologically normal adults. These Lewy bodies are of the classical (brain stem) type: usually roughly spherical, with an eosinophilic core surrounded by a paler "halo" (Figure 5). One or more Lewy bodies may be present in the cytoplasm of a single neuron. Electron microscopy shows the core to consist of amorphous, electron-dense material and the halo to comprise



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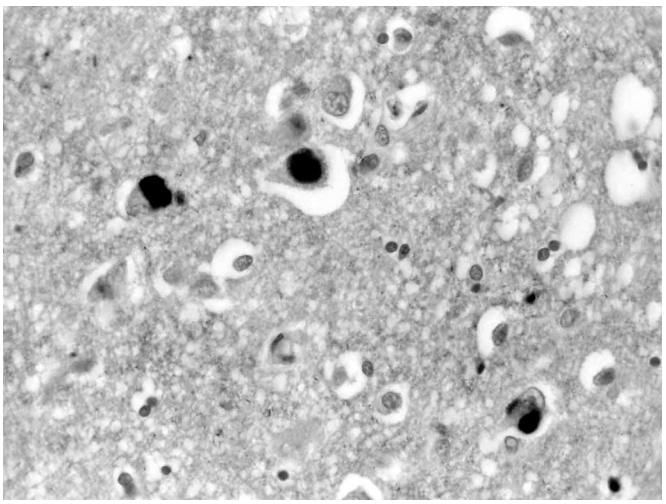


(b)

Figure 5 (a) Incidental Lewy body (arrow) in the substantia nigra of an 84-year-old man who did not have clinical features of Parkinson's disease. (b) The principal constituent of the Lewy body is α-synuclein, here demonstrated immunohistochemically in Lewy bodies in the cerebral cortex

radiating filaments between which are scattered granules of lipofuscin and neuromelanin, mitochondria, dense-core vesicles, and other organelles (Forno, 1996). The principal constituent of the Lewy body is α-synuclein (Spillantini *et al.*, 1997; Wakabayashi *et al.*, 1997), a protein that is normally associated with presynaptic vesicles (Iwai *et al.*, 1995). Its functions are still unclear, but may include protection against oxidative stress, maintenance of the presynaptic vesicular pool, and a role in synaptic plasticity (Hashimoto *et al.*, 2002; Kaplan *et al.*, 2003; Murphy *et al.*, 2000). Other constituents of the Lewy body include phosphorylated neurofilament subunits (Hill *et al.*, 1991), ubiquitin (Love *et al.*, 1988), epitopes of complement proteins (Yamada *et al.*, 1992), multicatalytic proteinase (Masaki *et al.*, 1994), cyclin-dependent kinase 5 (Brion and Couck, 1995), and several other proteins (for review, see Pollanen *et al.*, 1993).

Lewy bodies occur in Parkinson's disease, dementia with Lewy bodies, and other Lewy body diseases (*see* **Chapter 96, Other Dementias** (Lewy Body etc.)). The prevalence of brain stem Lewy bodies is much lower in adults who do not have neurological disease. Perry *et al.* (1990) observed Lewy bodies in 2.3% of 131 subjects between 51 and 100 years who had been screened to exclude neurological or psychiatric disorders. In a series of 273 brains from non-Parkinsonian patients, Gibb and Lees (1988) found the prevalence to increase from 3.8 to 12.8% between the sixth and ninth decades. A lower age-specific prevalence was reported by Wakabayashi *et al.* (1993): an increase from 0.7% to 6.5% over the same age span. It has been suggested that incidental Lewy bodies are a manifestation of preclinical Parkinson's disease (Gibb and Lees, 1988; Wakabayashi *et al.*, 1993).

CENTRAL WHITE MATTER

As noted earlier (see *Brain weight*), with increasing age, the white matter declines in volume to a greater extent than does the gray matter, although the two processes are obviously related since the degeneration of a nerve cell is accompanied by the loss of its myelinated axon, and the latter usually occupies a greater volume than the cell body and dendrites. In a morphometric comparison of three groups of neurologically normal adults, $\leq$50 years, 51–70 years, and 71–93 years, Meier-Ruge *et al.* (1992) found a 16–20% loss of white matter volume in the elderly compared with the young adults and a 10–15% loss of myelinated fibers. In a stereological study of changes in cranial white matter between 18 and 93 years, males were found to have a total myelinated fiber length of 176 000 km at 20 years and 97 200 km at the age of 80 (Marner *et al.*, 2003). In females, the lengths were 149 000 km at 20 and 82 000 km at 80 years. These figures correspond to a decrease of 10% per decade, and a sex difference of 16%. The loss predominantly affects small caliber fibers. Other age-related changes in the white matter include a tendency for axons in some regions to form dystrophic swellings, and an accumulation of ubiquitinated dotlike structures (see *Dystrophic axons and ubiquitinated deposits*, explained previously).

In many neurologically normal, elderly subjects, scattered hyperintensities and more diffuse high signal regions are demonstrable in the cerebral white matter on T2-weighted MRI, particularly in the periventricular region. The histological correlates of these "lesions" are somewhat inconsistent. Some are probably infarcts; others are foci of rarefaction or gliosis, often perivascular. Correlations have been described with denudation of the ependymal lining of the lateral ventricles (Scheltens *et al.*, 1995) and perivenous collagenous thickening (Moody *et al.*, 1995). The substrate of some MRI hyperintensities may remain obscure despite careful histological examination (Grafton *et al.*, 1991).

SPINAL CORD AND NERVE ROOTS

The degenerative changes of the spinal column, such as cervical spondylosis and intervertebral disk disease which become increasingly frequent and pronounced with age, are often associated with degenerative changes in the spinal cord. These include anteroposterior flattening of the lower cervical cord and various degrees of loss of neurons from the anterior horn (Wang *et al.*, 1999). Degeneration of posterior column fibers, particularly in the cervical region, is common in the elderly (Ohnishi *et al.*, 1976), and often accompanied by large numbers of copora amylacea (see following text). A morphometric study by Low *et al.* (1977) of the intermediolateral column of the spinal cord in adults, revealed a progressive loss of preganglionic sympathetic neurons with age, amounting to about 8% per decade. A similar rate of attrition of myelinated fibers was noted in the T6–8 rami communicantes, containing the preganglionic sympathetic nerve fibers (Low and Dyck, 1978). The authors suggested that this loss may account for the tendency to postural hypotension in the elderly. It should be noted, however, that there are also alterations in the paravertebral and prevertebral sympathetic ganglia of elderly subjects (see *Sympathetic ganglia*, in the following text). The population of motor neurons in the lumbosacral spinal cord declines slightly with age. Tomlinson and Irving (1977) found that the decline occurred only after 60 years of age but Kawamura *et al.* (1977a) recorded a gradual loss of motor neurons in the L3–5 segments from early adulthood onwards. Not surprisingly, the latter authors also found that there was a corresponding age-related loss of myelinated fibers from the L3–5 anterior spinal nerve roots (Kawamura *et al.*, 1977b).

GLIOSIS

The number of astrocytes and the extent of associated gliosis have generally been thought to increase with age in most parts of the central nervous system. Beach *et al.* (1989) assessed the severity of gliosis at different ages by immunostaining sections for glial fibrillary acidic protein (GFAP). They found that gliosis increased with age in the cerebral cortex, white matter, and subcortical nuclei, but that its severity and distribution were very variable. Whereas the white matter of young adults showed an even pattern of GFAP immunoreactivity, that in the elderly tended to be uneven. Gliosis was accentuated around blood vessels. Terry *et al.* (1987) reported that the increase in the number of glia in the elderly was more pronounced in the frontal and temporal cortices than in the parietal cortex. In contrast to these older studies, more recent stereological analysis of neocortical cells by Pakkenberg *et al.* (2003) revealed no significant difference when the number of neocortical glia in six elderly individuals, of mean age 89.2 years, was compared with that in six young adults with a mean age of 26.2 years.

CORPORA AMYLACEA

Corpora amylacea are spherical inclusions, predominantly located in astrocyte processes, although they can also occur within axons. They are composed largely of sulphated polysaccharides (polyglucosans) and stain deeply with hematoxylin, periodic acid-Schiff and methyl violet. Minor constituents include ubiquitin, heat-shock proteins (Martin *et al.*, 1991; Cisse *et al.*, 1993), tau (Loeffler *et al.*, 1993; Singhrao *et al.*, 1993), certain complement proteins (Singhrao *et al.*, 1995), and oligodendrocyte proteins – myelin basic protein, proteolipid protein, galactocerebroside, and myelin oligodendrocyte protein (Singhrao *et al.*, 1994). On electron microscopy, corpora amylacea appear as densely packed 6–7-nm filaments that are not bounded by a unit membrane (Ramsay, 1965). Toward the center of the inclusions, the filaments may be admixed with amorphous granular material.

Corpora amylacea increase in number with normal aging, particularly in the subpial and subependymal regions of the brain (Figure 6), around blood vessels, and in the white matter of the spinal cord (Martin *et al.*, 1991), although not to the extent that they do in Alzheimer's disease and other neurodegenerative disorders. The subpial region of the inferomedial part of the temporal lobe is a site of predilection for accumulation of these bodies. Several hypotheses have been proposed to account for their formation and distribution. It was suggested by Tokutake *et al.* (1995) that they are involved in astrocytic absorption and accumulation of inorganic materials from the blood and cerebrospinal fluid, by Cisse and Schipper (1995) that they are a product of degeneration and autophagy of mitochondria, and by Singhrao *et al.* (1995) that they may shield immunogenic products of neuronal and oligodendroglial degeneration from lymphocytic recognition and autoimmune activation.

BLOOD VESSELS AND AMYLOID ANGIOPATHY

The development of atherosclerotic and hypertensive changes and their relationship to brain hemorrhages and infarcts

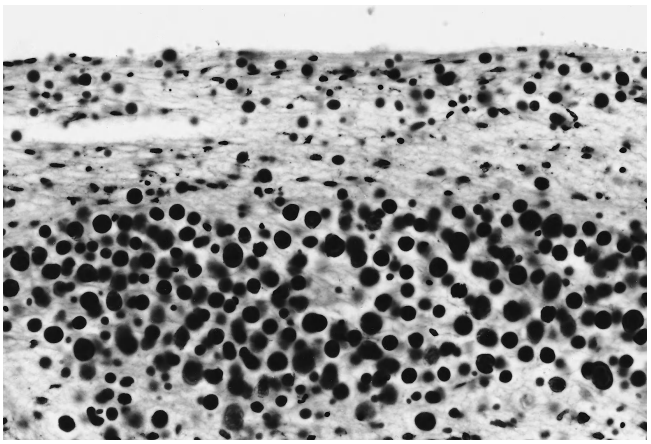
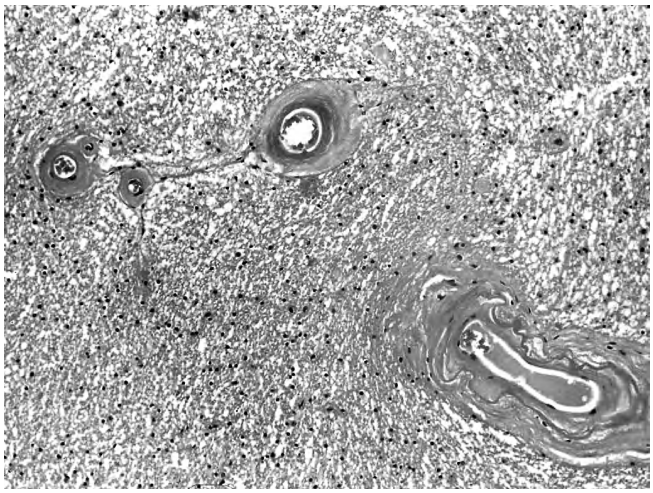


Figure 6 Numerous periventricular corpora amylacea in an 87 year old



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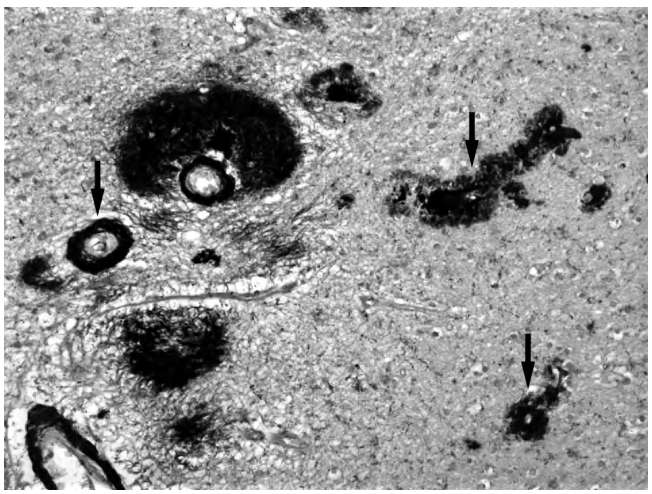

(b)

Figure 7 (a) Degenerative change affecting arteries and arterioles in the cerebral white matter. The tunical media and adventitia have been replaced by a thick layer of hyaline collagenous connective tissue. There is also some fibrous thickening of the intima. (b) Severe CAA, in which Aβ-immunopositive amyloid has replaced the tunica media and adventitia of several blood vessels in the cerebral cortex, and in some cases has also infiltrated the adjacent brain parenchyma. Note the narrowed lumen of some of the affected blood vessels (arrows)

are considered in **Chapter 71, Acute Stroke** and **Chapter 72, Secondary Stroke**. In the elderly, mild loss of smooth muscle cells, medial fibrosis, and hyaline change are very common in parenchymal blood vessels in the brain and spinal cord, particularly in the basal ganglia and cerebral white matter (Hauw *et al.*, 2002) (Figure 7a). Mineralization of vessel walls is also common, especially in the globus pallidus and deep cerebellar white matter. The smooth muscle degeneration and fibrosis are exacerbated in patients with hypertension (Masawa *et al.*, 1994). A mild degree of cerebral atheroma is also common, even in the absence of hypertension and other specific risk factors such as cigarette smoking and diabetes mellitus (*see* **Chapter 122, Type 2 Diabetes Mellitus in Senior Citizens**; **Chapter 48, Hypertension**). These changes decrease the compliance of cerebral blood vessels and probably contribute to an increased tendency to tortuosity or "corkscrewing" (Fang, 1976) and an enlargement of the perivascular spaces.

Many elderly people have patchy, segmental deposition of amyloid in the media and adventitia of blood vessels in the cerebral cortex and leptomeninges (Figures 3b and 7b). This abnormality is termed *cerebral amyloid angiopathy* (CAA), although it is not always confined to the cerebrum and may also involve the cerebellar cortex and leptomeninges, and rarely other parts of the central nervous system (CNS). CAA is present in about 30% of the normal elderly (Tomonaga, 1981; Esiri and Wilcock, 1986; Vinters and Gilbert, 1983; Love *et al.*, 2003), and over 90% of patients with Alzheimer's disease (Esiri and Wilcock, 1986; Ellis *et al.*, 1996; Premkumar *et al.*, 1996; Chalmers *et al.*, 2003), in whom the CAA tends to also be more severe – involving a greater proportion of blood vessels, over a greater part of their circumference, and sometimes extending into the adjacent brain parenchyma (so-called *dyshoric change*). In contrast to the predominance of Aβ_{1-42} in plaques, Aβ_{1-40} predominates in CAA although Aβ_{1-42} is also present. Sporadic Aβ-related CAA is very rare before 60 years, but thereafter increases in prevalence with age (Love *et al.*, 2003). The pathogenesis of CAA remains unclear. Some observations suggest that Aβ is deposited from interstitial fluid as it passes along perivascular drainage pathways toward the subarachnoid space (Weller *et al.*, 2000; Weller and Nicoll, 2003); degenerative vascular changes that impede the flow of fluid along these pathways may partly account for the increased prevalence of CAA with age. However, it is likely that multiple factors contribute to development of CAA (Love, 2004).

The deposition of amyloid progressively replaces, first the tunica media, and then the adventitia, with resulting loss of vascular compliance and contractility. In severe cases, the amyloid extends into the adjacent brain parenchyma (Figure 7b). CAA tends to narrow the lumen, because of thickening of the vessel wall, exacerbated in some cases by concentric separation of the amyloid-laden media and adventitia. Severe CAA may compromise the viability of affected blood vessels (Prior *et al.*, 1996). Not surprisingly, therefore, CAA carries a risk of focal hemorrhage or infarction (Okazaki *et al.*, 1979; Itoh *et al.*, 1993; Cadavid *et al.*, 2000). As would be expected from the distribution of the vascular amyloid, associated hemorrhages tend to be superficially situated within the brain parenchyma and to rupture into the subarachnoid space, or to occur primarily within the subarachnoid space (Okazaki *et al.*, 1979; Yamada *et al.*, 1993). CAA may also cause ischemic damage to the white matter, probably through a combination of luminal stenosis, thrombosis, loss of autoregulation, and vasospasm.

APOE genotype is linked to several aspects of CAA pathology. In Alzheimer's disease, the presence and severity of CAA are strongly associated with possession of *APOE* ε4 (Premkumar *et al.*, 1996; Chalmers *et al.*, 2003). In the absence of Alzheimer's disease, this association is weak or absent (Love *et al.*, 2003). In patients with CAA, possession

of *APOE* $\varepsilon 2$ is a risk factor for cerebral hemorrhage (Greenberg *et al.*, 1998; Nicoll *et al.*, 1997), probably because this allele is associated with the development of additional vasculopathic changes such as fibrinoid necrosis (Greenberg *et al.*, 1998; McCarron *et al.*, 1999). *APOE* $\varepsilon 4$ has been reported to be associated with cerebral hemorrhage in patients with CAA in some populations (Greenberg *et al.*, 1995) but not others (Itoh *et al.*, 1996; Nicoll *et al.*, 1997). However, interpretation of this latter association is complicated by the fact that possession of $\varepsilon 4$ is also associated with increased mortality after cerebral hemorrhage (McCarron *et al.*, 2003); series that are based largely on postmortem diagnosis of CAA-associated hemorrhage are therefore likely to be skewed toward the inclusion of $\varepsilon 4$-positive cases.

CHOROID PLEXUS

Intracellular accumulations of amyloid fibrils are a constant finding in choroid plexus epithelium in the elderly (Eriksson and Westermark, 1986). They are usually abundant in Alzheimer's disease (Miklossy *et al.*, 1998; Wen *et al.*, 1999). The fibrils form circular cytoplasmic inclusions (Figure 8) known as *Biondi rings* (Biondi, 1934; Eriksson and Westermark, 1990). Ependymal cells may also accumulate amyloid fibrils, but these take the form of slender wisps rather than rings. Ultrastructurally, Biondi rings consist of densely packed straight and paired helical filaments (Eriksson and Westermark, 1986; Miklossy *et al.*, 1998; Wen *et al.*, 1999). They are immunopositive for Aβ. Miklossy *et al.* (1998) found them also to react with antibodies to P component, ubiquitin, fibronectin and tau but not neurofilament proteins.

With age, the choroid plexus tends to undergo multifocal mineralization, in the form of roughly spherical, concentrically laminated deposits known as *psammoma bodies* (Figure 9). These usually form in the fibrovascular cores of the papillae. Kwak *et al.* (1988) found that the age-specific prevalence of choroid plexus mineralization in CT brain scans increased from 0 below 10 years, through 5.9% between 10 and 14 years, 17.4% between 15 and 19 years, 51.5% between 30 and 39 years, to 74.4% in patients over 80 years in age.

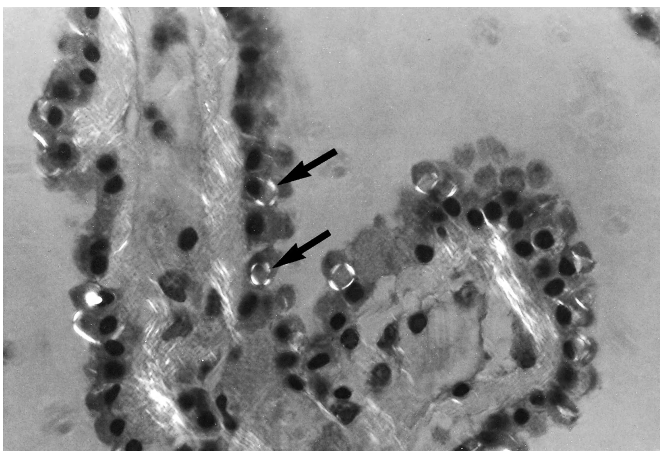

Figure 8 Several birefringent Biondi rings (arrows) in the choroid plexus of an 84 year old

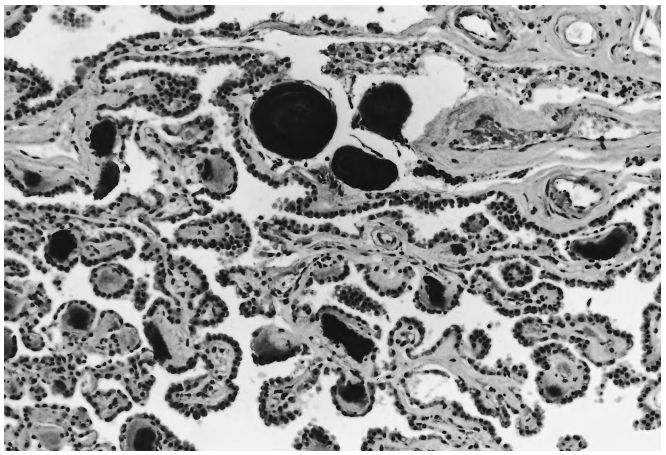

Figure 9 Darkly stained psammoma bodies in the choroid plexus

PINEAL

During adolescence and early adulthood, the pineal may undergo cystic expansion. On review of MRI scans of 6023 subjects, Sawamura *et al.* (1995) found that pineal cysts were more common in women, in whom the prevalence was greatest (5.8%) between the ages of 21 and 30 years. The finding of cysts is less common in subsequent decades, reported figures for their overall prevalence ranging from 1.3% (Sawamura *et al.*, 1995) to 2.4% (Golzarian *et al.*, 1993). The cysts are usually incidental findings on radiological investigation or at autopsy. Rarely, they may compress the aqueduct and cause hydrocephalus, or produce Parinaud's syndrome due to compression of the tectum of the midbrain (Fetell *et al.*, 1991).

Foci of mineralization (corresponding histologically to psammoma bodies) are radiologically detectable in a small percentage of children as early as the first 6 years of life (Winkler and Helmke, 1987). There is a steep rise in the incidence of pineal mineralization during the second decade of life after which the deposits may undergo remodeling (Schmid and Raykhtsaum, 1995), but there is no further significant change in their size or age-specific prevalence (Hasegawa *et al.*, 1987; Galliani *et al.*, 1989).

PITUITARY

The effects of aging on hypothalamo-pituitary function are discussed in **Chapter 119, The Pituitary Gland**. A mild degree of fibrosis, due to interstitial deposition of collagen, is common in the anterior lobe of the pituitary in the elderly,

particularly in men (Sano *et al.*, 1993). From early adulthood onwards, there is also a significant decline in the number and size of growth hormone-producing somatotroph cells in the lateral wings of the gland (Sun *et al.*, 1984; Sano *et al.*, 1993). Sano *et al.* (1993) did not find significant alterations in the relative numbers of other cell types in pituitaries of patients over 90 years of age. Zegarelli-Schmidt *et al.* (1985) observed thyrotroph hypertrophy and hyperplasia in some aged pituitaries but these changes bore no consistent relationship to the histological appearances of the thyroid gland in the same patients.

Small intracellular and interstitial accumulations of endocrine-type amyloid may be found in the normal pituitary from the third decade onwards (Tashima *et al.*, 1988). These become more numerous with increasing age and can be found in about two thirds of pituitaries in the elderly (Tashima *et al.*, 1988; Bohl *et al.*, 1991). Similar age-related intracellular and interstitial accumulations of amyloid occur in other endocrine glands, including the adrenals and parathyroid glands (Bohl *et al.*, 1991).

PERIPHERAL NERVE

Jacobs and Love (1985) found little change in the total number of myelinated and unmyelinated nerve fibers in the sural nerve from childhood through middle age. Over the same period, there is, however, a gradual decline in the densities of myelinated and unmyelinated nerve fibers in the sural nerve (and other peripheral nerves that have been studied) as the amount of endoneurial collagen and the separation between adjacent nerve fibers increase (Ochoa and Mair, 1969a,b; Tohgi *et al.*, 1977; Jacobs and Love, 1985). After 60 years, both the density and the absolute number of fibers tend to decrease, mild to moderate degeneration of myelinated and unmyelinated fibers becomes increasingly common and a small proportion of fibers shows changes of segmental demyelination and remyelination. The degeneration of myelinated fibers is accompanied by a variable amount of regenerative activity. These changes affect the relationship between the axon calibre and the myelin sheath thickness (*g* ratio), which is much more variable in old age than in younger age. Also affected is the normally linear relationship between internodal length and fiber diameter. The demyelination and remyelination causes marked variation in the internodal length along individual fibers, and the degeneration and regeneration produces relatively large fibers with long sequences of uniformly short internodes, 300–400 μm in length. Other findings in peripheral nerves of the elderly include a tendency to reduplication of endoneurial vascular basement membranes and some thickening of the basement membrane in the outer layers of the perineurial sheath (Jacobs and Love, 1985).

SYMPATHETIC GANGLIA

Lipofuscin can be identified within sympathetic neurons as early as at 4 months of age (Koistinaho *et al.*, 1986), and the amount increases steadily throughout life (Helen, 1983; Hervonen *et al.*, 1986; Koistinaho *et al.*, 1986). Hervonen and colleagues noted that the autofluorescent color of the lipofuscin under ultraviolet light changed from yellow to orange with increasing age, possibly due to the accumulation of neuromelanin in the noradrenergic neurons (Hervonen *et al.*, 1986; Koistinaho *et al.*, 1986). Another feature of aging in sympathetic ganglia is an increasing prominence of dystrophic preterminal axons (Schmidt *et al.*, 1990; Schroer *et al.*, 1992; Schmidt, 2002). These develop at an earlier age in patients with diabetes mellitus (Schroer *et al.*, 1992). The swollen argyrophilic axons tend to cluster around scattered nerve cells, which may be indented by the swellings. They are more numerous in the celiac and other prevertebral ganglia than in paravertebral ganglia such as the stellate ganglion. Schmidt *et al.* (1990) found that the dystrophic axons could be labelled with antibodies to tyrosine hydroxylase and neuropeptide tyrosine (NPY), but not other neuropeptides (vasoactive intestinal peptide (VIP), substance P, gastrin-releasing peptide/bombesin or met-enkephalin). Other age-related changes that have been noted in the sympathetic ganglia include a reduction in the number of neurons innervated by enkephalin-immunoreactive nerve fibers (Jarvi *et al.*, 1988) and, with the accumulation of lipofuscin, a decrease in the quantity of catecholamines in the neuronal perikarya (Hervonen *et al.*, 1978).

KEY POINTS

- Age is associated with progressive brain atrophy, much of which is due to loss of white matter.
- The extent of neuronal loss varies in different parts of the brain and spinal cord.
- Plaques, neurofibrillary tangles and Lewy bodies can occur in neurologically normal people but are much more numerous and extensive in Alzheimer's disease and Lewy body diseases.
- Other age-related changes include granulovacuolar degeneration and the formation of Hirano bodies in the hippocampus; dystrophy of axons in the posterior column and anterior horn of the spinal cord, in the substantia nigra and globus pallidus; accumulation of corpora amylacea; and development of cerebral amyloid angiopathy.
- Amyloid fibrils in the choroid plexus and ependymal cells are a constant finding in the elderly.

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PART II

Human Aging: Social and Community Perspectives

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9

The Demography of Aging

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INTRODUCTION

We examine several dimensions of past, current, and future demographic changes and the health dynamics of aging in the United States and other developed countries. Models of the demographic and health dynamics of elderly and oldest-old populations require updating as information about the characteristics of those populations accumulates from (a) demographic sources (e.g. population censuses and vital statistics), (b) specialized longitudinal surveys of elderly populations, (c) epidemiological and clinical studies of elderly subgroups, and (d) by integrating multiple data sources in comprehensive models of health, aging, and mortality (Manton *et al.*, 1994b). This later approach will increase in importance with time as the linkage of biomolecular mechanisms with population dynamics becomes increasingly important in assessing the macro/population influences of accumulated knowledge from epidemiological, clinical, and basic science studies. This is neither meta-analysis (statistical study of multiple clinical data sets) nor bioinformatics (analyses of laboratory studies to find common patterns). It is a new scientific discipline born of the mathematical integration of medicine, mathematics, and biodemography. When populations are successfully modeled at micro (biomolecular), meso (organ systems and individuals), and macro (population) levels the models can be applied to economic and policy studies – in both government and commercial service (to optimize the effects of medicine and medical research on population health). To understand how these models will evolve we start with a discussion of the application of basic demographic techniques.

Probably the most basic view of the demography of aging is that a trio of forces, each driven by multiple social and physiological processes, determines the current and future growth of the elderly and oldest-old populations in the United States and other developed countries. Two of these are the larger size of recent birth cohorts who will become the elderly in the near future, and decreases in mortality at earlier ages allowing larger proportions of birth cohorts to survive to ages 65+. The third factor, discussed separately, is mortality declines at late ages, and their age variable relation to, and interaction with, changes in health and functioning.

The first two forces are now well understood – though their magnitude is not appreciated. In the United States (as elsewhere), the oldest-old (85+) population in 2005 is composed of persons born in 1920 – or earlier. From the 1920 US birth cohort, 18.6% of males and 35.1% of females, or 796 100 persons, are expected to reach age 85. Since life expectancy (LE) at age 85 for this cohort is roughly 5.3 (males) to 6.6 (females) years, this implies a US population aged 85+ in 2005 of 4.9 million persons.

The largest US baby boom cohort (1961) was 4.3 million persons. If 1920 male and female survival rates were applied to the 1961 birth cohort, then 1 154 550 persons would survive to 85 – or 45% more persons than from the smaller 1920 birth cohort. US survival improved from 1920 to 1960. Of persons born in 1960, 34.4% of males and 49.9% of females are expected to reach 85. Applying these proportions to the 1961 birth cohort implies 1 812 450 persons would reach 85 – an increase of 57.0% over the number surviving to 85 from the 1961 birth cohort than if 1920 mortality rates had not changed. Increased birth cohort size and reduced early mortality increases the number of persons passing 85 by 127.7%.

If all cohorts were similar in size, these two forces would imply (assuming life expectancy at 85 increases to 7.5 years) 13.5 million persons aged 85+ – increases of 2.7 million persons due to larger cohort sizes and 5.9 million due to mortality declines. This increase would take 42+ years to realize, that is, the birth cohort of 1961 passes 85 in the year 2046. These simple calculations, using actuarial survival statistics and population counts, gives a sense of the relative contributions of birth cohort size and improved early mortality to increases in the size of future elderly populations. Uncertainty about exact changes in the size and composition of the elderly population is largely due to uncertainty about mortality declines at late ages. Some projections envision larger populations reaching ages 85+,

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for example, 40+ million persons might reach ages 85+ in 2050 if significant progress in improving known risk factors is assumed (Manton *et al.*, 1994b).

Thus, if US social, economic, and health conditions remain stable, the potential for large increases in the elderly and oldest-old population exists in the birth cohorts comprising the current US population and their early health and mortality experiences. Looking at the situation in reverse, the elderly and oldest-old populations currently being examined epidemiologically, clinically, and physiologically come from cohorts born long ago (e.g. in 1915, pre-WWI (World War I), and 1930, the beginning of the great depression), which were relatively small at birth, and which experienced what today would be extraordinary, and excessive, mortality risks and adverse early health experiences (e.g. exposures to many childhood diseases which are now prevented by vaccination, or for which there are effective medical treatments; for many European countries, there are also the effects of injuries suffered by combatant males in WWI and WWII).

This brings us to the third force, that is, mortality experienced at late ages (e.g. ages 85, 95, and 100+) and antecedent health conditions. Late age mortality interacts with antecedent health and disability conditions (e.g. by mortality selection) which have dramatically changed across current elderly, and near elderly, cohorts. An understanding of the demography of aging requires appreciating the health dynamics, current and historical, characterizing cohorts forming the elderly population.

MODELS OF CHRONIC DISEASE AND MORTALITY TRENDS

The idea that mortality, and other age-related health conditions, are mutable to late ages (i.e. age 85+) is relatively new (Lakatta, 1985). The idea that function can be regenerated, and the physiological clock run backwards, is even newer, although for open physical systems the possibility was identified by Prigogine and Stengers (1997). In the United States, mortality was thought to have reached irreducible levels by the late 1950s or early 1960s because male survival decreased in that period – though female survival continued to improve. Social Security actuaries assumed ultimate life expectancy limits would be reached in the United States in 2000 in Social Security Trust fund projections made in 1974. In 2001, the life expectancies of 74.6 and 80.0 years, for males and females respectively, were already 5.0 years and 2.9 years above this "ultimate" limit to life expectancy.

In Table 1, we present data (CIA, Central Intelligence Agency, Fact book http://www.cia.gov/cia/publications/factbook/) on total, male, and female life expectancy in 2004.

For the small country of Andorra, the total life expectancy of 83.5, and the female life expectancy of 86.7 years, causes one to think the ultimate limit to life expectancy of 85 years posited by Olshansky and Fries is too low. The female life expectancy of 84.5 years in Japan, and the total life expectancy of 81.0 years also suggests one be skeptical about "ultimate" life span limit estimates.

Other authors suggested US stagnant male mortality conditions 1954–1968 reflected increased chronic disease risks due to the nature of industrial societies. Antonovsky discussed why risks might be elevated for cardiovascular diseases. Omran posited a model of the stages of the epidemiological transition of which the third, and end, stage characterized economically developed societies as having a high prevalence of chronic degenerative and manmade diseases with static life expectancy. Much of this pessimism was due, however, to congenital disorders, like Down's syndrome, where life expectancy could increase past reproductive ages generating a "pandemic," or cascade, of chronic degenerative disease.

Many demographers generate model life tables to describe mortality and in estimating life expectancy "limits". Bourgeois-Pichat projected a maximum life expectancy of 73.8 years for males, and 80.3 years for females, in 1978. A 1982 study of the Japanese economy used life expectancy limits of 79.8 years for males (not yet achieved) and 80.7 years for females. Japanese life expectancy at birth, among the world's highest in 2004 (see Table 1), far exceeded limits assumed for females in 1982. In France, life expectancy in 2004 was 75.8 years for males and 83.3 years for females – exceeding Bourgeois-Pichat's 1978 estimate of a female life expectancy limit by 3.0 years.

Swedish data have been used to model late age mortality because of its high quality. Because vital statistic systems have now been computerized in many developed countries, for many years the Swedish data no longer have special status as the basis for "curve fitting" models to apply to other countries.

Life expectancy limits estimated only from total and cause specific mortality trends were problematic (Manton *et al.*, 1991). New models incorporating health data and biological mechanisms are necessary for forecasts (Manton, 2004a).

Table 1 Life expectancy for selected industrialized countries (2004)

Country		Japan	Andorra[a]	Germany	France	Sweden	Canada	United States
Population (Millions)		127	0.1	82	60	9	33	293
Life expectancy	Total	81	83.5	78.5	79.4	80.3	80	77.4
at birth	Male	77.7	80.6	75.6	75.8	78.1	76.6	74.6
(years)	Female	84.5	86.6	81.7	83.3	82.8	83.5	80.4

[a]Highest life expectancy in 2004 C.I.A. Fact book.

Analyses of mortality to late ages suggest why human life expectancy limits are difficult to estimate. First, human life spans are long (e.g. it will take 120 to 130 years for a recent, large birth cohort to die out at current mortality levels in Japan, France, and other developed countries (Manton and Stallard, 1996)), making it difficult to get reliable data on the full mortality experience of a birth cohort (let alone for multiple birth cohorts). Second, human populations are free living and cannot be studied in experimentally controlled environments. Hence, the proportion of human life expectancy potential realized in any population is a smaller, and less certain, proportion of their biological potential than can be observed in animal models in experimental conditions (Carey *et al.*, 1992). Third, for much of human history, fertility was a more dynamic factor controlling population growth, and shaping population structure, than mortality. Thus, after large increases in US life expectancy at birth from 1900 to 1950 (i.e. from 47.3 years in 1900 to 68.2 years in 1950, an increase of 20.9 years or 0.42 years of life per calendar year) the rate of increase in life expectancy at birth slowed (e.g. from 68.2 to 70.8 years for 1950 to 1970, or 0.13 years of age increase per calendar year). From 1970 to 2000, life expectancy increased from 70.8 to 77.0 (6.2 years), or 0.21 years per calendar year (a 50% acceleration over the 1950 to 1970 period), with recent increases accelerating owing to declines in cancer mortality.

For certain periods, US male life expectancy declined. From 1954 to 1968, male mortality rates increased 0.2% per year; they declined 0.8% per year for females. From 1970 to 2001, life expectancy at age 65 for males and females combined increased (i.e. from 15.2 years in 1970 to 18.1 years in 2001, or 0.1 years of age per calendar year) and represented a larger proportion (45%) of the gain in life expectancy at birth (6.4 years) than before 1970. Gains were, in part, achieved by reducing mortality in "uncharted" territory, that is, ages 85+. The first well-documented reports of centenarians occurred about 1800. The first reliably documented report of a survivor to 110 (a "super" centenarian) was in 1931. The first documented survivor to 120 (eventually dying at age 122 years) was recorded in 1995. It may be that a 130 year old is alive but not yet discovered.

For the last 30 years, the centenarian population in the United States and several other developed countries (Manton and Stallard, 1996) has grown 7% per year. As higher proportions of larger, more recent birth cohorts survive to late ages, reductions in mortality at those ages will contribute proportionately more to life expectancy gains. In response, we redesigned the 1994, 1999, and now 2004 NLTCS (National Long Term Care Survey) to have over samples (540, 600, and ∼1600 cases respectively) at ages 95+ to have adequate precision to study both health care use and the biological processes determining health and mortality at advanced ages.

What we observed about health changes in the 1982 to 1999 NLTCS was remarkable – and contrary to most models of human aging. In Figure 1(a) and (b), we show changes in (a) life expectancy and (b) active life expectancy (ALE) (i.e. period lived free of serious disabilities (Manton, 2004a)) in 1982 and 1999.

The change in life expectancy was 4.5 years. The change in ALE was 3.8 years. Thus, most (84%) of the gain in life expectancy was in healthy years of life. In Figure 2, we look at the acceleration of the improvement of functioning from age 65 to 100.

In Figure 2, we can examine rates of change in the difference between ALE and LE in 1982 and 1999. We see that differences between LE and ALE were similar in 1982 and 1999, never being much higher than 20% (left axis) – though 1999 differences shifted to the right about five years at age 85. Despite higher life expectancy at all ages 65+, the difference at age 85 is only slightly higher than (at age 80) in 1982. After age 85, the ratio of ALE and LE differences over age suggest a small difference, and stable rates of change from 1982 to 1999, up to age 105. This is why we can expect future declines in disability, and increases in ALE, that is, improvements are manifest to age 105.

Further complicating efforts to predict life expectancy are gender and cause specific differences in mortality. From 1950 to 1970, male life expectancy at 65 increased 0.3 years (i.e. from 12.8 to 13.1 years) with life expectancy declining 1954 to 1968. Female life expectancy increases were 2.0 years from 1950 to 1970 (i.e. from 15.0 to 17.0). From 1970 to 2001, life expectancy at 65 for both US males (13.1) and females (17.0) increased 3.3 and 2.4 years – to 16.4 and 19.4, respectively. There were larger changes in cause specific mortality. US age-standardized heart disease mortality declined 57.8%, and stroke mortality 68.0%, from 1950 to 2001. Age-standardized cancer mortality increased 11.4% up to 1990. From 1990 to 2001, they declined over 9%. This decline was due to both social (smoking cessation) and treatment innovation – despite the criticism of the "war on cancer" (Bailar and Gornik, 1997). Weisenthal (2004) suggests application of "drug efficiency testing" at the individual level could improve the efficacy of chemotherapy by 20 to 1.

An area recalcitrant to treatment until recently was neurodegenerative disorders, for example, Alzheimer's disease. Recent analyses of the 1982 to 1999 NLTCS show large declines in severe cognitive impairment. In 1994 and 1999, severe cognitive impairment was found to map to four ICD-9 (The Ninth Revision of the International Classification of Diseases) codes. Of these codes, those representing dementia due to circulatory disease (e.g. sequalae of stroke), or mixed processes, showed most of the declines, that is, Alzheimer's disease alone was stable (Manton *et al.*, 2004a; Manton and Gu, 2005a).

Epidemiological studies showed supplemental vitamins C and E and aspirin reduced dementia by circa 90% (Zandi *et al.*, 2004), ibuprofen by as much as 80% (in't Veld *et al.*, 2001), and statins by 73% (Wolozin *et al.*, 2000), which is "proof of concept" that not just circulatory dementia could be reduced with existing medications but also, in the future, Alzheimer's disease. This seems contradictory to many estimates of future Alzheimer's disease risk (Manton, 2004a; GAO, 1998; Evans, 1990).

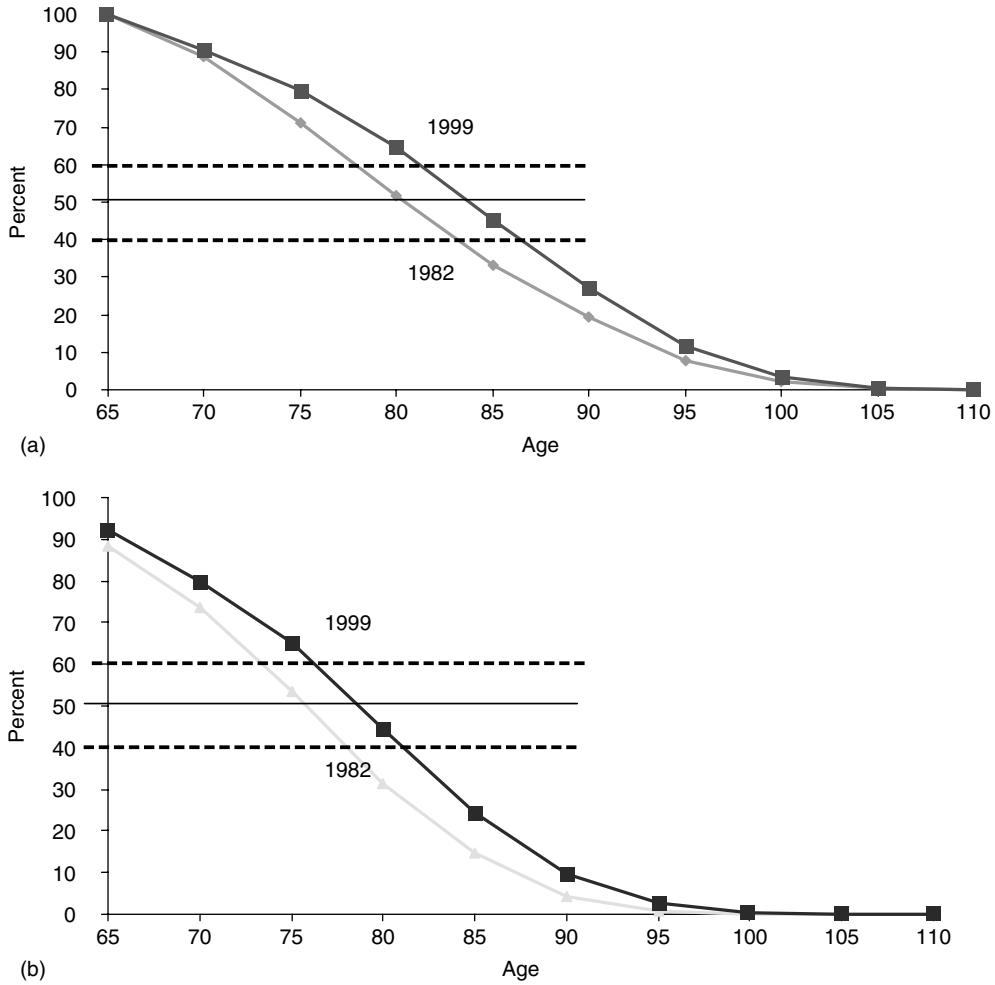

Figure 1 (a) 1982 and 1999 Life expectancy estimates; (b) 1982 and 1999 Active expectancy estimates

The nature of medical conditions evolved as more persons survived to late ages, for example, up to the 1940s and 1950s, much concern was directed to effects of rheumatic fever or syphilis on the heart, hypertension, and stroke (Kaplan and Keil, 1993). In the 1950s and 1960s, hypertensive heart disease declined while atherosclerotic heart disease increased. The mean age at which hip fractures occurred in Britain from 1944 to 1990 increased from 67 to 79 – a 12 year of age increase in 46 years. Concurrently, the nature of hip fractures shifted from intra- to extracapsular fractures. The nature of osteoporosis, the process underlying most US hip fractures, differs from ages 55 to 74, where it depends on postmenopausal change in estrogen levels, to ages 75+ where it is related to age-related defects in the vitamin D endocrine system.

Clearly, more basic physiological processes were at work, and over a longer period of time, than anticipated by efforts to estimate life expectancy limits based on total and cause specific mortality trends, and by efforts to relate changes to significant, but recent, changes in "standard" chronic disease risk factors. One study suggested US stroke mortality started to decline by 1925 (Lanska and Mi, 1993). Fogel (1994) showed US declines in chronic diseases may be even more long lived. He compared the prevalence of chronic diseases in Civil War veterans age 65 to 84 applying for pensions in 1910 (US birth cohorts of 1825 to 1844) with the prevalence of chronic diseases for WWII veterans over 65 assessed in the 1985–1988 National Health Interview Surveys (i.e. 1905 to 1924 cohorts). He found chronic disease prevalence at 65+ declined 6% per decade between 1910 and 1985–1988. The prevalence of heart diseases was 2.9 times higher in Civil War veterans aged 65+ in 1910 than in WWII veterans aged 65+ in 1985–1988. Declines in chronic diseases set the stage for subsequent declines in mortality up to several decades later.

Fogel (1994) attributed changes in chronic morbidity to economic and productive factors affecting early nutrition which increased stature and body mass index (BMI) over time. Many changes between Civil War and WWII veterans predate documented US increases in cholesterol and fat consumption – estimated to have peaked in 1959. One possible explanation of the effects of nutrition on health was the impact of protein, micronutrient, and caloric deficiency on fetal development. This was attributed to effects of

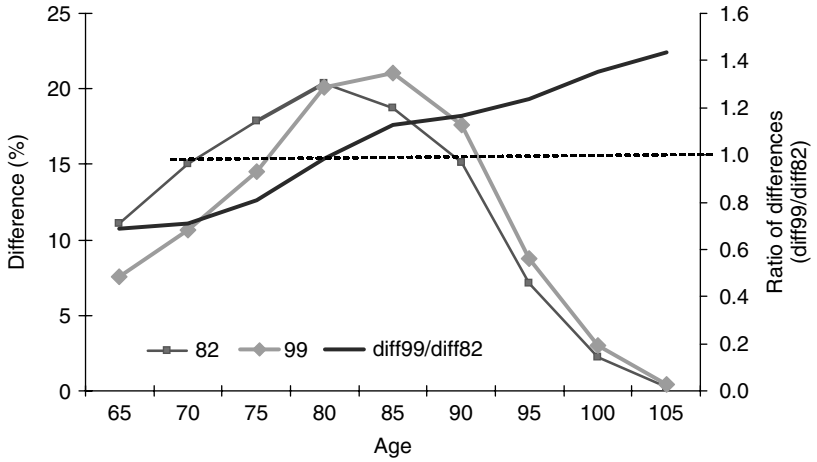

Figure 2 Difference between LE and ALE

maternal nutritional deficiencies on the fetal development of organs such that a physiological priority was assumed to exist which dictated which organs received adequate nutrition under conditions of protein and caloric deprivation. If the central nervous system received the highest priority for nutrients, organs like the liver (affecting cholesterol metabolism and thrombolic factors) and pancreas (affecting glucose metabolism) might be susceptible to developmental restrictions that became manifest in chronic disease risks at later ages. There is evidence for this in studies relating the ratio of placental to birth weight, and of weight at one year of age to chronic disease at later ages. Barker and Martyn found higher weight at one year inversely related to ischemic heart disease, systolic blood pressure, and impaired glucose tolerance in adults, and possibly to fibrinogen levels in men aged 59 to 70. The relation of systolic blood pressure to placental weight for women and men age 46 to 56 was direct.

Others suggest nutritional deficiencies affect persons most at ages where the most rapid physical growth occurs with the highest protein, caloric, and other nutrient needs. This is consistent with Fogel's (1994) use of the Waaler curve to plot changes in BMI and chronic disease risks. It is also consistent with the results of Tango and Kurashina, who found Japanese male cohorts born 15 years before WWII (i.e. birth cohorts of the early SHOWA period 1925–1939; aged 5 to 20 during WWII when there were nutritional shortages in Japan) had elevated mortality from diabetes mellitus, ischemic heart disease, peptic ulcer, cirrhosis, and suicide. These cohort differences in male cause specific mortality are likely due to poor nutrition during early, critical stages of adolescent male growth spurts. Deficiencies involved gross energy (caloric), proteins, and micronutrients, for example, in periods of rapid skeletal growth, vitamin D serum levels are highest; and vitamin C (affecting collagen formation) and B (affecting methionine metabolism and growth hormone release) needs are elevated (McCully, 1983). One large-scale population experience that could be definitive in testing the Barker hypothesis is the Leningrad siege in WWII where there were roughly ~250 000 survivors in 2004.

Two other models may help explain why chronic disease and mortality risks in specific birth cohorts may be related to nutritional and hygienic factors over long periods of time. One suggests that the effect of viral and bacterial infections on chronic disease has changed over time (as well as the natural history of the chronic diseases) due to changes in food processing and hygiene. Such arguments have been used to explain why some diseases have strong geographic patterns, for example, association of multiple sclerosis with temperate climates. For atherosclerosis, there is evidence to relate its initiation (i.e. injury to arterial endothelium starting inflammatory and wound building activity stimulated by dietary cofactors such as serum cholesterol and aggravating conditions such as hypertension) to viral and bacterial insults. This model derives support from evidence that atherosclerotic plaques have a monoclonal origin, suggesting a somatic mutation is involved in plaque initiation (Benditt and Benditt, 1973). Various infectious agents have been found in plaques; or in circulating immunological complexes in cases with circulatory disease versus controls. Among agents implicated are *Chlamydia Pneumoniae*, CMV (cytomegalovirus) (Mozar *et al.*, 1990), and other herpes viruses. One mechanism that could be involved in infectious agent damage to arterial endothelium involves platelet derived growth factor (PDGF). PDGF may play a central role in atherogenesis because it is both a mitogen and chemoattractant. There is a striking homology (87%) between the amino acid sequence of PDGF and a protein from an oncogene (v-sis) in the simian sarcoma virus. This homology suggests PDGF is important in the proliferation of cells transformed by a virus. Cells transformed by retrovirus, DNA viruses, and cells with somatic mutations appear to secrete PDGF molecules. Cells virally transformed appear to express a previously repressed cellular gene (c-sis) for PDGF. An immunological factor identified as raising the risk of myocardial infarctions, especially for males, is null allele C4B*Q0. There is evidence to suggest immune mechanisms are involved in hypertension, with some data pointing to predisposing genes in the

major histocompatability complex, either secondary to hypertension induced vascular damage (causing positive feedback in plaque growth) or as a primary abnormality. However involved, reductions in infectious disease exposures might reduce hypertension prevalence in recent cohorts.

Data from Hiroshima suggest ionizing radiation is another exogenous stressor involved in hypertension and cardiovascular disease. In Hiroshima, there was acute γ radiation. In Chernobyl, the most damaging radiation is β (electrons) due to biological incorporation of ^{90}Sr in bone and ^{137}Cs in soft tissue. The radiation flux of these isotopes is relatively high though they have a long half-life, that is, about 30 years. With this type of radiation, there appears to be an acceleration of basic age processes (Manton *et al.*, 2004a) consistent with the well-known free radical theory of aging. This syndrome involves cataracts, stroke, circulatory diseases, and neurodegeneration. Effects on neurodegeneration originally were not viewed as plausible because it was believed neurons seldom divided. There is now evidence neuronal regeneration occurs in several areas of the brain (e.g. in the hippocampus and the substanta nigra) for the brain is an area of high metabolic activity where baseline free radical production is high and where protein formation in synaptic gaps is sensitive to even very low doses of radiation (Manton *et al.*, 2004a).

The evidence suggests atherosclerotic circulatory diseases and their catastrophic manifestations are thrombotic, occlusive events leading to ischemia in critical organ systems, due to a multistage pathological process where initial damage to the arterial intima stimulates inflammatory and immunological responses, where LDL (low density lipoprotein) cholesterol becomes oxidized forming foam cells from monocytes/macrophages drawn to the site of the injury, which then are integrated in plaque. Involved in plaque elaboration are complex processes of autocrine and paracrine mechanisms of vascular response to injury (Dzau *et al.*, 1993). Other stages of the process involve intracellular absorption of calcium leading to calcification of plaques and inflammatory responses leading to plaque rupture. Immunological responses to infectious agents directly stimulating plaque ruptures (and subsequent thrombotic events) are also suggested by the antiphospholipid syndrome.

To explain how infectious disease involvement with atherosclerosis relates to long-term population health and mortality changes, Mozar *et al.* (1990) suggested changes in circulatory disease risk can be traced back at least to 1910, when 8% of US deaths were attributed to heart disease. This proportion rose to 30% by 1945, and to 54% by 1968. A similar trend occurred in the United Kingdom with diseases of the heart and blood vessels responsible for 11.4% of all deaths in 1910, rising to 36.3% in 1959. In the United States, the peak heart disease risk was reached in 1968. Mozar *et al.* (1990) suggest this was due to ingestion of atherogenic viruses during the prewar period (i.e. initial injuries led to processes with lengthy latency times; autopsy studies found fatty streaks and plaque development began at early ages, possibly as early as age 3 years in the aorta (Pathobiological Determinants of Atherosclerosis in Youth Research Group (PDAY), 1990), even in less developed countries where heart disease risks do not increase late in life), which interacted with increased fat consumption and other risk factors (e.g. the methionine-homocysteine model of atherogenesis) up to 1970.

The nutritional (hygienic) factor argued by Mozar *et al.* (1990) to be associated with declines in heart disease risk was commercial food processing – initiated before the turn of the century. The use of commercial food processing accelerated after WWII as economic conditions improved, large proportions of the US population moved from rural to urban areas, and efforts to control livestock infections such as vesicular xanthema (a viral disease of swine discovered in 1932) were started, for example, in California in 1945–1949. An outbreak of vesicular xanthema in 1952 mandated thermal preparation of food fed to swine. A hog cholera eradication program began in 1962. The Swine Health Protection Act passed in 1980.

The risk of viruses and other infectious agents in chronic circulatory disease is not limited to injuries to the arterial endothelium but may involve stimulation of autoimmunological factors. A well studied infectious disease important in chronic disease risk that was a major concern in past years (i.e. rheumatic heart disease) are group A streptococci infections, especially of virulent strains, for example, M types 3 and 18 associated with rheumatic fever and M1 with toxic shock due to production of a pyrogenic exotoxin A. Certain strains (e.g. M1) disappeared in the United States 30 to 40 years ago. They recently reappeared in selected geographic areas in the United States, suggesting a cyclical decline and reemergence of virulent strains (Kaplan, 1993). This cyclical pattern can be related to the HLA (human leukocyte antigen) typing of individuals to see how autoimmunological responses relate to rheumatic heart disease. The disappearance of the most virulent strains about 1950 to 1960 is consistent with declines in cardiovascular mortality due to atherosclerosis beginning in 1968 – suggesting a role as a disease cofactor.

Nutrition affects a host's immunological competency. Poor nutrition, especially in childhood, might lead to less effective immunological responses to viral and bacterial challenges. The physiological response to the acute phase of infection requires energy. Poor nutrition can reduce efficacy of the host's response to disease, allowing it to cause greater physiological damage requiring greater energy expenditures to fight the disease process and further reducing nutritional resources for normal development – setting the stage for future chronic disease.

A third factor that could become important is ionizing radiation, not necessarily from atomic bombs or nuclear terrorism, but environmental contamination of water and food sources due to the leaking of radionucleides from storage sites (e.g. the Hanford plant) or as might occur during decommissioning of nuclear power plants. This is the type of damage that occurred in the former Soviet Union, for example, from the Mayak plutonium production facility in Chelyabinsk, Russia.

As for cardiovascular disease, new genetic and molecular evaluation and assay techniques allow identification of viruses and other infectious agents causing several types of

cancer. Epstein-Barr virus is implicated in the etiology of human lymphoid and epithelial malignancies. *H. pylori*, a causative agent in peptic ulcers, is associated with gastric cancer, and possibly other malignancies (e.g. liver cancer). Both Rb and P53, growth regulating genes whose normal function is to arrest cell growth when mutations are detected, can be disturbed by viral infections allowing malignant growth. *H. pylori* is of interest in that its infection rate is related to water quality. Thus, long-term improvements in water quality may be responsible for US cohort specific declines in gastric cancer. Elevation of gastric cancer risks in the upper midwest of the United States may be due to the use of well water in rural areas (*H. pylori* grows well in still water in wells or cisterns). *H. pylori* remains highly prevalent in developing countries (e.g. West Africa) and has a high seroprevalence in elderly US cohorts.

Thus, long-term trends in both circulatory and neoplastic disease and mortality appear to partly depend on viral and bacterial infections as initiating events or cofactors and may depend in the future on radioecological events. Reductions in standard chronic disease risk factors can only be documented, in the United States population, from the early 1960s (e.g. smoking declines, reduction of unhealthy fat consumption). Reductions in hypertension were first documented in the National Health and Nutrition Examination Surveys in 1960–1962. As genetic and molecular biological assays become more sensitive, we may find many other chronic diseases are dependent on a variety of infectious and other environmental agents. Changes in the human environment (e.g. improvement in water quality reducing *H. pylori* infection) or in food processing (e.g. elimination of viral infections in livestock, or thermal processing of food) may be partly responsible for large cohort related declines in circulatory diseases in the United States.

Cancer risks are now decreasing in the United States. It has been proposed that common processes underlie both cancer and aging. Warner *et al.* (1995) related these processes to effects of caloric restriction (CR) on programmed cell death (PCD). They suggest CR upregulates expression of antioxidant genes and attenuates formation of reactive oxygen species – and possibly DNA and mitochondrial damage caused over age. The emphasis on effects of antioxidants on aging and cancer leads to a third model of changes in chronic disease risks and their contribution to late age health changes.

Another hypothesis is that long-term changes in micronutrients alter chronic disease risk. Antioxidant vitamins A, C, and E seem to affect cardiovascular disease by lowering the potential for LDL cholesterol to become oxidized, consumed by macrophages, and trapped in atherosclerotic plaques as foam cells. Vitamin A and E are redifferentiating agents that repair some genetic damage and antioxidants preventing certain chemical reactions from causing somatic mutations or other cell damage. They may improve immunological responses at late ages (Beregi *et al.*, 1991). Zandi *et al.* (2004) suggest that up to 93% of Alzheimer's disease may be prevented by supplementation with vitamins C and E and low dose aspirin.

Vitamin D, a vitamin/enzyme/hormone, has powerful effects on bone metabolism; especially in late onset (i.e. ages 75+) osteoporosis (type II) in females. This may interact with cardiovascular diseases by affecting cellular calcium metabolism, parathyroid hormone activity, and hypertension. It may interact with iron (Fe) and magnesium (Mg) metabolism (Moon *et al.*, 1992) and is a powerful cellular differentiating agent. As such it (or, its antagonists) might prevent strontium 90 uptake in radioecological disasters as Chernobyl.

Vitamin D supplementation in milk and other foodstuffs has been done for a long time in the United States and Canada. One strategy to examine its effects on chronic disease is to trace the epidemic of atherosclerosis and ischemic heart disease and the ratio of male to female deaths. In the United States, this ratio was near one until the mid-1920s. Then the male predominance in ischemic heart disease increased steadily until 1968. Moon *et al.* (1992) pointed out that curative effects of cod liver oil on rickets were documented in 1917. In 1923, the United States imported 0.5 million gallons of fish liver oil, and in 1930, 2.8 million gallons. UV irradiated milk was introduced in the United States in 1924. Manufacture of vitamin D_2 and D_3 increased from 35 lbs in 1948 to 14 000 lbs in 1972. By 1970, vitamin D_2 was added to many food products. There was a concurrent decline of Mg in the US diet. Mg mediates effects of vitamin D on cellular calcium absorption (Moon *et al.*, 1992). Vitamin D hypervitaminatosis infers with Mg absorption. Oversupplementation of D aggravated Mg deficiencies in the United States diet. Mg deficiency may have additional effects on circulatory disease because it appears to stimulate renin release through the elevation of prostaglandins; and suppress aldosterone production by mobilizing intracellular calcium.

In the late 1960s, the FDA began considering limiting vitamin D supplementation. Regulations restricting vitamin D supplementation were implemented in 1972 – coincident with the beginning of the decline in heart disease.

The sex ratio of femoral neck fractures was used to trace origins of the US osteoporosis epidemic. This ratio suggests (based on Rochester, Minnesota, data) that osteoporosis began its upsurge in the late 1920s – about the same time ischemic heart disease began increasing. Vitamin D intake, its increase from 1920 to 1970 and its subsequent decrease, could explain the interaction of atherosclerosis and osteoporosis for females, and their joint trajectories. Vitamin D increases Fe absorption, which may lead to increased free radical generation and oxidation of LDL cholesterol. This might explain the rapid increase of atherogenesis in females postmenopausally, that is, Fe stores in females increase and, with excess vitamin D, increase calcification of atherosclerotic plaques.

Another model for explaining long-term trends in circulatory diseases is the homocysteine theory (McCully, 1983). Ingestion of the sulfur based amino acid methionine (an essential amino acid for mammalian growth) produced, after demethylation, homocysteine. Elevated levels of homocysteine, due to genetic predisposition or dietary deficiency of vitamins B_6 and B_{12}, had toxic effects on arterial

endothelium. Lesions created by elevated homocysteine levels showed the characteristic fibrous nature of atherosclerotic plaques – but not with lipid deposition if cholesterol is not elevated. The theory suggests fibrous plaques are not produced unless vitamin B deficiency allows accumulation of homocysteine and a toxic metabolite, homocysteine thiolactone. The metabolism of homocysteine is affected by vitamin C. Though ascorbic acid is a potent reducing agent, after oxidative conversion to semidehydroascorbic acid, its physiological function is to oxidize the sulfur atom in homocysteine. Three stages for methionine utilization are (a) demethylation and dehydration of methionine to homocysteine thiolactone, (b) oxidation of homocysteine thiolactone to homocysteic acid by semidehydroascorbic acid, and (c) reaction of homocysteic acid with ATP (adenosine triphosphate) to form active coenzymes to synthesize sulfate esters of connective tissue proteoglycans.

Methionine deficiency inhibits growth and wound healing – like scurvy. In scurvy, the lack of dehydroascorbic acid inhibits formation of sulfated proteoglycans. Increased conversion of methionine to homocysteine thiolactone increases production of sulfated proteoglycans matrix, deposited in atherosclerotic plaques, which accelerates growth and stature in homocystinuria. Age changes in homocysteine hepatic metabolism may explain why children in rapid growth phases are less susceptible to atherogenic effects of homocysteine. Stimulation of growth is due to homocysteic acid, which has a similar effect to somatomedin (the serum polypeptide mediating the effect of pituitary growth hormone on cartilage) on sulfate binding in cultured cartilage fragments – suggesting a relation of homocysteic acid, somatomedin, and the action of growth hormone. After normal growth ceases, and epiphyses ossify, growth stimulation affects cells of blood vessels (especially smooth muscle cells) rather than chondrocytes and osteocytes in growing bone. The homocysteine model also suggests a basis for the age dependence of osteoarthritic diseases and effects of growth hormone and somatomedin on the aging of connective tissue. Some evidence suggests the agent mediating the growth of smooth muscle cells is carried by platelets and released during platelet aggregation and adherence to injured intima. Calcification of fibrous connective tissue is stimulated as is the disruption of intermolecular cross-linking in newly synthesized collagen fibrils, which may be due to the reaction of homocysteine with allysine to form tetrahydrothiazine adducts. This may interfere with intermolecular cross-linking in collagen and elastin.

The relation of this mechanism to increased heart disease in the twentieth century may be due to an increased dietary ratio of animal to plant protein (dietary intake of methionine is correlated with cholesterol intake). This may explain the relation of increased body size with atherosclerosis. Vitamin B_6 levels decrease through life to the eighth decade because serum glutamine oxaloacetic transaminase activity decreases. When the elderly are treated with pyridoxine, transaminase levels return to levels of younger persons (McCully, 1983; von Eckardstein *et al.*, 1994). Also, since pyridoxine is water soluble, as the lipid content of the diet increases, pyridoxine availability may decrease.

To explain US population trends in heart disease, quantities of synthetic pyridoxine hydrochloride were examined (McCully, 1983). US production increased from 1900 kg in 1944 to 30 000 kg in 1963. Imports increased from 9100 kg in 1963 to 17 700 kg in 1969, to 59 500 kg in 1972 (yielding a threshold consumption of 0.79 mg day^{-1}) to 275 000 kg in 1978 (3.42 mg day^{-1}). This increase is consistent with post-1968 declines in coronary heart disease. Since B_6 supplementation will prevent arterial damage, but not reverse it, the decline in circulatory disease should increase as younger cohorts who had adequate supplementation reach older ages. Supplementation is also necessary because thermal food processing (which may have decreased viral exposures in animal protein) degrades natural pyridoxine. This is controllable by consuming adequate synthetic vitamin B_6 and B_{12} (von Eckardstein *et al.*, 1994). The problem increases with age due to altered vitamin intake, absorption, or metabolism.

Dietary intake of at least two other trace minerals may affect long-term heart disease and stroke mortality trends by affecting blood pressure. One is reduced salt intake which lowers blood pressure and reduces abnormalities of calcium metabolism, incidence of renal stones and bone demineralization. Potassium, found in many fruits and vegetables, also decreases blood pressure. Increases in fruit consumption may be involved with early reductions in stroke.

New explanations of these processes derive from better understanding of cellular bioenergetics – especially the function of the mitochondria. This suggests that, in addition to the CR model, they are the effects of thyroid hormone on mitochondrial function (Manton, 2004b). It is known thyroid hormone administration increases oxygen consumption by mitochondria (Venditti *et al.*, 2003). The effect may be short- as well as long-term. Short-term influence (within minutes of the hormone treatment) results in enhanced expression of the mitochondrial genome. Thyroid hormone increases levels of mitochondrial transcription by elevating mRNA synthesis and improving their stability. Long-term influence (after 24 hours) involves the stimulation of mitochondriogenesis (Enriquez *et al.*, 1999; Wrutniak-Cabello *et al.*, 2001; Weitzel *et al.*, 2003). This may explain why honey bees, where a nutritional intervention (royal jelly) containing a protein with partial structural similarity to human thyroid hormone, may stimulate production of cytochrome C in mitochondria with life span epigenetically increased 30-fold or more despite elevated metabolic rate (Manton *et al.*, 2005). Intervention effects were shown in mice where mitochondrial functions of old mice was returned to that of young mice by administration of alpha lipoic acid (an antioxidant zwitterion) and L-acetylcarntine, an agent stimulating fatty acid metabolism (Hagen *et al.*, 2002; Liu *et al.*, 2002).

Historically, deficiencies leading to explicit disease syndromes were prevalent until the role of specific vitamins and minerals in those diseases were identified and supplemental sources sought. At levels less deficient than those causing specific deficiency syndromes (e.g. scurvy, pellagra, osteomalacia, rickets), vitamin deficiencies may have contributed to long-term population changes in chronic disease risks.

To make the ebb and surge of specific chronic diseases over time consistent with the models described above, there had to be changes, not only in mortality at late ages, but also in the nature of age-related chronic disease processes over the past 150 years as nutrition (both macro and micronutrients), food hygiene (e.g. *H. Pylori* infections; toxins due to food spoilage), and viral and bacterial exposures changed. Changes may also affect the expression of genetic diseases by altering gene–environment interactions or by changing the inflammatory response of the host to stress, for example, altering serum levels of IL-6 (Cohen *et al.*, 1997). The average health characteristics of the very elderly population may evolve in the future as different cohorts, with different early health experiences, enter this age group. As the profile of chronic diseases affecting elderly populations changes over their life span, one also is aware of long-term changes in age-related chronic disease – and in aging changes.

MORTALITY SELECTION AND TRAJECTORIES

Hygiene and nutritional changes caused differences in chronic disease risks across birth cohorts. These, and other, factors (e.g. smoking) may have altered age trajectories of cohort mortality. Specifically, many demographic models use a Gompertz function to describe age increases in mortality. However, at late ages the trajectory of human mortality deviates from the Gompertz overpredicting increases in mortality (Manton and Stallard, 1996).

One explanation of deviations from the Gompertz (beginning about age 85) is mortality selection. For example, the prevalence of the B gene of the fourth component of complement (C4B*Q0) is a risk factor, in men, for myocardial infarction. The prevalence of this gene dropped for males in the fifth and sixth decades of life due to adverse affects on longevity. Its prevalence declined at later ages in females. In Italian centenarians there was decreased thyroid autoantibodies compared to persons in their 80s (Marriotti *et al.*, 1992). The prevalence of the ApoE-4 genotype in Finnish centenarians was lower than at earlier ages. In lung cancer, genetic susceptibility involves the cytochrome P450 enzyme system. The proportion of genetically related lung cancer cases declines sharply between ages 50 and 70. In Swedish twins (Marenberg *et al.*, 1994), the relative risk of CHD (Congenial Heart Disease) mortality declined from 14 to 15 to 1 in midage to 1 to 1 above 85. Thus, many studies of genetically controlled diseases showed change in genotype prevalence due to mortality selection. In clinical examinations of long-lived groups, health at late ages (e.g. 80+) is often better than for persons, say, aged 70–79 (Campbell *et al.*, 1993).

Effects of mortality selection on the age trajectory of health parameters can be monitored in longitudinal studies where risk factors, or disabilities, are measured multiple times. In analyses of Framingham data (46 year follow-up), and of 18 years of follow-up in a nationally representative study of disabled elderly (1982 to 1999 NLTCS), the mortality selection of persons with adverse risk factor profiles, or poor functional status, was noted over age. At late ages (e.g. 95+) selection was so strong that prevalence of adverse risk factor profiles, or poor functioning, started to decrease because mortality rates for very elderly persons with impaired health were greater than the incidence of the adverse health state (Manton *et al.*, 1994a).

As a consequence of selection, whereas human mortality rates increase 8 to 10% per year in middle age, the rate of mortality increase at late ages is slower. In seven studies where mortality was observed to ages 100+, rates increased an average of 3.1% per year between 100 and 110 (Manton and Stallard, 1996). For US males, cohort mortality reached a high constant level at ages 100 to 110. US female cohort mortality increased 3.0% per year of age from 100 to 110. The average US cohort mortality rate at age 110 was 41%; the average for the seven studies was 45% (Manton and Stallard, 1996).

The 1982 to 1999 NLTCS data show this plateau. We examined an alternate model where a plateau is due, not only to a genetically heterogeneous population, but also to a balance of degenerative and regenerative physiological processes (Manton *et al.*, 2004b). This suggests engineering reliability models, such as the Weibull, are not sufficient in that they describe failure in a homogenous system – not a complex heterogeneous one. It is no longer sufficient to describe a plateau as a genetically determined trait but as a temporally (absolute clock-time – not simply age) changing equilibrium of decay and repair functions.

In analyses of the actuarial experience of 11 large insurance companies, there was no credible evidence of human mortality rates exceeding 50% at any age. Recently the level of the plateau was fixed at 40%. Ungraduated insurance data suggest that, above 95, mortality reaches 25% for both genders and then fluctuates randomly. In animal models, similar phenomena were observed. Carey *et al.* (1992) found, in large experimental populations, mortality reached a high constant level after a large proportion (90%) of the population died. This is manifest in the United States by a decline in per capita, per annum Medicare expenditures at late ages, that is, expenditures were several fold higher at ages 65–70 than for centenarians.

If human mortality rates increase very slowly at late ages, profound changes will be required in assessing elderly populations. One is that the number of extreme elderly persons will be larger than now anticipated. In developed countries with reliable data (Manton and Stallard, 1996), the centenarian population has grown 7% per year for 30 years. The number of US centenarians in 2000, 50 454, will increase to 150 000 by 2020 and to 313 000 by 2040 – without assuming large changes in life expectancy or dealing with the large post-WWII baby boom cohorts who become centenarians after 2047. In Social Security Trust fund projections, mortality rates are assumed to increase 5 to 6% per year of age above 100 – a rate of increase higher than in the data (Manton *et al.*, 2004b).

From 2035 to 2050, the US centenarian population is expected to grow to 0.6 million persons. The US population

aged 95+ in 2050 would be 3.8 million persons. The 85+ population would be 18.9 million persons – or 4.8% of the US population. The 65+ population would be 20.4% of the total US population. These are "middle" range projections. Alternate series, assuming greater life expectancy increases, project 2.6 million centenarians in 2050 with 26.4 million persons 85+ and 93.1 million 65+; or 0.63, 6.4, and 22.7% of the total US population (i.e. based on life expectancy at birth in 2050 of 83.8 versus 91.1 years for males and females respectively; the intermediate assumption was 79.7 and 85.6 years for males and females respectively in 2050). Second, for individuals at late ages one will have to use different estimates of life expectancy than are available from actuarial estimates (Manton, 2004a). This could change calculations for assessing cost effectiveness of specific medical interventions at late ages.

Third, the expectation about comorbid conditions, and the average health of individuals at specific ages, will have to be evaluated taking into account the birth cohorts from which the patient comes, and the likely prior health experiences of persons in that cohort who survive. It may be aging processes in such persons progress at slower rates than in the population.

FUTURE CHANGES IN THE DEMOGRAPHY AND HEALTH OF THE ELDERLY: POTENTIAL SOCIOMEDICAL RESPONSES

With extreme elderly populations of the size discussed, the levels and mixes of services to be provided will have to be adjusted. Changes projected for the United States are not the most extreme. In Japan, using 2004 life expectancies at birth of 76.7 years for males and 84.5 years for females, the 65+ population will be more than 28% of the population in 2024.

The implications of such changes are dramatic requiring coordinated changes in (a) societal views of aging, (b) monitoring health of persons at specific ages, (c) the organization of acute and LTC health services for elderly populations, and (d) how medical options are evaluated that are to be offered to persons at extreme ages.

First, the popular perception of aging, and elderly persons, will change so sociomedical implications of age are less distinct, that is, individuals have to be assessed more on functional age, and less on chronological age, when considering the economic and social roles they play and how they should be medically treated. For this to have an effect, two other processes must operate. The first, consistent with evidence on the plasticity of aging parameters, is that physiological function is being preserved (and possibly promoted) to late ages. Fiatarone *et al.* (1994) showed resistance training and supplemental nutrition could improve muscle strength of elderly, frail individuals, for example, the average strength gain in the quadriceps of frail persons aged 86 to 96 was 174%. Kasch *et al.* showed declines in cardiovascular function for active persons were half the rate found in other studies. The image of "normal" aging must also be changed in the mind of the elderly individual. By identifying elements of aging with treatable disease processes, senescence is transformed from a mysterious, global biological force into more manageable and specific disease mechanisms. With this image, individuals will be more likely to make lifestyle changes, and seek treatments, to modify health and function.

The potential can be illustrated using the 1982, 1984, 1989, 1994, and 1999 NLTCS to estimate changes in chronic disability prevalence by age (Figure 3).

In Figure 3 are estimates of changes in the US chronically disabled population representing (a) constant 1982 age and sex specific disability rates, and (b) extrapolating 1999 rates to 2004. The difference is a decline of 43% in the chronically disabled or institutionalized population by 2004 over what 1982 rates would have generated. At ages 65 to 74, the number of chronically disabled persons in 1999 is nearly constant despite a population increase of 30%. Growth of the disabled population is slowed at ages 75 to 84 and 85+. The difference in estimates is 2.6 million, that is, if rates had not changed from 1982 to 2004, there would be 9.9 million disabled persons in 2004 versus the 7.3 million using declines observed 1982 to 1999. Using the rate of decline in disability 1989 to 1999, the difference is 3.1 million (i.e. 9.9–6.8 million).

DISCUSSION

The evidence suggests we can expect future elderly cohorts to live longer, and to have better health and functioning. This raises the question as to how health service systems will deal with this rapidly growing group and their changing health characteristics. What has happened in the United States is that health and LTC (long-term care) services have been redirected toward the community, and housing options have been defined to bridge the gap between traditional nursing homes and standard housing. This is reflected in changes in the US health care system. Medicare coverage is now often supplemented by private health insurance. Hospitalization rates and lengths of stay are down. What increased dramatically are Home Health Agency (HHA) and skilled nursing facility use, which, by 1995, constituted 8% of all Medicare expenditures – roughly $14 billion. Concurrently, growth of Medicaid reimbursed nursing home use declined. Most recently, we have found, despite arguments of some economists that more resources will be required to keep individuals healthy at late ages, per capita inflation adjusted Medicare expenditures declined for the nondisabled population and increased for the disabled populations.

Efforts to prevent both morbidity and disability among the elderly should be extended. Medicare based demonstration programs show physical activity can be increased. Physical activity (actually the lack) is, itself, a primary risk factor for stroke – and possibly other chronic diseases.

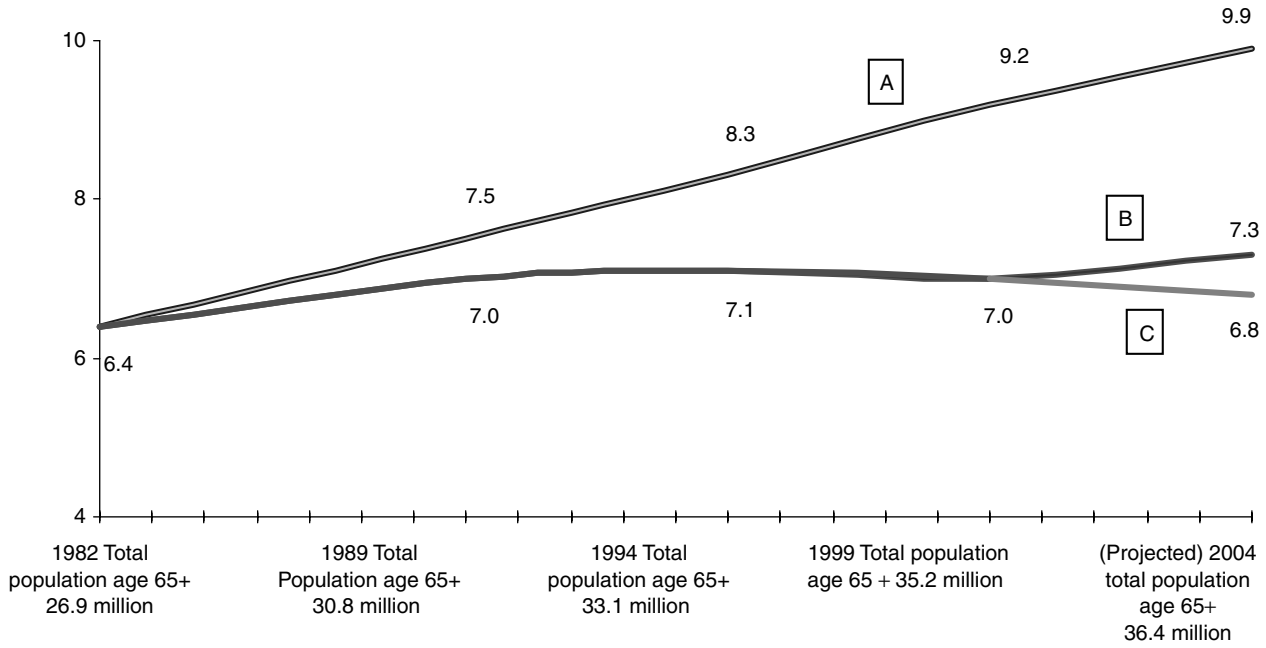

Figure 3 Number of chronically disabled Americans aged 65 and over (in millions)

Better evaluations of the efficacy of treatments at late ages are needed. Hosking *et al.* showed surgical interventions in patients aged 90 to 103 had become less hazardous – intra-operative mortality dropped from 30 to 8% over 30 years. Ko *et al.* show the increasing efficacy of coronary interventions in elderly (80+) patients. Elayda *et al.* showed uncomplicated aortic valve operations were successfully performed in patients aged 80+. Long-term (five years) survival rates in persons with simple aortic valve replacement were better than the survival in SSA (Social Security Area) cohort life tables. As pacemakers increase in sophistication, their use in elderly patients improves outcomes. Dual chamber, demand driven pacemakers may be particularly useful for the elderly because of increased reliance with age on atrial function for cardiac output. There are interventions with low mortality that increase the function of elderly persons. Hip and knee replacements are in this category, as well as plastic lens implants for cataracts.

Hence, the cost benefit ratios of medical procedures at late ages may be underestimated because the life expectancy of individuals at late ages, and the amount of functional capacity that can be regained, is underestimated (Manton and Gu, 2005b). A reason may be because trends in disability and mortality among populations with particular health characteristics may not be correctly represented in evaluations of patients for the medical and surgical procedures now available for elderly populations. Certain situations, such as long waiting periods for "elective procedures" in some European health care systems, may have more adverse effects at late ages than in younger populations and operate as a "self-fulfilling" prophecy about limitations to late age interventions. Such problems will emerge increasingly in the future as the number of very elderly persons increases and prior health histories evolve. One factor to which recent changes in disability may be related is education. Education is projected by Preston to improve with the proportion of persons aged 85 to 89 with less than eight years of schooling declining from 60+% in 1980 to 10 to 20% by 2015. A number of health behaviors are associated with education; as well as the risk of dementia.

The very elderly (95+) are a group for which we do not have extensive data from which to extrapolate effects of medical interventions. Studies focusing on the elderly, such as the isolated systolic hypertension intervention program, often find significant benefits in intervening in disease. Thus, evaluation of both future increases in health service needs for the elderly population, as well as evaluating potential gains for elderly individuals with specific health profiles, need to consider the implications of long-term demographic and health changes.

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KEY POINTS

- Vitality determines mortality and fertility.
- Vitality links birth-death processes.

- Vitality is driven by mitochondrial function under thyroid control.
- Mitochondria are regulated by thyroid hormone.
- Free radical chemistry is central to cellular bioenergetics.

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10

Social and Community Aspects of Aging

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INTRODUCTION

The interactions of social and community factors and aging are extraordinarily complex (Figure 1). It is important for the health-care professional to be aware of the impact of social and community factors on the health and well-being of the older person.

DEMOGRAPHY OF AGING

The Graying of Nations

The graying of nations (Butler, 1979) is a metaphor that has been used to describe the demographic changes that have taken place in all industrially developed countries during the past 100 years. It describes an increase both in the numbers of elderly people and in the proportion of the population that is elderly.

Absolute Aging

In both developed and developing nations, there has been a rapid growth in the numbers of elderly people. This has led to a need to shift resources from young to old and to redesign communities to deal with the problems of disability and aging. The rate at which a nation has aged, its gross domestic product and the political will of the nation to recognize the geriatric imperative are all factors that decide the quality of life for older persons.

The Causes of Absolute Aging

The increase in numbers of older people is primarily due to the increased expectation of life at younger ages that has resulted from improved sanitation, better nutrition, housing, and working conditions. More recently, vaccinations of children and older persons, treatment of infectious diseases, improved management of chronic conditions, enhanced neonatal survival and improved care for persons with disabilities have all further increased life span.

The number of elderly people in a society depends primarily on the number of births 70+ years previously and the subsequent mortality of that cohort over those 70 years.

Relative Aging

The relationship of the number of older to the number of younger people in a society is of importance. Three factors determine the rate of relative aging: fertility rates, mortality rates, and, at a national level, patterns of migration.

As a country develops economically, there is usually a decline in mortality, which increases the numbers of older people. However, it is not until fertility declines, usually about 20 years later, that the relative age of the population begins to increase. This has happened in all the developed countries, except those whose age structure has been significantly affected by immigration.

Rising life expectancy and declining birth rate have noticeable effects on the age structure of a population. The old age dependency ratio, that is, the number of people aged over 65 per 100 persons of working age (15–64 years old), will increase by 2050 to over 2.5 times in the developed countries from just under 8.7 to over 22.6. In the developed countries, it will double to 4.4. The old age dependency ratio is most useful both for those primarily concerned with the management and planning of staff-intensive caring services and for economists and actuaries trying to forecast the financial consequences of pension policies (Figure 2). The demographic trend in many less-developed countries has a less dramatic effect on the economic systems than in many industrial countries, primarily due to the fact that less-developed countries usually have no or only rudimentary

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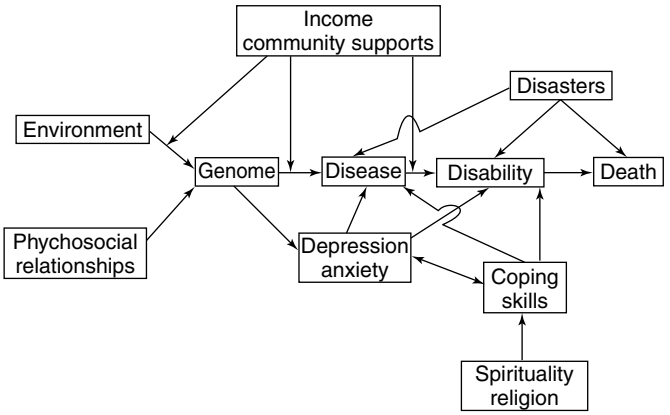

Figure 1 An illustration of the complex interrelationship between community/social aspects of aging, the genome and the progression of disease and disability toward death in the older person

pension systems. However, the societal implication of the demographic development in these countries remains precarious as a declining number of young people are available to take care of an increasing number of older people (UN website, 2004).

Retirement Migration

The distribution of old people, and thus their proportion in the population, varies very much from one part of a country to another. Although the main reasons for this range are variations in mortality and fertility rates, the migration of retirees also affects distribution.

In the United States, the general trend has been a migration from colder to milder climate, especially to Florida, South Carolina, Arizona, Nevada, and California. Longino (1990) described migration patterns of older people in terms of three moves. The first generally occurs at retirement, and involves moving for improved amenities (such as weather) and to maintain friendship contacts. The second move is precipitated by moderate functional disabilities, complicated by widowhood, and is often toward the community in which an adult child resides. The third move is due primarily to severe disabilities, and is local and toward an institution such as a congregate living or custodial facility (see discussion on Housing Problems).

In England, there has also been a southern migration, particularly to the southern coastal areas. Karn (1977) showed that people moved soon after retirement for a variety of reasons (Table 1). With the development of the European Union, many persons from the United Kingdom now migrate upon retirement to Southern Europe. The effect on aging of these diverse language, cultural, and health-care systems represents fascinating study for the future. Migration over the lifetime from a poor to a more advantaged community could improve the mortality of the migrants (Brimblecombe *et al.*, 2000).

While migration for functional elderly to better climates is on the whole positive, the development of disability often leads to frustration. With aging and the onset of cognitive and other problems, older persons often require

Table 1 Main reasons for retirement move

	Bexhill	Clacton
Sample number	503	487
Reasons for moving		
Better climate; cleaner air; sea air	33	19
Health reasons	11	18
Flat country	1	1
To get away from town or live in a quiet place	16	10
To live in a bungalow	4	9
Having to leave a tied house	5	5
The expense of living in the previous place	5	9
To have a change	7	9
To join friends or relations	10	15
Other	7	6

Reproduced from Karn V., Retiring to the Seaside, 1977, by permission of Taylor & Francis.

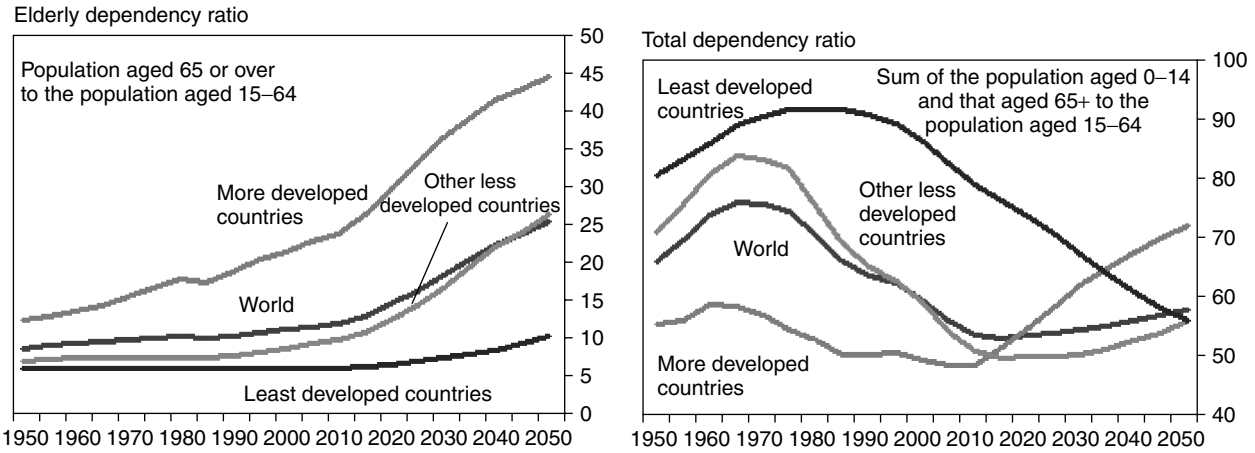

Figure 2 Demographic dependency ratio (*Source*: UN (2004 Revision))

an advocate to help them make health-care decisions and to deal with financial problems. The loss of the ability to drive safely dictates that choosing a place to migrate to, must take into account the availability of transportation and the juxtaposition of essential shopping and entertainment facilities. In the United States, a new profession of case manager has developed. Case managers are used extensively by concerned adult children to provide care for their older parents who live at a distance.

Effects of Immigration

Two forms of immigration can affect the older person: (1) migration as an adult and (2) migration beyond pensionable age. Adult immigrants may have different rates of certain diseases in older age than the population they immigrated to, for example, immigrants from Yugoslavia and Hungary had a higher stroke incidence than Swedes living in Malmo, Sweden (Khan *et al.*, 2004). Alternatively, immigration can lead to altered disease patterns. Japanese immigrants to Brazil have different cancer mortality rates than do Japanese in Japan (Iwasaki *et al.*, 2004). Immigrants may or may not adapt to diet and health practices of their host country. For example, older Koreans in the United States often continue to utilize traditional Korean medicine (Hanbang) (Kim *et al.*, 2002). Surprisingly, immigrants to the United States have a lower overall mortality than their American born counterparts (Singh and Siahpush, 2001). Quality of life may also change. Polish-American ethnic elderly had a significantly better subjective quality of life than Polish-immigrant elderly, who in turn had a better subjective quality of life than Poles in Poland (Berdes and Zych, 2000). Studies of Chinese immigrants to Canada and New Zealand have suggested a high rate of depression in older Chinese immigrants compared to the general population.

Immigration has assorted effects on aging. These may either be beneficial or deleterious. Awareness of health attitudes and health problems specific to older immigrant populations are an essential part of the therapeutic armanterium of health-care professionals.

The Male-to-female Ratio

The sex ratio of men to 100 women in the older age-groups is an aspect of population aging meriting special mention. The expectation of life at birth (Table 2) is about 5 years greater for females in most developed countries than it is for males. In Britain, the difference between the life expectancy at the age of 60 is about 3.5 years. In the United States, the sex ratio declines by 67% from ages 65–69 to 100+ (Figure 3).

There are biological and social reasons for the differences in life expectancy and also for the fact that there are more older women than old men. Biologically, the high mortality of male fetuses and infants and the inhibitory effect of estrogens on the development of atherosclerosis both play a part. However, social influences appear to be more important. In the early twentieth century, there were more men than women among the elderly of several developed countries, so the reversal of the sex ratio is a relatively recent phenomenon. The change would seem to have been due to the differing lifestyles of men and women. The prevalence of cigarette smoking, high alcohol consumption, and exposure to hazards of the workplace have penalized men in comparison to women. In some rapidly developing nations, such as India and Bangladesh, the ratio of older males to females is close to 1.

A higher death rate of men than women during wars has also affected the ratio, while higher rates of mortality from homicide and road traffic accidents continue to have an effect during peacetime. This is particularly evident in modern Russia where there is an 11-year difference between males and females related to societal problems, following the fall of the Soviet Empire. Finally, decreased death rates during pregnancy and decreased number of pregnancies has dramatically decreased female mortality (Table 3).

As the lifestyles of men and women become more alike, the gap will probably narrow; changes in female morbidity and mortality associated with increased consumption of

Table 2 Expectancy of life in males and females from birth

Country	Males	Females
Australia	77	83
Bangladesh	61	61
Canada	76	83
France	75	83
Germany	75	81
India	63	64
Japan	78	84
Netherlands	76	82
Russia	62	73
United Kingdom	76	81
United States	76	80

From OECD Factbook: Economic, Environmental and Social Statistics (2005); http://fiordiliji.sourceoecd.org accessed 6/22/2005.

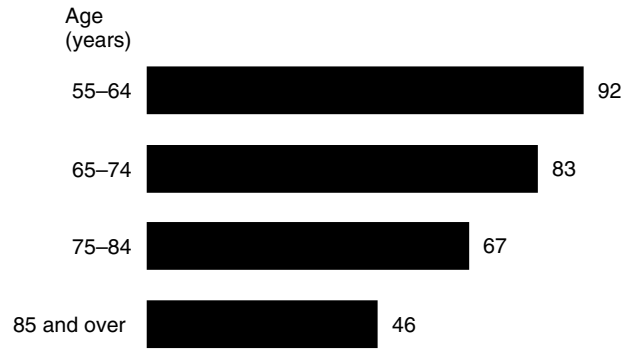

Figure 3 Sex ratio of people 55 years and over by age: 2002 (Number of men per 100 women) (*Source*: US Bureau of the Census, Annual Demographic Supplement to the March 2002 Current Population Surveys)

Table 3 Estimated average number of children to parents born in different years

Year of birth of parent	Average number of children	Average number of children surviving to age 45
1871	4.8	2.7
1881	4.1	2.5
1891	3.3	2.2
1901	2.6	2.0
1911	2.2	1.7
1921	2.0	1.6

Source: Reprinted from Care of the Elderly: Meeting the Challenge of Dependency 4th edition, AN Exton-Smith, J Grimley Evans. Copyright 1977 with permission from Elsevier.

alcohol and cigarettes are trends already apparent in younger cohorts.

The Changing Family

The structure of the modern family in the postindustrialization period has been influenced by increased age at marriage, increased divorce rate (50% in the United States), high geographic mobility, an increasing proportion of women in the labor force and fewer children. In the United States, these trends have been exacerbated in the "baby boomer" generation (those born between 1945 and 1965).

These trends would seem to make it more difficult for people to look after their elderly relatives when they become dependent. In many cases, this has created the "Sandwich Generation", where the middle-aged person needs to provide care for both dependent children and parents. Nevertheless, there is no evidence that the modern family in Britain or the United States cares less for its elders than did the family in the past. In fact, in the United States about 80% of older persons have living children, two-thirds of whom live within 30 minutes of the elderly parent. Furthermore, about 75% of those over 65 have some contact (personal or by telephone) each day. Support from adult children (transportation, financial and emotional) make it possible for 95% of people over 65 to live in the community and, of those, 54% live with spouse alone, 15% with other relatives, and 31% live alone (Administration on Aging, 2004). The vast majority (82%) live independently. Of those who need assistance for functional disabilities, 30% of the needs are met by family members, with the balance being met by a combination of family and formal community agency services.

Only 4.5% of older persons in the United States live in nursing homes, belying myths that families do not provide at least as much support as they did in the past.

GROWING OLDER – THE SOCIAL PROCESS

Although the distinction is arbitrary, it is useful to try to separate the effects of the physical processes affecting people as they grow older from the effects of the social consequences of attaining an advanced chronological age. There are three of these physical processes – aging, disease, and disability – and these overlap with each other and with the social process which is often called *growing old* (Figure 4).

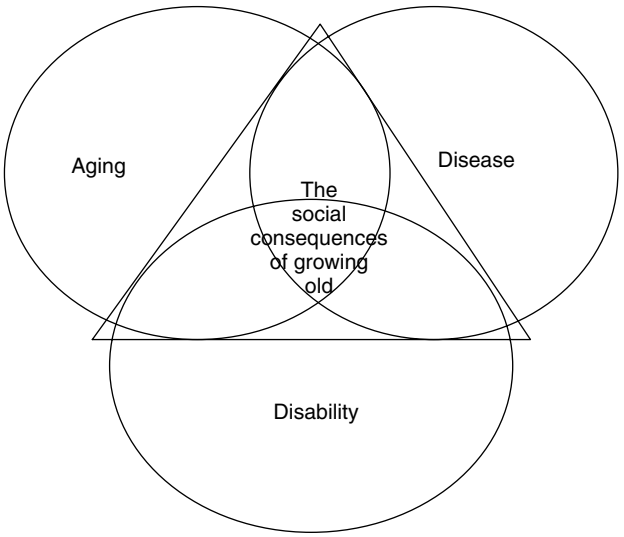

Figure 4 Aging, disease, disability and the social consequences of growing old

In this chapter, we will consider the social problems that occur as a result of growing old.

A Life Course Perspective on Age

It is useful to view older people as a product of life course events. These are depicted in Figure 5, in which life activities are arrayed against chronological age, representing what is culturally the "normal" course of events. Thus, infancy, childhood and adolescence occur in the first two decades of life and involve preparation for a job while living at home as a dependent. Adulthood and middle age bring with them increasing involvement in work, marriage and creating a family in an independent setting. Persons in old age, however, will have experienced departure of grown children, retirement, perhaps death of a spouse, family and friends and increasing dependency, especially from functional health limitations.

From a social psychological perspective, the transition from youth to adulthood may be seen as increasing attachment to one's social groups through meaningful and productive roles. Likewise, the transition from adulthood to old age may be seen as detachment from one's social groups as these meaningful and productive roles are given up. This may help account for the reports that the very old are, or at least perceive themselves to be, isolated, a "burden to society" and to have feelings of unworthiness. In fact, clinical depression is a common problem for older people, which could be exacerbated by these perceptions.

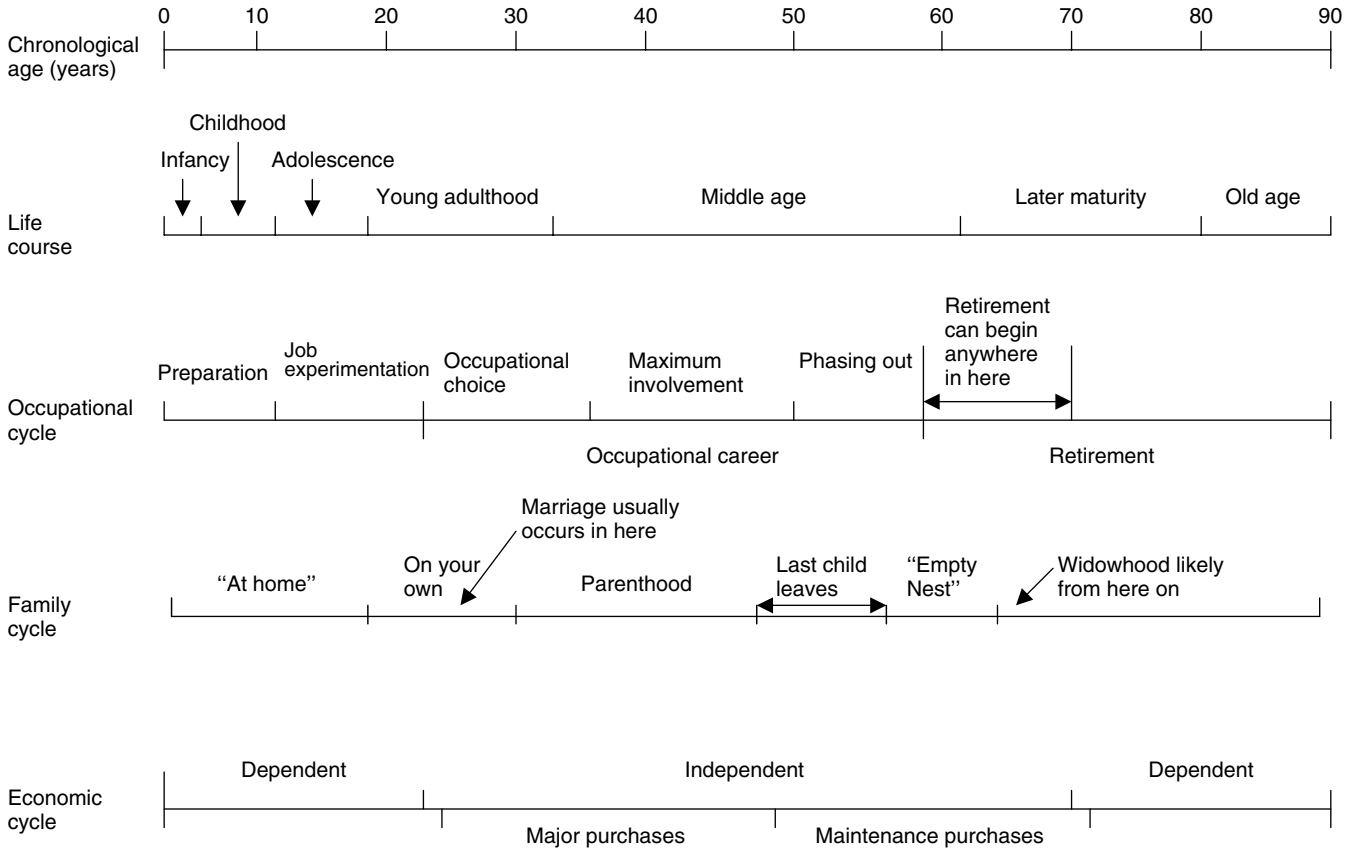

Figure 5 Relationships among age, life cycle, occupational cycle, and family cycle (These relationships fluctuate widely for specific individuals and for various social categories such as ethnic groups or social classes) (Reproduced from (Atchley RC, 1977). Copyright The Thomson Corporation)

Social Problems

When people talk about the social problems of elderly people, they are usually referring to certain practical problems that occur more frequently among older people, principally poverty, housing problems, difficulties with transportation, and isolation.

The reasons why older people suffer from certain types of social problems more frequently than younger people are listed in the following.

Poverty

Many of the problems of older people are simply due to the inability to purchase needed services to maintain an acceptable quality of life.

Immobility

The high prevalence of disabling disease combined with the difficulties older people have with public transport, compounded by poverty that restricts their use of cars and taxis, makes them less mobile than younger people. Immobility is the cause of many social problems.

Attitudes of Older People

Because of their upbringing, older people are, in general, less assertive than younger people. Because many were brought up in a culture in which the individual had fewer rights than he/she has today, many are less inclined to appeal against official decision, to seek the help of elected representatives, or to try to overcome bureaucratic inertia than younger people. In the United States, this is changing rapidly, with older persons becoming much more assertive. This began with the "gray panther" movement, and is expected to become even more prominent as the "baby boomers" generation reach old age.

POVERTY

The word poverty is so commonly used that it may seem unnecessary to define, but the word has two aspects which need to be distinguished – poverty threshold and relative poverty – and this distinction is particularly important at a time when there are rapid fluctuations in prices and wages.

Poverty threshold is defined by comparing a household's income with the level of prices of the basic commodities

necessary for life – the subsistence level, sometimes called the "*poverty line*" or "*bread line*". Those whose incomes are below the minimum level necessary for subsistence are deemed to be living in poverty.

The definition of relative poverty is made by comparing a household's income with the average level of incomes in their society. Although individuals' incomes may be sufficient to provide themselves and their dependents with the necessities of life, they may find their relative poverty upsetting because it symbolizes their low status. J. K. Galbraith, a famous American economist, has described the condition of relative poverty eloquently: "People are poverty stricken when their income, even if it is adequate for survival, falls markedly below that of the community. Then they cannot have what the larger community regards as the minimum necessary for decency and they cannot wholly escape, therefore, the judgment of the larger community that they are indecent. They are degraded, for in the literal sense they live outside the grades or categories which the community regards as acceptable".

In the United States, the median household income in persons over 65 years of age has increased from $16 882 to $23 152 (in 2002 dollars). Since the mid-1960s, poverty rates for persons 65 years and older have declined from nearly 30% to 10%. Older persons now have similar poverty rates to those seen in working persons. Over the same period, there has been an increase in poverty rates for those under 18 years of age (Figure 6). Between 1984 and 2001, the median net worth of households headed by a person age 65 years or more has increased by 82%. However, older white households have nearly 5 times the net worth of older black households.

Figure 6 Poverty rates by age: United States, 1966–2002. Note: Data shown are the percent of persons with family income below the poverty level. See Data Table for data points graphed and additional notes (*Source*: US Census Bureau, Current Population Survey)

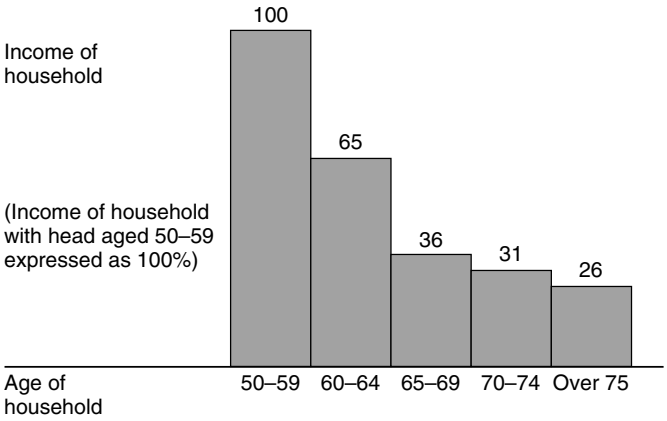

Figure 7 Income of household for various age-groups. From Age Concern (1977)

Social security provided 90% of income for one-third of Americans over 65 years of age. Other sources of income reported were assets (55%), private pensions (29%), government pensions (14%), and earnings (22%).

What is hidden by a simple comparison of "pensioner households" with "young households" is that there is a very wide range of wealth within the group of pensioner households. In general, older people are poorer (Figure 7).

The wide disparity is not due to a drop in income as people grow older, but to the fact that the proportion of people in each age-group who have an occupational pension decreases the older the age-group considered. This, in turn, is due to the fact that occupational pensions are a relatively recent innovation and it is therefore only younger retired people, those retiring more recently, who have qualified for them. The difference between the income of different age-groups of retired people is accentuated because men die younger than women, on average, so that the older groups consist of relatively more women, many of whom are eligible for neither national insurance nor occupational pensions and depend on a supplementary pension which is set at the lowest social security rate. Poverty is most common, therefore, among elderly women, particularly among those who never married.

HOUSING PROBLEMS

Environmental Problems

For some older people, the cause of their housing problem is not their dwelling but its environment. Many of those who lived in the city centers when they were first married have seen the neighborhood change. Some feel that the area has "gone down", that those who now live there do not have the same standards as they do, and that they are now aliens in a hostile environment in which they once felt at home.

The problems of elderly people in city centers and areas of urban deprivation are serious and difficult to remedy because often the best remedy is a move to another area in which the person may feel equally alien, although the majority of those who move do settle well and happily.

Structural Problems

Often, it is the dwelling itself that is the principal cause of the older person's concern. Common problems and their solutions can most easily be presented in a table (Table 4).

The services listed here are not universally available, and even where such services exist, older people often have difficulty mobilizing them. Every health professional can help by being aware of the range of services available, suggesting ways in which the dwelling can be improved and helping the person to contact the appropriate services.

Difficulties Caused by Disability

Sometimes the dwelling itself is suitable until the onset of disability, and the type of problem that most commonly causes a housing problem is the onset of a disabling disease that affects the older person's ability to climb the stairs, either stairs inside the house leading to the bathroom and toilet or the stairs leading to an apartment. Sometimes the circulation space within the house is too small to allow easy movement from room to room for a person using a wheelchair or walking aid.

The optimum solution to this type of difficulty is adaptation to the dwelling, and the domiciliary occupational therapist is the professional with the skill to do this. Solutions include the installation of ramps and indoor elevators. Adaptation of the kitchen and bathroom and addition of handrails can increase the safety of the house.

Table 4 Solutions to housing problems

Problem	Solution
Lack of toilet, bath, or hot water	The provision of grants and loans to help those who do not have the necessary capital
Difficulties with decorating, minor repairs such as broken windows and major repairs such as rewiring	Help from voluntary services with decorating and minor repairs Provisions of grants and loans for major repairs
The cost of rent and rates or property taxes	The provision of financial help with heating costs
Problems caused by disability	Adaptation of the dwelling, for example, ramps, rails, chair elevation
Difficulty with heating	Installation of more effective and efficient heating Improved insulation

Making a Move

The doctor's opinion about housing decisions is often as highly respected as his or her opinion about health decisions, particularly on that most difficult decision – "should I move or stay put"? Obviously, each case is unique but it is possible to list guidelines for decision making. Tables 5 and 6 give good and bad reasons for moving. One of us (JEM) uses the analogy of bungee jumping. When living alone is no longer as safe as bungee jumping, then it is time to move to a protective environment.

In general, every attempt should be made to solve the housing problem from which the old person feels he or she has to move away to remove the need for a move. That is not to say that there is never a need to move. Children often want their parents to move before it is necessary and older adults put off the move as long as possible. The development of "smart homes", lifeline alarms, and so on, are further delaying the time to when a decision has to be made to move. The decision of whether an older adult should move into a relative's home or to an institutional environment represents one of the hardest decisions associated with aging for both the older person and the caregiver.

Sheltered or congregate housing in the United Kingdom and senior apartment buildings or assisted living facilities in the United States are the types of housing that most people think of when new housing for elderly people is mentioned, although many move to independent flats or bungalows. Congregate housing offers security and reassurance and a well-designed and heated environment to elderly people and thus meets the needs of many frail elderly people, particularly those who are:

- nervous of living alone;
- anxious that they are not able to call anyone if they should fall ill;
- at risk of hypothermia or hyperthermia;

Table 5 Bad reasons for moving

- Because of structural problems; the possibility of solving the structural problems should always be explored first
- Because of financial problems; the provision of the full range of financial benefits may solve the problem
- Because of disability; the advice of an occupational therapist should be sought
- To move away from an area in which the old person feels "no one cares"; more people may be assisting than he or she is prepared to recognize

Table 6 Good reasons for leaving

- To move nearer a son, daughter, or relative who is willing and able to offer care
- To move away from a dwelling that is impossible to repair, improve, or adapt
- To move away from an environment that is causing severe depression or anxiety
- To move to sheltered housing if living alone is no longer safe

- isolated, although it should be said that some people feel just as isolated in sheltered housing as in an independent dwelling.

Sheltered housing is not always suitable for the person who has antisocial tendencies or for the very confused person because the caregiver cannot cope with a large number of dependent people or with very dependent people. The fact that the caregiver lives on site has many benefits, but it also has its drawbacks because he or she may be called incessantly by a confused person. It may be that the provision of more staff, that is, the creation of "very sheltered housing", will overcome some of the problems in sheltered housing, but it is always important to remember that the majority of disabled elderly people live and will continue to live in independent dwellings.

RETIREMENT

The concept of retirement was developed by the German chancellor Otto von Bismarck in the nineteenth century. His generals had asked that at some time they might be allowed to stop leading troops into battle. Bismarck asked his actuaries to calculate the age at which a general was unlikely to still be alive. When they told him it was 65 years, he magnanimously told his generals that they would be allowed to retire at 65 years of age with a state pension. He then introduced a national pension scheme to undermine the growing power of the Socialist Democratic Party.

Before World War II, retirement in Britain was a rarity with only the rich and those who were incapable of keeping a job retiring. In 1901, 60% of men over 65 years of age were in paid work. This number had declined to 48% in 1931 and to 13% by 1980. Following the passage of the Old Age Pensions Act of 1908, the first old age pensions were paid in England to just under half a million people (mainly women) in 1909. Following World War II, there was an increase in occupational pensions and deliberate attempts by employers and the government to force retirement. Technological developments were, in part, responsible for the erosions of the light work jobs often held by older persons. To some extent, the "Structured retirement" of the 1950s and 1960s was partly responsible for the marginalization of older people and their definition as a distinct, dependent social work. Toward the end of the twentieth century, retirement has become more acceptable, with many persons retiring in their early 50s.

In the United States, retirement became a reality for most old persons with the introduction of Social Security. The concept of retirement to "the golf course" has become a glamorized component of American Life. While Social Security is the bedrock of American retirement, for many it is their pension from their employer and personal investment that has allowed earlier retirement. In the present, insecurity about the ability of the government to fund social security and the government health plans for the old (Medicare) and the poor (Medicaid) is creating numerous, often scatterbrained, schemes on how to alter the retirement system. Some older Americans have, in retirement, been at the forefront of the modern globalization movement by retiring to Mexico or Costa Rico, where they can better leverage the buying power of the dollar.

THE "GOLDEN AGE" MYTH

Not only are modern societies those in which work is seen to be important, they are also societies in which wealth is an important determinant of status. The low income of elderly people, therefore, not only symbolizes the low esteem in which they are held but also perpetuates it. There is a myth about old age in times past that states that there was at one time a "Golden Age" for elderly people, an age in which it was good to be old and in which elderly people were loved and respected. The myth has become elaborated with time and some people believe that the Golden Age was destroyed by the industrial revolution because the traditional skills of elderly men and women, which they passed on to the younger generations by the fireside and in the inglenook, were rendered redundant by the speed of change at that time (Fischer, 1977).

Attractive though this myth is, there is no substance for it in fact. There never was a Golden Age for elderly people (Laslett, 1968). Rich and powerful elderly people were certainly able to hold onto their position of power and respect.

Poor elderly people usually finished up in the workhouse, and it is important to remember that in many societies the proportion of elderly people living in this situation was higher in times past than it is today, and that the quality of care in modern institutions far surpasses that seen even a quarter of a century ago. If ever there was a "Golden Age" for older persons, it is today.

AGISM

"Agism", like "racism" and "sexism" is a prejudice. People who hold agist views believe that all people over the age of 65 are of declining intelligence, unable to change or learn, rigid, conservative, and dull. They assume that any physical or mental change is due to the aging process and is, therefore, untreatable. They also have a certain set of expectations about the way older people should behave, for example, that it is not normal for older people to drink to excess, show an interest in sex, or even to argue forcibly with people with whose views they disagree. Many people, both old and young, hold agist views and assume that all physical and mental changes are due to "old age", that is, the aging process.

It is only in the last few decades that health professionals have begun to appreciate the difference between the effects

of the aging process and the effects of disease; it is not surprising that many people assume that all the changes they see in old age are due to "old age". It is extremely important to recognize that older persons, like young persons, show large variability in most characteristics.

The two main effects of agist beliefs among older persons are:

1. Failure to seek help for treatable medical problems – "What else can you expect at my age"?
2. Failure to comply with medical advice – "It was kind of the doctor to give me tablets but there's no point in taking them, it's just old age that's the problem".

Societal agist beliefs lead to undervaluing the contributions of older persons and providing inadequate societal resources for them. Political activism is needed to combat agism. Persons at all levels of the community and health professions often pay lip service to the aging demographic imperative, but fail to provide the financial benefits needed to overcome agist policies. Much of the media has recognized "agism" as politically incorrect and has tended to overcompensate by making older persons highly functional and cute. Some realistic movies about persons with Alzheimer's disease have attempted to be more balanced.

THE EFFECT OF SOCIAL FACTORS ON THE AGING PROCESS

George Valiant (2003) in his pioneering studies on aging in Harvard graduates and inner city persons living in Boston provided a framework for the effect of social relationships on aging successfully (Figure 8). He found that not smoking, exercise, not drinking alcohol to excess, obesity, and a stable marriage were the factors that predicted successful aging. Modern studies support the concept that social connection and perceived social support have an effect on health but mainly in persons facing crises, stressors and/or adversity (Johnson and Krueger, 2005). When *drosophila* flies are placed in a stressful environment they have increased mortality (Parsons, 2002). In humans, social isolation or perceived lack of social support leads to more diseases and a higher mortality rate.

Allostatic load is an index of wear and tear on the physiological systems of the body. Allostatic load has been shown in a longitudinal study to be related to heart disease, physical function, cognitive function, and death (Karlamangla *et al.*, 2002). The degree of allostatic load could be significantly modulated in men with strong emotional supports. This was not true in women. Other studies have demonstrated the importance of perceived control and economic variables in modulating the health effects of the social environment. This has led to the development of the concept of socioeconomic resiliency. An example of these interrelationships was shown by Suda *et al.* (2001) when they found that having the person delivering meals-on-wheels sit with the older persons while they ate decreased both their nutritional risk and their dysphoria.

Thus, the effect of social relationships on an older person developing and coping with disability depends not only on the strength of the relationship but also on the ability for the person to accept the relationship (e.g. are they depressed? Or did they have a lifelong inability to bond with others?) and their innate coping skills, as well as their economic status and the inherent severity of the disease process (Figure 9).

Over half of men and women over 65 years of age do not engage in leisure-time physical activities (Figure 10). This is despite the fact that endurance and resistance exercise can modulate disease processes and slow down the development of frailty, disability, and death. Exercise enhances frontal lobe cognitive function and may slow down the development of cerebral atrophy. Thus, there is a need for increasing the awareness of the benefits of physical activity with aging. It is important that simple ways to improve physical fitness,

Figure 8 Valiant, G – effect of social relationships on aging successfully

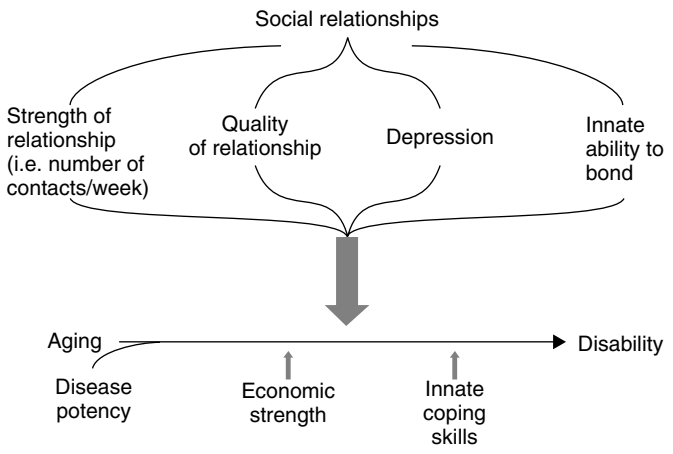

Figure 9 Factors modulating the ability of social relationships to modulate the aging process

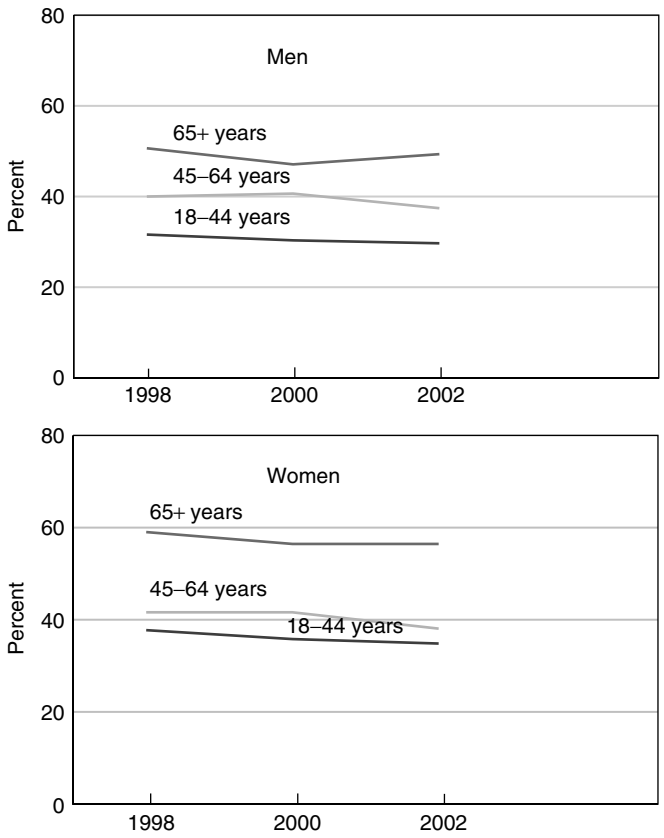

Figure 10 Adults not engaging in leisure-time physical activity by age and sex: United States, 1998–2002. Note: See Data Table for data points graphed, standard errors, and additional notes defining leisure-time physical activity (*Source*: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey)

for example, climbing stairs rather than taking the elevator, can be as effective as organized activities. The importance of balance exercises, such as Tai Chi, to reduce falls needs also to be stressed.

LIFESTYLE, NUTRITION, AND HEALTHY AGING: LESSONS FROM THE SENECA STUDY

The Survey in Europe on Nutrition and The Elderly: A Concerned Action (SENECA) examined lifestyle and nutrition in 19 towns throughout Europe, from Denmark to Portugal. All participants were born between 1913 and 1918. There was a large variation in lifestyle factors (de Groot *et al.*, 2004). In Padua, Italy, 78% of older persons drink alcohol on most days compared to Culemborg in the Netherlands where less than 20% drank regularly. Smoking varied from 7% in Vila Franea de Xira in Portugal to 41% in Roskilde, Denmark. The percent of people who still played sports varied from 4% in Portugal to 32% in Yverdon, Switzerland. Physical activity and smoking habits both predicted death and dependency. However, the relationship varied greatly from town to town, with the highest mortality rate in males being in the Netherlands, while the lowest death rate was in Bentanzor, Spain, a city in which the percentage playing sports was only half of that in Culemborg, but alcohol intake was nearly double. Cross-sectional studies such as the SENECA represent an important tool to understand how social factors modulate disability and mortality.

Another tool to examine the effects of social factors on aging is longitudinal studies in populations that are undergoing rapid change in their lifestyle. One such population is the Okinawans in Japan. This area, famous for its centenarians, has undergone rapid change from a caloric restricted, sweet potato-based diet to a rice and meat diet with greater calories and, at the same time, has decreased their energy expenditure. Early reports suggest that these lifestyle changes may be deleterious as males in Okinawa now have a life span that has sunk from 1st to 26th among the prefectures in Japan.

RELIGION AND SPIRITUALITY

There is an emerging literature recognizing the role of religion and spirituality in the preservation of psychological and physical health of older persons. Thus, for example, Koenig *et al.* (1995) reported that in medical inpatients religiosity correlated with a lower likelihood of feeling downhearted and blue, boredom, loss of interest, restlessness, feeling hopeless or feeling as if other people were better off. Brown and Gary (1994) found that fewer depressive symptoms were associated with religious involvement in a group of urban African-American males. In Israel, religious orthodoxy was found to be protective against death from coronary heart disease, independent of lifestyle correlates (Goldbourt *et al.*, 1993). Lack of comfort from religion and failure to participate in church events was associated with an increase in death following heart surgery (Oxman *et al.*, 1995). In patients with lung cancer, prayer was, in part, responsible for psychological well-being (Meraviglia, 2004). Positive religious coping methods were found to be associated with health improvements. On the other hand, persons who were not at peace with religious issues, or saw God as punishing, had worse outcomes. Spirituality in Britain was shown to be a significant predictor of psychological well-being in frail older persons. Spirituality, but not religiosity, was associated with self-appraised good health (Daaleman *et al.*, 2004). Spirituality is associated with a greater ability to deal with grief. In non-Judeo-Christian cultures, the role of spirituality is less clear; a study in Japan showed mixed effects; spirituality was positive in Thais (Pincharoen and Congdon, 2003; Kawa *et al.*, 2003). Of interest, religious television or radio was associated with worse physical functioning and greater medical comorbidity (Koenig *et al.*, 2004).

Overall, the role of religion and spirituality can be summarized as predominantly improving psychological health with a lesser effect on physical health. There is a small literature suggesting that not all forms of religion are positive. The

most parsimonious model for describing the role of religion and spirituality on health is to assume that it increases coping skills and enhances access to support groups. Health-care professionals need to be aware of the religious and spiritual affiliations of their patients and, in appropriate cases, be prepared to incorporate them into a holistic model of health care. Prayer is a commonly used coping strategy for many older persons dealing with disability or life-threatening illnesses. Involvement of a person's religious leader as part of the team approach to health care is important. In some countries, this may stretch to the need to involve the local shaman in the health-care team.

ANTIAGING MEDICINE

Since the beginning of time, persons have sought the mythical fountain of youth (Fisher and Morley, 2002). This has led over the centuries to numerous unscrupulous people selling their version of "snake oil" to vulnerable older persons. Within recent times, pseudoscientific claims associated with the growth hormone and dehydroepiandrosterone as agents that will "reverse the aging process" regularly appear in newspapers, magazines, and books. Many of these claims are based on flawed studies originally published in mainstream medical journals. Others are based on hypotheses developed by scientists and published in mainstream literature and then translated as fact by the lay press. A recent example of this is the theories of Aubrey de Grey, which are futuristic and not yet ready for "prime time" (de Grey *et al.*, 2002). In a 2003 book, Ronald Klatz and Robert Goldman claimed that "the future of antiaging medicine promises the elimination of the disability, deformity, pain, disease, suffering and sorrow of old age. In a few decades, the traditional enfeebled, ailing elderly person will be but a grotesque memory of a barbaric past". Hyperbole such as this is reminiscent of the popular book, *The Art of Living Long* written by the Italian, Luigi Comaro, in 1550.

The desire for longevity has led to eloquent claims by Linus Pauling that megavitamins will protect the cells from free radical damage. The concept that excess vitamins will rejuvenate remains alive today, despite studies suggesting that instead of prolonging life, they may shorten it.

Within the next decade, we will be faced with the possibility that stem cells can reverse aging of muscle and cure Alzheimer's disease. This research is accruing at increasing speed in Israel and South Korea, while under embargo in the United States. Such social factors will limit the rigor of scientific exploration into the role of stem cells and may eventually limit their use only to the very rich.

From this brief recounting, it is clear that social factors have played, and will continue to play, a major role in the development of antiaging medicine. Further, its availability to the general public depends on the decision of regulatory agencies such as the Food and Drug Administration in the United States.

THE ENVIRONMENT AND THE GENOME

There is an increasing literature that the environment can modulate gene expression. Two examples of the environment interaction have been found with the APOE4 gene: (1) Head injury accelerates Alzheimer's disease in persons who have the APOE4 allele (Mayeux *et al.*, 1995); (2) APOE4 is a risk factor for ischemic heart disease predominantly in smokers (Humphries *et al.*, 2001). The interaction of a major life event with a genetic predisposition increases the likelihood of major depression. Physical exercise produces different responses depending on the person's angiotensin converting enzyme insertion deletion genotype.

Similarly, the development of the fledgling science of pharmacogenomics has shown that the efficacy and side effects of drugs are associated with specific alleles. For example, persons with the apolipoprotein E allele have different responses to the antidepressant, paroxetine, dependent on the allele (Shanahan and Hofer, 2005). Side effects from paroxetine are related to the number of C alleles of HTR2α.

These simple examples represent only the start of the exploration of gene/environment interactions. As shown by centenarians and other long-lived persons, it is both the genome and the environment that eventually determines the successful aging potential of a person. The new social science of aging in the twenty-first century will require the inclusion of the person's genetic background to allow full interpretation of environmental effects.

ELDER ABUSE

Approximately 5% of older persons suffer elder abuse. In most cases, this is not due to physical violence or theft (though these instances are unfortunately not rare), but are more often due to neglect. Thus, poor nutrition or worsening of pressure ulcers is commonly associated with poor care. Even health professionals have practiced elder abuse, ranging from the notorious English physician serial killer, Dr. Shipman, to the use of physical restraints. Overall, persons who abuse older persons are more likely to have been abused when they were young and to have a mental illness. The solutions to elder abuse are complex ranging from criminal prosecution and separation of the elder from the abuser to psychosocial therapies including such options as daycare, respite for the caregiver and increased home care.

THE INTERNET

At present, older persons are much less likely to use the Internet than are middle-aged adults or children. However, this is changing rapidly. Many nursing homes offer Internet facilities for older persons to communicate with the children and grandchildren as well as to access the news. Older

persons are also using the Internet to obtain health-care information. With the movement of the "baby boomers" in the United States into the young-old over the next decade, these uses are expected to increase exponentially. There will also be increased communication between physicians and their patients via the Internet. We can also expect to see an increase in telemedicine as a more technologically adept group of persons join the aging cohort.

CULTURAL COMPETENCY

Shifts in populations have led to the requirement that health professionals acquire cultural competency and that social policy adapts to create more health professionals from ethnic minorities. A dramatic example of the effect of migration has been seen in the United Kingdom. In the 1950s, Bethnal Green was a predominantly white, working-class neighborhood, whereas in the 1990s it had changed to Tower Hamlets, the home of large numbers of Bangladeshi immigrants. Woodford has transformed to the home for many affluent Asians and Wolverhampton now has a substantial population of persons of Caribbean origin. Changes such as these require training programs for health professionals in the beliefs of different cultures and how they impact the interactions between older persons and their health-care providers.

DISASTERS

The events of 9/11 focused the attention of the world on the devastating effects of disasters. In all disasters, older persons are disproportionately affected. Studies in North Africa have shown that older persons are more likely to be left behind when genocide occurs and younger persons flee, creating separation between the generations. Older persons are also more likely to die during migrations from enemy troop areas and during periods of famine. In developed countries, heat waves are the most common disaster causing death. Over 400 older persons a year die from heat-associated death in the United States. Heat waves are often associated with power outages, which lead to air-conditioning being unavailable. This has been characterized as a "disaster within a disaster". The appropriate measures for preventing heat-related deaths are outlined in Table 7.

During disasters, such as hurricanes and earthquakes, one-third of older persons have a worsening of their medical conditions. The disruption of services following these disasters can lead to isolation of the older person, loss of home services and loss of access to prescription medicines. The appropriate contents of a disaster kit for older persons are listed in Table 8. Following disasters, there is an increase in myocardial infarctions. For example, the Hanshen-Awagi earthquake in Japan was associated with a threefold increase in myocardial infarctions.

Table 7 Preventing heat-related deaths

- When available, use home air-conditioning
- If no home air-conditioning is available, try to go to an air-conditioned mall
- Check frequently on persons at high risk
- Wear lightweight, light-colored clothing
- Reduce strenuous activities
- Drink plenty of fluids
- Avoid alcohol and caffeine
- Take cool showers or baths frequently
- Municipalities should develop a comprehensive heat emergency response plan including early warnings, appropriate health messages, and transportation to emergency shelters

Table 8 Items to be included in a senior disaster preparedness kit

Identification bracelet
Extra pair of glasses/hearing aids
List of medications
List of diseases
Set of emergency prescriptions
3 days to 1 week medication supply
Flashlight
Extra batteries
Pet evacuation plan
Family pictures
Emergency numbers (including a contact for at least one family member who lives in another geographical area).
A copy of FEMA's "Are You Ready?" emergency preparedness handbook

Table 9 Symptoms of nerve agent

- Excessive tearing and salivation
- Miosis
- Ptosis
- Nausea
- Vomiting
- Bronchospasm
- Bradycardia
- Muscle fasciculations
- Paralysis
- Restlessness
- Delirium

Deaths from fires are common in older persons. Persons living in mobile homes or old homes with faulty electrical work are at particular risk. Smoking and excessive alcohol use are human behaviors that are often associated with fires. Smoke detectors are a community action that can save lives.

Terrorism affects many countries. While a bombing incident is easily recognized, there is a need for surveillance techniques to detect outbreaks of disease as was shown in the slow recognition of the salmonella outbreak by the terrorist cult in Oregon in 1980 and the anthrax outbreak in the United States in 2001. The anthrax outbreak demonstrated that older persons had a greater susceptibility to biological agents and a poorer outcome than young persons. Terrorist attacks may include (1) biological agents, for example, smallpox, ricen, anthrax, plague, salmonella, ebola; (2) chemical agents, for example, vesicants (blistering agents) such as lewisite or mustard gas or cholinesterase inhibitors from the G group (GB-Sann, GD-Soman) or the V-group (VX); (3) nuclear

weapons or attacks on nuclear power plants or nuclear waste transport systems. The symptoms produced by cholinesterase inhibitors are listed in Table 9.

It is the responsibility of all to see that older persons are properly prepared for disasters, cared for during disasters, and returned to their homes after disasters.

KEY POINTS

- Genome/environmental interactions play an important role in the development of disease and disability with aging.
- Disasters have a disproportional effect on older persons.
- Religion and spirituality have positive effects on aging.

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11

Sexuality and Aging

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INTRODUCTION

Sexuality remains an important component of quality of life throughout the life span. The spectrum of sexuality and aging is outlined in Table 1. The full expression of sexuality is dependent on biological, psychological, and social factors. Testosterone is a driver of sexuality in both sexes, but its effect is modulated by psychological and social factors. The effects of aging on sexuality can create major anxiety, but with adequate education, sexuality can remain enjoyable throughout life. There is much misinformation about sexuality. While open discussion of sexuality has become much more common in the last 40 years, many older persons come from a generation where sexuality remains a taboo subject. This chapter will explore both the biology of sexuality and aging, as well as the emergence of the special needs of a substantial cohort of older gays and their unique needs. The role of disease in sexuality of older persons will be addressed. Finally, the problems faced by older persons who have had lifelong paraphilias will be considered.

SEXUALITY AND THE OLDER WOMAN

The major sexual problems reported by older women include lack of orgasm, lack of sexual interest, a decline in lubrication, failure to find an appropriate partner, dyspareunia, problems with safe sex, sexual aversion, and extramarital affairs (Nusbaum *et al.*, 2004). The number of older females who have intercourse decline from 30 to 78% at 60 to 70 years to 8–43% at 80 years. Most older persons who are still sexually active have intercourse on an average of once a week. Approximately 45% of older women masturbate. Of those still having intercourse, 73% enjoy intercourse and the rest tolerate it. Only 21% of women over the age of 75 years still have a partner. Most studies have shown that the majority of physicians do not include sexual concerns and questions as part of their general history taking. Figure 1 provides the spectrum of sexuality and the older female.

A number of diseases have a major impact on sexuality in women. The disease that most alters a woman's self-image is breast cancer. Up to 40% of women with breast cancer have a reduction in their sexual activity (Kaiser, 2003). The effect of breast cancer on sexuality is highly dependent on the relationship the woman has with her partner. Urinary incontinence can modify sexual interactions in up to a third of women. Severe incontinence may lead to the need for separate beds. Uterine prolapse is more likely than incontinence to alter sexual relationships.

Urogenital atrophy, due to estrogen deficiency, leads to vaginal dryness, vaginal bleeding, urge incontinence, urinary frequency and dysuria, irritation and pruritus of the labia and mons, dyspareunia, and urinary tract infections. All of these changes can lead to sexual dysfunction. A number of lubricants are now available to allow women to overcome vaginal dryness. Estrogen creams, tablets, and rings may also be useful in the management of severe vaginal dryness. However, it must be remembered that vaginal estrogen is absorbed and may have all the effects of oral or parenteral estrogen.

Menopause occurs in women with an average age of 52 years. Epidemiological studies have suggested that the older a woman is at menopause, the longer she will survive following menopause. Smoking is a major cause of an early menopause.

The major symptom of menopause is hot flashes. These occur in 85% of women at the time of menopause. While in most women hot flashes last less than 5 years, a few women continue to have hot flashes into their 80s. Environmental factors such as spicy foods and hot weather, and psychological factors, for example, stress, can be precipitants of hot flashes.

Menopause is not necessarily associated with a decline in libido. Some women find the cessation of menses liberating. Use of estrogen is declining following the results of the Women's Health Initiative and the HERS study. These studies showed that both estrogen alone and estrogen plus progesterone were associated with an increase in myocardial

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infarction, stroke, pulmonary embolism, and breast cancer (Grady *et al.*, 2002; Rossouw *et al.*, 2002). This was balanced by a decrease in hip fracture and colon cancer. Unfortunately, estrogen also appears to accelerate the onset of cognitive impairment in older women (Espeland *et al.*, 2004).

Testosterone levels decline rapidly between the ages of 20 to 40 years in women (Morley and Perry, 2003). There is then a slight increase in testosterone levels in women between the ages of 60 to 80 years. Testosterone, tibilone (an estrogen-progestagen-testosterone), and dehydroepiandrosterone (DHEA) all improve libido in older women. Besides increasing libido, testosterone has also been reported to improve general well-being, decrease mastalgia, decrease headaches, and increase bone mineral density and muscle mass (Table 2). The testosterone products available for women are listed in Table 3.

Table 2 Testosterone and women

Table 1 Sexuality and aging – the spectrum

- Biological
  - Hypgonadism
  - Erectile dysfunction
  - Disease
- Psychological
  - Depression
  - Sexuality attitudes
  - Perception of sexual attractiveness
- Social
  - Social interactions
  - Partner availability
  - Physical fitness
  - Community education
  - Awareness of sexuality

Table 3 Testosterone products available for older women

- Testosterone
  - Compounded vaginal creams
  - Gels
  - Testosterone undecanoate
  - Estratest (estrogen plus methyltestosterone)
- Tibolone
- (DHEA)

DHEA, Dehydroepiandrosterone.

Female hypoactive sexual desire disorder is defined as persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. This must cause marked distress or interpersonal difficulty. The condition cannot be

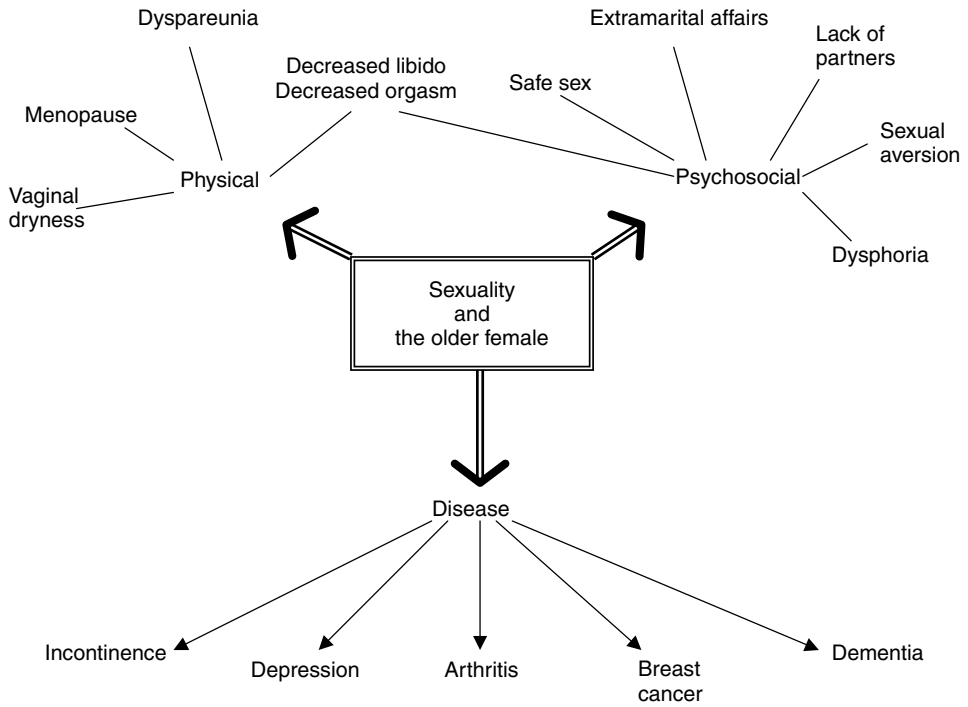

Figure 1 Sexuality and the older female

Table 4 Management of sexual dysfunction in older women

- Listen/ask
- Permission giving
- Provide information
- Specific suggestions
  - Vibrators
  - Paraclitoral stimulation
  - Lubricants
- Sex therapy

better ascribed to another psychiatric condition, for example, depression, or to the effects of a substance, for example, medication or a general medical condition. The approach to the management of sexual dysfunction in older women is given in Table 4.

It is important to recognize that for many older women intimacy and "cuddling" are more important than intercourse. The sensitive clinician needs to recognize the specific needs of the individual and then work with her to obtain her goals. Some women will choose to use complementary therapies such as black cohosh or dong quai soy. It is important to recognize that there is no long-term data on their efficacy or safety. At present, the use of estrogen in women over 60 years of age should be avoided whenever possible. There is a clear need for increased research on sexuality in older women.

ERECTILE DYSFUNCTION

Erectile dysfunction is defined as the inability to attain or maintain a penile erection sufficient for sexual performance on at least two-thirds of occasions (Morales, 2003). Physiologically, older males have an increased time for development of erection and less full erections with a decreased pre-ejaculatory secretion. During orgasm, there is a decline in expulsive force and urethral contractions. Following ejaculation, there is a rapid tumescence with rapid testicular descent. The refractory period is markedly prolonged.

A number of older males have an active sex life (Bortz *et al.*, 1999). However, studies in Germany and South America have found that 53% of men 70 to 80 years have some degree of erectile dysfunction (Rosen *et al.*, 2004). The Massachusetts Male Aging Study showed that at 40 years of age, severe erectile dysfunction was present in 5.1% and moderate erectile dysfunction in 17% (Derby *et al.*, 2000). By the age of 70, 15% had severe dysfunction and 34% moderate dysfunction. In the Olmsted County Study, 30% of men over 70 years of age had no erections, and only 10% had intercourse more than once a week (Masumori *et al.*, 1999). The major risk factors for developing erectile dysfunction are heart disease, diabetes mellitus, and hypertension.

Erections occur when the smooth muscle of the corpora cavernosa relaxes, allowing pooling of blood. Figure 2 demonstrates the different neurotransmitters involved in producing penile erection.

Approximately half the males with erectile dysfunction are found to have vascular disease as a cause. Other causes include medications, psychogenic causes, neuropathy, diabetes mellitus, thyroid disease, and hyperprolactinemia. Thiazide diuretics is the number one medication-associated cause of erectile dysfunction worldwide. Tobacco use is associated with increased erectile function. In dogs, nicotine decreased cavernous nerve stimulation and increased erections. In humans, smoking two cigarettes decreases the quality of papaverine-induced erections.

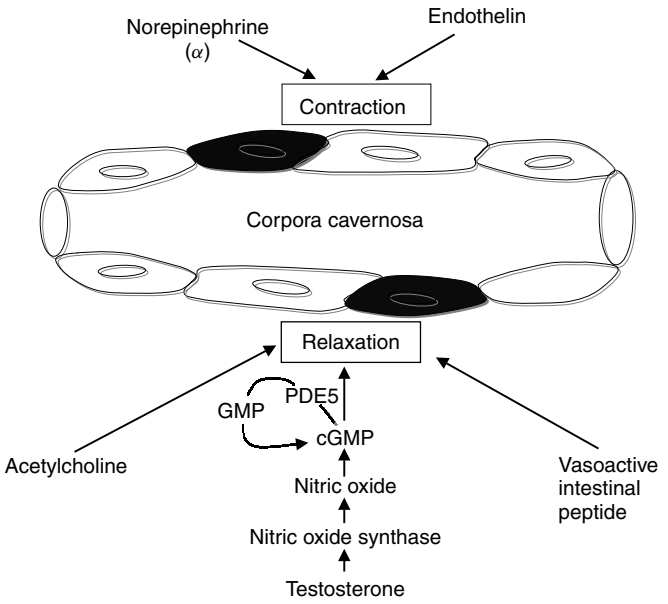

Figure 2 Neurotransmitters involved in producing a penile erection

While low testosterone levels decrease the production of nitric oxide synthase, most studies have failed to show that hypogonadism is a major cause of erectile dysfunction (Slag *et al.*, 1983). Nevertheless, persons with low testosterone have poor quality erections. Testosterone treatment improves the quality of erections produced by phosphodiesterase-5 inhibitors.

Table 5 lists the causes of erectile dysfunction and Table 6 lists the available management strategies for erectile dysfunction.

Table 5 Causes of erectile dysfunction

Vascular	– Atherosclerosis – Vascular leak
Medications	
Neurological	– Peripheral neuropathy – Spinal cord disease – Temporal lobe epilepsy
Urologic	
Endocrine	– Diabetes mellitus – Hypothyroidism – Hyperthyroidism – Hyperprolactinemia
Peyronies Disease	
Recreational Drugs	– Tobacco – Alcohol – Opiates

Table 6 Treatment options for an older male with erectile dysfunction

1. Psychological
2. Drugs
   - Sildenafil/Vardenafil
   - Uprima (Apomorphine SR)
   - Phentolamine
3. Intracavernosal injections
   - Alprostadil
   - Papaverine
   - Phentolamine
4. Vacuum tumescence device
5. Penile prosthesis

Table 7 Pharmacokinetics of the phosphodiesterase-5 inhibitors

	Sildenafil (hours)	Vardenafil (hours)	Tadalafil (hours)
T Cmax	1	1	2
T 1/2	4	4–6	17.5

Table 8 Side effects of phosphodiesterase-5 inhibitors

- Headache
- Flushing
- Dyspepsia
- Rhinitis
- Visual disturbance
- Hypotension
- Death (avoid nitrates)

The most common treatment for erectile dysfunction is a phosphodiesterase-5 inhibitor. This works by blocking the breakdown of cyclic GMP that has been generated by nitric oxide. There are 3 phosphodiesterase inhibitors in general use viz sildenafil, vardenafil, and tadalafil. The pharmacokinetics of these drugs is given in Table 7. The major side effects of phosphodiesterase-5 inhibitors are headache, flushing, dyspepsia, rhinitis, visual disturbances, hypotension, and death (Table 8). Persons on nitrates and α-adrenergic blockers should avoid phosphodiesterase-5 inhibitors. With aging, all phosphodiesterase-5 inhibitors have increased plasma concentration or area under the curve.

Vacuum tumescence devices are useful for older persons who wish to have intercourse rarely, for example, once a month. Intracavernosal injections with vasoactive agents can produce a response rate as high as 74% in older males.

A number of complementary medicines claim to improve erections, such as canthandrin or ginsenorides. These do not work and can produce hematuria.

Overall, modern medicine will allow the majority of older males to obtain an erection (Table 6). It is important to include the partner in decisions concerning which approach is best. It is important not to assume that an older male's partner is his spouse.

ANDROPAUSE

It is now recognized that testosterone levels decline at the rate of 1% per year (Matsumoto, 2002). This decline leads to 3–5% of persons 40 to 50 years of age and 30 to 50% of persons over 70 years of age having biochemical hypogonadism. Other estimates suggest that 20% of persons 40 to 70 years of age are hypogonadal. When testosterone levels fall below the normal level for men 20 to 40 years of age and this is accompanied by symptoms, such as a decline in libido or fatigue, the person is recognized as having andropause or androgen deficiency in aging males (ADAM). Other terms that have been used historically, for example, climacteric or male menopause, are no longer considered acceptable. Two symptom-screening tests have been developed to screen for males with andropause. These are the aging male symptom (AMS) and the ADAM questionnaires (Morley *et al.*, 2000) (Tables 9 and 10). Both have excellent ability to detect males with biochemical hypogonadism but also are answered positively by a large number of males who are not hypogonadal, for example, older persons with depression.

The cause of the fall in testosterone with aging is multifactorial (Table 11). While levels of luteinizing hormone are slightly higher in hypogonadal older males, it is rarely out of the normal range. Thus, these males are considered to have secondary (hypothalamic-pituitary) hypogonadism. The major cause for this seems to be irregular (chaotic) secretion of gonadotrophin-releasing hormone from the hypothalamus. There is also an increase in negative feedback of testosterone at the pituitary level. A decline in testosterone response to human chorionic gonadotrophin is present in older men. There is a decrease in Leydig cell number.

With aging, there is an increase in sex hormone binding globulin (SHBG). This leads to less testosterone being available to the tissues. Thus, the tissue available testosterone can either be measured directly using a free testosterone value by dialysis or a bioavailable testosterone (ammonium sulfate precipitation technique). Alternatively, tissue available testosterone can be calculated using an SHBG, total testosterone, and albumin by utilizing the program available at www.issam.ch. Most experts feel that some measure of tissue available testosterone is preferable to measuring a total

Table 9 ADAM questionnaire

Yes	No	1. Do you have a decrease in libido (sex drive)?
Yes	No	2. Do you have a lack of energy?
Yes	No	3. Do you have a decrease in strength and/or endurance?
Yes	No	4. Have you lost height?
Yes	No	5. Have you noticed a decreased enjoyment of life?
Yes	No	6. Are you sad and/or grumpy?
Yes	No	7. Are your erections less strong?
Yes	No	8. Have you noticed a recent deterioration in your ability to play sports?
Yes	No	9. Are you falling asleep after dinner?
Yes	No	10. Has there been a recent deterioration in your work performance?

A positive answer represents yes to 1 or 7 or any 3 other questions. (Circle one)

Table 10 AMS questionnaire Which of the following symptoms apply to you at this time? Please mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none."

Symptoms:	None	Mild	Moderate	Severe	Extremely Severe
Score =	1	2	3	4	5
1. **Decline in your feeling of general well-being** (general state of health, subjective feeling)	☐	☐	☐	☐	☐
2. **Joint pain and muscular ache** (lower back pain, joint pain, pain in a limb, general backache)	☐	☐	☐	☐	☐
3. **Excessive sweating** (unexpected/sudden episodes of sweating, hot flushes independent of strain)	☐	☐	☐	☐	☐
4. **Sleep problems** (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)...	☐	☐	☐	☐	☐
5. **Increased need for sleep, often feeling tired...**	☐	☐	☐	☐	☐
6. **Irritability** (feeling aggressive, easily upset about little things, moody)...	☐	☐	☐	☐	☐
7. **Nervousness** (inner tension, restlessness, feeling fidgety)...	☐	☐	☐	☐	☐
8. **Anxiety** (feeling panicky)...	☐	☐	☐	☐	☐
9. **Physical exhaustion/lacking vitality** (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities)...	☐	☐	☐	☐	☐
10. **Decrease in muscular strength** (feeling of weakness)...	☐	☐	☐	☐	☐
11. **Depressive mood** (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use)...	☐	☐	☐	☐	☐
12. **Feeling that you have passed your peak**...	☐	☐	☐	☐	☐
13. **Feeling burnt out, having hit rock-bottom**...	☐	☐	☐	☐	☐
14. **Decrease in beard growth**...	☐	☐	☐	☐	☐
15. **Decrease in ability/frequency to perform sexually**...	☐	☐	☐	☐	☐
16. **Decrease in the number of morning erections**	☐	☐	☐	☐	☐
17. **Decrease in sexual desire/libido** (lacking pleasure in sex, lacking desire for sexual intercourse)...	☐	☐	☐	☐	☐
Have you got any other major symptoms? If Yes, please describe:	Yes	☐	No	☐	

Table 11 Age-related changes in testosterone regulation

- Loss of circadian rhythm
- Asynchronous production of GnRH
- Increased inhibitory effect of T at pituitary
- Reduced GnRH release of LH
- Decreased T response to HCG
- Altered receptor and postreceptor effects

testosterone in making the diagnosis of andropause (Morley and Perry, 2003).

It is essential to recognize that the response to testosterone depends on the ability of testosterone once it is in the cell to translocate to the nucleus and bind to the receptor, and the receptor responsiveness. The binding capacity of the receptor depends on the number of CAG repeats in the receptor. The lower the number of CAG repeats, the better the binding capacity of the receptor. The effect of aging on the intracellular trafficking of testosterone, the ability of testosterone to bind to the receptor, and receptor responsiveness is just starting to be explored.

The symptomatic concept of andropause has been recognized since the time of the Chinese Text of Internal Medicine. The major symptom of andropause is a decline in libido. A decline in libido may also be due to depression, illness, or death of a spouse. Testosterone replacement restores libido in 70–80% of persons. Testosterone is also essential for the production of nitric oxide synthase. Production of nitric oxide is essential for firmness of the erection. Thus, low testosterone levels can lead to soft erections or failure of phosphodiesterase-5 inhibitors to produce an erection. Low testosterone levels are associated with a low ejaculatory volume.

The effects of testosterone in older males are listed in Table 12. Testosterone increases muscle mass and strength. Testosterone stimulates the stem cells to produce satellite cells (these are responsible for repair of skeletal muscle)

Table 12 Effects of testosterone in older males

- Improved libido
- Improved erectile function
- Increased hematocrit
- Increased muscle mass
- Increased muscle strength
- Increased IGF-1
- Decreased fat mass
- Decreased leptin
- Increased bone mineral density
- Decreased LDL and HDL cholesterol
- Increased brachial artery flow
- Decreased ST depression and angina
- Enhanced spatial cognition

Table 13 Testosterone therapies and the older male

- Injections
- Patches
- Gel
- Oral
- Inhalation
- Pellets
- Buccal/sublingual

and also increase protein synthesis in skeletal muscle and inhibit the ubiquitin-proteasome system, which is responsible for muscle breakdown. Testosterone inhibits adipocyte precursor cells, resulting in a loss of fat mass. Testosterone may improve function, but at present, there is limited data in this regard. Testosterone increases bone mineral density in the lumbar spine and the hip. Testosterone improves visuospatial cognition. Testosterone increases the hematocrit. Testosterone may have beneficial effects on the cardiovascular system. Testosterone's negative effects include gynecomastia, water retention, and possibly sleep apnea. The effects of testosterone on the prostate are uncertain. Testosterone cannot be given to persons with active prostate cancer.

The history of testosterone replacement stretches from the end of the nineteenth century when Brown-Sequard injected himself with an animal extract of testosterone. During the early twentieth century "monkey gland," goat testicle, and even human testicular transplants were done on the rich in an attempt to rejuvenate them. The available and experimental forms of modern testosterone replacement are listed in Table 13. At present, most men with andropause choose to use the testosterone gel forms of treatment. After the gel, the next most popular form of treatment is testosterone injections. Selective androgen receptor molecules (SARMs) have been developed to avoid the sexual stimulant properties of testosterone and enhance the anabolic features of testosterone replacement. These can be steroids, for example, nandrolone or oxandrolone, or a series of nonsteroid moleculares that can be ingested orally.

Libido represents an important component of sexuality in older men. The treatment of depression, and where appropriate testosterone replacement, can markedly enhance libido in older men.

SEXUALITY AND DISEASE

Disease can greatly alter the sexuality of an individual. Pain and disability can interfere with sexual intercourse. Fatigue reduces libido. Negative self-image is commonly associated with diseases. Depression, with or without other systemic diseases, can lead to a decline in libido or erectile function. Many systemic diseases reduce testosterone, leading to a decrease in libido (Morley and Tariq, 2003).

Diabetes mellitus causes early onset of erectile dysfunction and a decreased libido. Males with diabetes mellitus have low testosterone. Women with diabetes mellitus have clitoral damage. Women with diabetes have a decline in libido and vaginal lubrication, but minimal change in the ability to attain orgasm. Amputations and dysphoria can further alter sexuality in persons with diabetes.

Hip arthritis causes both stiffness and pain, which interfere with sexual intercourse. Judicious use of pain medication prior to intercourse, alterations in positions for intercourse, and positioning of pillows can all enhance the sexual experience for persons with arthritis.

Persons with left cerebrovascular hemisphere strokes have a marked decrease in libido. Coital frequency is markedly decreased in two-thirds of persons following a stroke. Persons with a stroke can often have hemineglect and their partners need to be aware of this problem. Men and women with Parkinson's disease have a high prevalence of sexual dysfunction. Very low testosterone levels have been reported in men with Parkinson's disease.

Death during sexual intercourse in persons with cardiovascular disease are extremely rare, with an estimated rate of 0.2 per 100 000 being reported in males (Jackson, 2000). Cardiovascular disease and hypertension are major risk factors for erectile dysfunction. Persons with two or three vessel disease have softer erections and more erectile dysfunctions than those with one vessel disease. In females, heart disease is associated with decreased libido, vaginal dryness, dyspareunia, orgasmic difficulty, and decreased genital sensation. Saint Louis University has developed a series of instructions for patients for resuming coitus following myocardial infarction (Table 14).

THE OLDER HOMOSEXUAL

There are approximately 3 million older gays in the United States. It is estimated that approximately 4% of older women are lesbian and/or bisexual. Older gays tend to have a higher use of alcohol and tobacco. The Women's Health Initiative found a slightly greater rate of obesity and dysphoria in older lesbians (Valanis *et al.*, 2000). Breast cancer was more common in lesbians.

Over 10% of AIDS cases occur in persons over the age of 65 years. Half of these cases are due to contaminated blood products. Condom use is extremely rare in gays over 50 years of age. HIV testing is rare in older gays.

Table 14 Instructions for patients and their spouses after myocardial infarction

- Sexual activity may be resumed as soon as you can bring your heart rate to 120 beats per minute without occasioning chest pain or shortness of breath, the equivalent of climbing two flights of stairs rapidly.
- If chest pain develops during intercourse, take a nitroglycerine. If the pain does not subside within 15 minutes, consider that an emergency.
- If chest pain regularly develops during sexual intercourse, take a nitroglycerine 10 minutes before attempting sex.
- No sexual position is the best or is prohibited. Some patients may find one position preferable for their needs.
- Altered desire after a heart attack is usually due to psychological factors, such as fear of another attack. Please discuss these problems with your physician.
- Altered ability to obtain an erection after a heart attack may be due to medications or to vascular disease of the penis. These are both treatable. Please discuss this with your physician.
- If the female has decreased vaginal lubrication or pain during intercourse, ask your physician to prescribe a lubricant or, in some cases, you may need estrogen replacement.
- There is no time of day during which we know that sex is safer or more dangerous. Please be advised that sexual activity in a novel situation, for example, with a partner other than your spouse, appears to be associated with increased problems.
- Discuss your sexual needs and concerns frankly with your spouse.
- Any questions or concerns you have should be brought to the attention of your physician or nurse. It is best that both you and your spouse read these instructions. Feel free to have your spouse discuss his or her problems with the health professional team.

Homophobia leads to many older gays not identifying themselves to health-care providers. Many physicians assume that their older patients are heterosexual. Unmarried homosexual partners are often poor as they grow old as they are ineligible, in the United States, for social benefits such as Social Security. A major issue occurs when the partner becomes sick, as the homosexual partner often has no rights to make health-care decisions for their ill partner. It is important that older gays have a durable power of attorney for health, designating their partner as the decision maker.

PARAPHILIAS

Paraphilias are unusual sexual behaviors. The advent of the Internet has greatly increased awareness of persons indulging in these behaviors. The most common paraphilias are erotic talk on the telephone or the Internet. Substantial numbers of persons practice exhibitionism, voyeurism, sadomasochism, sexual bondage, anal eroticism, and fetishes. Many of these practices are still indulged in by older persons. Some become exaggerated as the older person develops dementia and loses the normal social sensibilities. The physician needs to be aware that many of these are variants of normal sexuality and be able to help the older person.

Pedophilia is sexual abuse of a child by an adult. In one series of 261 cases, the child abuser was the grandfather in 16 cases (Jenny *et al.*, 1994). Pedophilia needs to be reported to the appropriate authorities.

SEXUALITY IN THE NURSING HOME

Sexuality does not necessarily cease on entry into a nursing home. However, within the nursing home there are multiple barriers to sexuality (Hajjar and Kamel, 2004). These include lack of privacy, lack of a partner, staff and resident attitude, and knowledge concerning sexuality and family attitudes. Special ethical problems arise when two demented patients form a romantic liaison. Most ethicists feel that older persons should retain their right to continue appropriate sexual behavior in the nursing home. It has been suggested that older persons may wish to develop an advanced directive for sexual behavior.

From the facility point of view, it is essential that staff are educated and taught to be accepting of sexual behavior. Residents of nursing homes are entitled to privacy and, where wanted, conjugal visits. Unfortunately, sexual abuse of residents, including rape, is also a problem in nursing homes. Maintenance of a healthy sexual environment in the nursing home is often extremely difficult. Society needs to come to terms with the sexual needs of older persons in nursing homes.

CONCLUSION

Awareness of the sexual needs of older persons is an important quality-of-life issue. Health-care providers need to be open to discussing sexual needs of older persons and providing treatment where appropriate. Education of society and increased awareness of sexuality in elders is a key component of sexual health in the future.

KEY POINTS

- Sexuality remains important to quality of life throughout the life span.
- There are biological, psychological, and social components of sexuality.
- Depression is a major cause of disruption of sexual enjoyment.
- Alternative sexual lifestyles are not unusual in older persons.

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12

Physical Fitness and Exercise

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INTRODUCTION

The interaction of physical activity, exercise, and physical fitness with health and aging is complex and multifaceted. Although many questions remain about mechanisms of effect and dose–response curves (Bouchard, 2001), a synthesis of the literature indicates many potentially positive effects of participation in physical activity on the aging process (Mazzeo *et al.*, 1998. Most recent position stands and policy recommendations include physical activity prescriptions for health promotion and disease prevention (American College of Sports Medicine *et al.*, 1998) as well as chronic disease treatment in older adults. However, there is still skepticism among some clinicians and investigators as to the actual potency of exercise for disease and/or disability prevention and treatment, particularly in already frail or near frail adults (Keysor and Jette, 2001). Exercise has not become fully integrated into usual geriatric medicine practice, and is still virtually absent from the core training of most geriatric medicine physicians and health-care professionals. Therefore, this chapter will attempt to provide a rationale for the use of exercise and physical activity for health promotion and disease prevention in older adults. Exercise will be discussed in terms of the specific modalities and doses that have been studied in randomized controlled trials for their role in the physiological changes of aging, disease prevention, and treatment of older persons with chronic disease and disability. Recommendations will be offered to address gaps in knowledge as well as clinical implementation needs in this field.

WHAT IS EXERCISE?

Any discussion of these issues must begin with definitions of the terminology. Physical activity has been traditionally defined as any bodily movement produced by contraction of skeletal muscle that significantly increases energy expenditure, although the intensity and duration can vary substantially. It should be noted that some forms of physical activity which may have particular relevance to an aging population (e.g. balance training) may not conform to this standard definition. This activity may be performed in leisure or occupational hours, and surveys for the older adult should capture both paid and unpaid (volunteer) work. Exercise is a subcategory of leisure time physical activity in which planned, structured, repetitive bodily movements are performed, with or without the explicit intent of improving one or more components of physical fitness.

Recently, efforts have been focused on merging these formerly distinct entities in order to promote "lifestyle integration" of exercise as a means to enhance long-term adherence. For example, taking the stairs instead of the elevator, standing on one leg while doing the dishes, or slowly standing and sitting without use of the arms represent ways of incorporating aerobic, balance, and strengthening exercises, respectively, into everyday activities. Current investigations are exploring whether such prescriptive techniques are superior to standard approaches for the promotion of behavioral change in older adults.

Physical fitness, by contrast, is defined as a set of attributes that contribute to the ability to perform physical work (e.g. cardiorespiratory endurance, muscle power, balance, flexibility, and body composition) or influence health status. "Metabolic fitness" has been advanced more recently as a term that encompasses a range of biologically important traits (increased insulin sensitivity, lipoprotein lipase activity, endothelial cell reactivity, heart rate variability, etc.) which may contribute to health status, but do not directly affect exercise capacity. Both genetic predisposition and lifestyle factors contribute to physical and metabolic fitness and the extent to which they are modifiable with exercise training.

Dose–response relationships between changes in fitness and better health outcomes have been defined for some, but certainly not for all diseases and syndromes (Bouchard,

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2001). Some modalities or doses of exercise that are promoted for older adults (mild calisthenics, slow-paced walking) have little or no discernable effects on physical fitness, but may possibly yield benefits in some domains. This area of investigation is critical for defining *threshold and optimal* levels of activity that are necessary for health promotion and disease management. It should be recognized that what is suitable for prevention may be entirely inadequate for treatment, as is the case with pharmacological management of chronic diseases as well. For example, aspirin may reduce the risk of ischemic heart disease, but a host of potent agents may be required once coronary occlusive disease is present and symptomatic.

DOES EXERCISE INCREASE LIFE EXPECTANCY?

The effects of exercise on total mortality are unlikely to ever be substantiated via randomized controlled clinical trials, given the impossibility of random assignment to various physical activity regimens over many decades. However, there is clear evidence of an inverse, linear dose–response relationship between the volume of physical activity reported in epidemiological studies (with sample sizes ranging from less than 500 to over 2.5 million individuals) and all-cause mortality rates. These relationships are demonstrable for both men and women, and for older as well as younger adults. Volumes of energy expenditure during exercise of at least 1000 kcal/week reduce mortality by about 30%, whereas reductions of 50% or more are seen with volumes closer to 2000 kcal/week, when more precise measures or estimates of physical activity participation incorporating fitness assessments are utilized instead of surveys. These changes in all-cause and cardiovascular mortality translate to an increase in life expectancy of approximately 2 years for those exercising at such volumes. Despite the consistency of the data from well-designed observational studies, many questions still remain regarding the minimum threshold for efficacy, the effect of exercise intensity, duration and frequency (apart from contributions to overall volume), the effect of nonaerobic modalities of exercise, and the mechanism of benefit. From a public health perspective, if small, effective doses of moderate-intensity activity are found to be as beneficial as longer bouts of vigorous activity, adoption of mortality-reducing physical activity recommendations by sedentary middle-aged and older adults may be more successful. Of particular relevance to the geriatric exercise prescription are studies which have demonstrated that a change from a sedentary to more active lifestyle in midlife or beyond is associated with a reduction in mortality. In the sections that follow, the focus is on changes in physical fitness and body composition, quality of life and disease burden, rather than on changes in longevity itself. It is in these domains that the centrality of physical activity patterns to optimal aging is perhaps most relevant to the concerns of the health-care professional and the older individual.

PRESERVING EXERCISE CAPACITY WITH AGE VIA AN ACTIVE LIFESTYLE

There is a great similarity between the physiologic changes attributable to disuse and those which have been typically observed in aging populations, leading to the speculation that the way in which we age may be modulated with attention to activity levels (Bortz, 1989). The most important physiological changes associated with aging or disuse that impact upon exercise capacity are presented in Tables 1–4. In most physiologic systems, the normal aging processes do not result in significant impairment or dysfunction in the absence of pathology and under resting conditions. However, in response to a stress, or significant disuse, the age-related reduction in physiologic reserves ("homeostenosis") may result in difficulty completing a task requiring near-maximal effort.

Although changes in maximal work capacity (aerobic fitness, or maximal oxygen consumption) will be immediately noticeable and disastrous for an elite athlete, they may accrue insidiously in nonathletic populations because most sedentary individuals rarely call upon themselves to exert maximal effort in daily life. Women are particularly susceptible here, because their initial reserve of muscle mass is so much lower than that of men, due to gender differences in anabolic hormonal milieu as well as lifestyle/occupational factors. They will therefore cross this threshold where losses of

Table 1 Changes in exercise capacity due to aging or disuse potentially modifiable by physical activity

Component of exercise capacity	Effect of aging or disuse
Maximal aerobic capacity	Decrease
Tissue elasticity	Decrease
Muscle strength, power, endurance, mass	Decrease
Oxidative and glycolytic enzyme capacity, mitochondrial volume density	Decrease
Gait speed, step length, cadence, gait stability	Decrease

Table 2 Changes in cardiorespiratory function due to aging or disuse potentially modifiable by physical activity

Cardiorespiratory function	Effect of aging or disuse
Heart rate and blood pressure response to submaximal exercise	Increase
Maximal heart rate[a]	Decrease
Resting heart rate	No change
Maximal cardiac output, stroke volume	Decrease
Endothelial cell reactivity	Decrease
Heart rate variability	Decrease
Maximal skeletal muscle blood flow	Decrease
Capillary density	Decrease
Arterial distensibility	Decrease
Vascular insulin sensitivity	Decrease
Plasma volume, hematocrit	No change, decrease
Postural hypotension in response to stressors	Increase
Total lung capacity, vital capacity[a]	Decrease
Maximal pulmonary flow rates[a]	Decrease

[a]No evidence yet that exercise can prevent or reverse these changes of aging.

Table 3 Changes in metabolism and body composition due to aging or disuse potentially modifiable by physical activity

Metabolic/body composition change	Effect of aging or disuse
Resting metabolic rate	Decrease
Total energy expenditure	Decrease
Thermic effect of meals	Decrease, no change
Total body water	Decrease
Total body potassium, nitrogen, calcium	Decrease
Protein synthesis rate, amino acid uptake into skeletal muscle, nitrogen retention, protein turnover	Decrease
Gastrointestinal transit time	Increase
Appetite, energy intake	Decrease, no change
Glycogen storage capacity, glycogen synthase, GLUT-4 transporter protein content, translocation to membrane	Decrease
Lipoprotein lipase activity	Decrease
Total cholesterol, LDL cholesterol	Increase
HDL cholesterol	Decrease or no change
Hormonal and sympathetic nervous system response to stress	Increase
Growth hormone, IGF-1[a]	Decrease
Heat and cold tolerance, temperature regulatory ability	Decrease

LDL, low density lipoprotein; HDL, high density lipoprotein.
[a]Most training studies show no change in growth hormone or circulating IGF-1 although tissue levels of IGF-1 may increase.

Table 4 Changes in central and peripheral nervous system due to aging or disuse potentially modifiable by physical activity

REM and slow wave sleep duration	Decrease
Cognitive processing speed, accuracy	Decrease or No change
Attention span	Decrease or No change
Memory	No change, Decrease
Executive function	Decrease or No change
Motor coordination, force control	Decrease
Neural reaction time, neural recruitment	Decrease
Autonomic nervous system function	Decrease

REM, rapid eye movement.

musculoskeletal capacity impact on functional status, at least 10 years before men do on average. (Guralnik *et al.*, 1993).

Another important consequence of age-related changes in physiologic capacity is the increased perception of effort associated with submaximal work (a lowering of the anaerobic threshold, or the approximate level at which significant dyspnea occurs). This changing physical capacity has the unfortunate negative side effect of increasing the tendency to avoid stressful activity. Such behavioral change compounds the sedentariness caused by changing job requirements or retirement, societal roles and expectations, and other psychosocial influences. Thus, a vicious cycle is set up: "usual" aging leading to decreasing exercise capacity, resulting in an elevated perception of effort, subsequently causing avoidance of activity, and finally feeding back to exacerbation of the age-related declines themselves secondary to the superimposition of disuse on biological aging.

Many studies suggest that chronic adaptation to physical activity can markedly attenuate decrements in exercise capacity that would otherwise occur with aging (see Tables 1–4), with the notable exception of maximal heart rate (due to declining sensitivity to β-adrenergic stimulation in the aging heart (Scarpace *et al.*, 1992)). Although peak exercise workload achievable is therefore always lower in aged individuals, the cardiovascular and musculoskeletal adaptations to chronic aerobic exercise enable the trained individual to sustain higher submaximal workloads with less of a cardiorespiratory response (heart rate, blood pressure, and dyspnea), as well as less overall and musculoskeletal fatigue.

Musculoskeletal function (strength, power, muscle endurance) in aging is dictated largely by the size of the muscle mass which is contracting, and to a lesser extent by changes in surrounding connective tissue in the joint (cartilage, tendons, and ligaments) and neural recruitment, conduction velocities, glycolytic and oxidative enzyme capacities, and fatigue patterns. Sedentary individuals lose large amounts of muscle mass over the course of adult life (20–40%), and this process, termed *sarcopenia*, plays a major role in the similarly large losses in muscle strength observed in both cross-sectional and longitudinal studies (Asmussen and Heeboll-Nielsen, 1961; Hughes *et al.*, 2002). However, unlike many other changes which impact on exercise capacity, muscle mass cannot usually be maintained into old age even with regular aerobic activities in either general populations or master athletes. Only overloading of muscle with weight-lifting exercise (resistance training) has been shown to largely avert losses of muscle mass (and also strength) in older individuals. For example, Klitgaard *et al.* (1990) found that elderly men who swam or ran had similar measures of muscle size, strength, and metabolism as their sedentary peers, whereas the muscle of older men who had been weight lifting for 12–17 years was almost indistinguishable, and even superior in some aspects, to healthy men 40–50 years younger than them.

Clearly, habitual exercise has the potential to lessen the impact of biological aging on two of the major elements of exercise capacity: aerobic fitness and muscle strength. Similarly, there is evidence that balance training and flexibility training (American College of Sports Medicine *et al.*, 1998) induce adaptations in associated declines in these areas.

OPTIMIZATION OF BODY COMPOSITION WITH AGING

"Usual aging" is associated with significant losses of bone and muscle (lean mass), and increases in adipose tissue, along with central and visceral shifts in the regional distribution of adipose tissue stores. The extent to which these changes occur in an individual depends upon a combination of genetic, lifestyle, and disease related factors that are all interrelated. All of these body composition changes may negatively impact upon metabolic, cardiovascular, and musculoskeletal function (Hughes *et al.*, 2001), even in the absence of overt disease, and therefore it is important to anticipate them and optimize lifestyle choices and other treatments

which can counteract the negative effects of aging and/or disease on body composition. As detailed in the sections that follow and outlined in Table 5, one of the most potent pathways from physical activity to health status involves the modulation of these age-related shifts in body composition by habitual exercise patterns.

Role of Exercise and Physical Activity in Bone Health and Fracture Risk

Age-related Changes in Bone

Bone mass begins to decrease well before the menopause in women (as early as the 20s in the femur of sedentary women), and accelerates in the perimenopausal years, with continued declines into late old age. Similar patterns are seen in men, without the acceleration related to loss of ovarian function seen in women. As with losses of muscle tissue (sarcopenia), many genetic, lifestyle, nutritional, and disease and medication-related factors enter into the prediction of bone density at a given age.

Physical Activity and Bone Health

A wealth of animal and human data provide evidence for a relationship between physical activity and bone health at all ages. Mechanical loading of the skeleton generally leads to favorable site-specific changes in bone density, morphology, or strength, whereas unloading (in the form of bed rest, immobilization, casting, spinal cord injury, or space travel) produces rapid and sometimes dramatic resorption of bone, increased biochemical markers of bone turnover, changes in morphology such as increased osteoclast surfaces, and increased susceptibility to fracture.

Comparative studies of athletic and nonathletic populations usually demonstrate significantly higher bone density in the active cohorts, ranging from 5 to 30% higher, depending upon the type, intensity, and duration of exercise training undertaken, and the characteristics of the athletes studied. Exceptions occur with nonweight-bearing activities such as swimming, or amenorrheic or competitive distance runners, who appear similar to controls. Similarly, on a smaller scale, differences are often observed between habitually active and sedentary nonathletic individuals.

Experimental evidence in animal models as well as some human data suggests that changes in bone strength not directly correlated with density may contribute to the overall benefits of mechanical loading for skeletal integrity and resistance to fracture (e.g. increased bone volume or altered trabecular morphology), so that evaluating bone density changes alone likely underestimates the skeletal effects of loading.

Consistent with bone density findings noted above, hip fracture incidence has been observed to be as much as 30–50% lower in older adults with a history of higher levels of physical activity in daily life, compared to age-matched, less active individuals. For example, in the prospective epidemiology of osteoporosis study (EPIDOS) study of 6901 white women over the age of 75 followed for 3.6 years, investigators found that a low level of physical activity increased the risk for proximal humerus fracture by more than twofold. The relative risk of fracture in sedentary women (RR = 2.2) was greater than that attributable to low bone density (RR = 1.4), maternal history of hip fracture (RR = 1.8), or impaired balance (RR = 1.8). The interaction

Table 5 Exercise recommendations targeting optimal body composition for older adults

Exercise recommendations	Decreased adipose tissue mass and visceral deposition	Increased muscle mass and strength	Increased bone mass, density, and reduced fracture risk
Modality	Aerobic or resistance training	Resistance training	• Resistance training or aerobic training[a] • High impact activities (jumping using weighted vest during exercise) if tolerated by joints • Balance training
Frequency	Aerobic: 3–7 days/week Resistance: 3 days/week	3 days/week	• Resistance or aerobic training: 3 days/week • Balance training: up to 7 days/week
Volume	Aerobic: 30–60 minutes/session Resistance: 2–3 sets of 8–10 repetitions of 6–8 muscle groups	2–3 sets of 8–10 repetitions of 6–8 muscle groups	• 30–60 minutes of aerobic training • 2–3 sets of 8–10 repetitions of 6–8 muscle groups • 50 jumps per session for high impact[b] • 2–3 repetitions of 5–10 different static and dynamic balance postures
Intensity	Aerobic; 60–75% of maximal exercise capacity (VO2 max or maximal heart rate) or 13–14 on the Borg Scale of perceived exertion Resistance: 60–80% of maximal strength (one repetition maximum)	60–80% of maximal strength (one repetition maximum)	• 60–80% of maximal capacity (one repetition maximum) as load • 5–10% of body weight in vest during jumps; jumps or steps of progressive height • Practice most difficult balance posture not yet mastered

[a]Aerobic exercise should be weight-bearing modalities of exercise with high ground-reaction forces (e.g. walking, jogging, running, stepping, rather than swimming or cycling).
[b]Thus far proven only in premenopausal women.

of these risk factors is indicated by the fracture rate, which rose from about 5 per 1000 woman-years in individuals with either bone fragility or high fall risk to 12 per 1000 woman-years for women with both types of risk factors. Such data suggest the great potential utility of multifactorial prevention programs for osteoporotic fracture that can address *both* bone density and fall risk (sedentary behavior, sarcopenia, muscle weakness, poor balance, polypharmacy, etc.) simultaneously.

Exercise Intervention Trials in Postmenopausal Women and Older Men

Metanalyses of the randomized controlled trials of exercise and bone density in postmenopausal women are outlined in Table 6. Significant changes in the femur, lumbar spine, and radius have been seen following aerobic training, resistance training, and combined programs of aerobic and resistive exercise. Unlike results obtained in younger women, isolated high impact training (jumping, skipping, heel drops) has not yet been found to be effective in studies of postmenopausal women. High dropout rates (30–50%) are problematic in these trials, raising the issue of generalizability and sustainability of the outcomes observed. This is particularly relevant to fracture prevention efficacy of exercise, as several studies have shown complete or partial reversal of gains in bone mineral density (BMD) after the cessation of training.

For older men and women, a combination of decreased anabolic hormones (estrogen, testosterone, growth hormone), increased catabolic milieu (higher leptin and cortisol associated with visceral adipose tissue), the emergence of musculoskeletal and other diseases, retirement, and reduced recreational activities have a major negative impact on bone as well as muscle tissue. The majority of studies demonstrating the efficacy of aerobic or resistive exercise on bone density have been conducted in women between 50 and 70 years of age, and it is not yet known if efficacy would be similar in older women with multiple comorbidities, who have usually been excluded from such trials. Both types of exercise have approximately equivalent effects on bone health in postmenopausal women of about 1–1.5% per year between exercisers and nonexercisers in meta-analyses of well-designed trials (Kelley, 1998a,b; Wolff *et al.*, 1999; Wallace and Cumming, 2000; Kelley *et al.*, 2001).

Optimal Exercise Modality and Intensity for Bone Health

The predominant exercise training factor that influences bony adaptation is the intensity and novelty of the load, rather than the number of repetitions, sets, or days per week, or even total duration of the program. This observation is also true for animal models of mechanical loading, in which bone is most sensitive to short periods of loading characterized by unusual strain distribution, high strain magnitudes, and rapid rate of loading.

The relative efficacy of aerobic versus resistive exercise regimens for postmenopausal women may be perhaps best assessed via studies that have directly compared various intensities of these two exercise modalities in randomized subjects. Kohrt *et al.* (1997) found that both aerobic activities with high ground-reaction forces (walking, jogging, stair climbing) and exercises with high joint-reaction forces (weight lifting, rowing) significantly increased BMD of the whole body, lumbar spine, and Ward's triangle, whereas only the ground-reaction group increased BMD at the femoral neck (Kohrt *et al.*, 1997). The weight-lifting group preserved femoral neck BMD relative to controls, as has been seen in other resistance training studies (Kerr *et al.*, 2001). However, lean mass and muscle strength increased only in the weight-lifting group, leaving overall benefits of these two types of exercise for ultimate fall and fracture prevention still unresolved. Kerr randomized 126 postmenopausal women to 2 years of high-intensity weight-lifting exercise, moderate-intensity aerobic training (circuit training and stationary cycling), or sedentary control condition. Total hip and intertrochanteric BMD was improved only by strength training, and was significantly different from aerobic training or control groups (+3.2% at 2 years). As most comparative studies other than Kohrt's (Kohrt *et al.*, 1997) and Kerr's (Kerr *et al.*, 2001) have not sought to optimize both modalities, it is still not possible to definitively choose one best modality for all bone sites. In general, the older the individual, the more favorable the resistance training appears, due to its broader benefits on muscle, bone, balance, and fall risk, relative to aerobic training. If aerobic training is chosen, however, activities that are weight bearing and higher impact have a greater efficacy than nonweight-bearing or low-impact aerobic activities.

It is important to consider not only the optimal modality of exercise, but also the relative intensity, as the skeletal adaptation is critically linked to the *intensity* of the loading (whether due to increased amount of weight lifted during resistance training, or higher ground-reaction forces during aerobic/jumping activities). Interesting results have been reported recently by Cussler *et al.* (2003), in a randomized trial of 140 postmenopausal women participating in a multimodal exercise program (high-intensity resistance training, and a weight-bearing circuit of moderate-impact activities including walking/jogging, skipping, hopping, stair climbing/stepping with weighted vests). Bone density improvements at the femoral trochanter were significantly and linearly related to total weight lifted during the 12 months, as well as total weight lifted in leg press, squats, and military press exercises, but not to volume or quality of the nonresistance training components of the program. High-intensity resistance training is also more beneficial than low-intensity training for muscle strength gains and muscle hypertrophy, as well as associated gait disorders, functional impairments, and disability, making it ideal as a multiple risk factor intervention strategy for injurious falls in osteopenic women.

Exercise in the Treatment of Osteoporotic Fracture

In older men and women who have already sustained an osteoporotic fracture, exercise is still extremely important to assist in recovery of function as well as prevent recurrent

Table 6 Metanalyses of physical activity and bone density

Reference	Population	Studies included	Total number of trials, subjects	Type of exercise	Study treatment effect[a]	Significance level
Berard *et al.* (1997)	Healthy women >50 years of age without osteoporosis	Prospective controlled intervention trials	18 trials 1966–1996	Walking, running, physical conditioning, aerobics		Lumbar spine <0.05 Forearm = ns Femoral neck = ns
Kelley (1998a)	Postmenopausal women	Prospective controlled intervention trials	10 trials 1975–1994; 330 subjects	Aerobic activity	Lumbar spine +2.83%	Lumbar spine <0.05
Kelley (1998a)	Postmenopausal women	Prospective controlled intervention trials	6 studies, 1978–1995	Aerobic exercise	Hip +2.42%	Hip <0.05
Kelley (1998b)	Postmenopausal women	Randomized controlled trials	11 studies 1975–1995; 719 subjects	Aerobic or strength training	Any exercise +0.27% Aerobic +1.62% Strength +0.65%	All sites <0.05
Wolff *et al.* (1999)	Pre and postmenopausal women	Prospective controlled intervention trials	25 studies, 1966–1996	Aerobic, high impact, or strength training at least 16 weeks duration	Premenopausal Aerobic + strength Lumbar spine +0.90% Femoral neck +0.90% Postmenopausal Aerobic Lumbar spine +0.96% Femoral neck +0.90% *Strength training* Lumbar spine +0.44% Femoral neck 0.86% Aerobic + strength Lumbar spine 0.79% Femoral neck 0.89%	All sites and modalities significant (<0.05) except for strength training in postmenopausal women
Wallace and Cumming (2000)	Pre- and postmenopausal women	Randomized controlled trials	32 studies, 1966–1998	Impact (aerobic or heel drops) and strength training	Premenopausal Impact Lumbar spine +1.5% Femoral neck +0.90% *Strength training* Lumbar spine 1.2% Femoral neck insufficient data Postmenopausal Impact Lumbar spine +1.6% Femoral neck 0.9% *Strength training* Lumbar spine 1% Femoral neck 1.4%	All sites and modalities significant (<0.05) except for femoral neck in premenopausal women
Kelley *et al.* (2001)	Pre- and Postmenopausal women	Prospective controlled trials	29 studies 1966–1998, 1123 women	Resistance training	Femur +0.38% Lumbar spine +1.26% Radius +2.17%	Femur nonsignificant Lumbar spine <0.05 Radius <0.05

[a] Study treatment effect is the difference between the percentage changes per year in bone mass (bone density or bone mineral content) in the training group minus the control group. A positive figure indicates a protective effect of exercise. Results are annualized for studies less than 12 months duration, assuming a linear rate of change in bone mass.

injurious falls (AGS/BGS, 2001; Hauer *et al.*, 2001). Progressive resistance training has been shown to be superior to standard physical therapy during the recovery from hip fracture in elderly patients. In addition, resistance training has been shown to be a potent treatment for depression in the elderly, and may thus be able to substitute for antidepressant medications, which are known to increase the risk of falls and hip fracture. A combination of resistance training and balance training may offer the best approach to rehabilitation in this setting, as it optimally targets several of the remediable physiological risk factors for falls, fractures, and disability in this cohort. Additional studies are needed to define the effects of training in this clinical setting on bone density and strength itself, as well as the optimal timing and duration of such interventions in the postfracture recovery period.

Role of Exercise and Physical Activity in Adipose Tissue Accretion and Distribution

The rising epidemic of obesity is now recognized internationally in both younger and older cohorts, and is projected, if it continues, to lead to major changes in related diseases such as diabetes, as well as life expectancy itself. Prevention of excess adiposity is both protective, and in some cases therapeutic, for many common chronic diseases, offering significant risk reduction in the case of osteoarthritis, cardiovascular disease, gall bladder disease, type 2 diabetes, breast, colon, and endometrial cancer, hypertension, stroke, and vascular impotence, for example. Although generalized obesity is associated with excess mortality, cardiovascular disease, osteoarthritis, mobility impairment, and disability, it is predominantly excess visceral fat that is associated with the derangements of dyslipidemia, elevated fibrinogen, hyperinsulinemia, glucose intolerance or diabetes, vascular insulin resistance, hypertension, and cardiovascular disease (Despres *et al.*, 2001) known as *metabolic syndrome* or *insulin resistance syndrome*. Reductions in visceral fat have been shown to improve glucose tolerance and insulin sensitivity in nondiabetic (Ross *et al.*, 2000), and type 2 diabetics subjects and changes in trunk fat correlate with improved glycemic control in type 2 diabetics (Castaneda *et al.*, 2002). Thus, the potential for exercise to impact favorably on the accretion and distribution of adipose tissue, as reviewed below, has enormous significance in that it may reduce the burden of disease expressed in the aging population.

Cross-sectional Studies of Physical Activity and Fat Mass

Numerous cross-sectional analyses have confirmed an inverse relationship between physical activity and abdominal fat. Master athletes compared to age and BMI-matched controls have lower waist circumference, and physically active women have lower waist-to-hip ratios than inactive women. Tremblay and colleagues determined that the higher the intensity of activity independent of energy expenditure, the lower the abdominal fat estimates for men and women. In a study of monozygotic and dizygotic female twins, physical activity was the strongest predictor of central obesity after controlling for genetic and environmental factors, and this persisted for those with a genetic predisposition to obesity.

Experimental Studies of the Influence of Physical Activity on Abdominal Fat

In the last few years, there has been accumulating evidence from well-designed studies supporting the benefit of physical activity in reducing total abdominal fat. There is no evidence that age limits abdominal fat loss secondary to exercise. In fact, most studies have included middle to older age populations who have higher accumulation of abdominal and visceral fat than younger adults. They are more likely to demonstrate a greater magnitude of change than subjects who have lower abdominal fat mass at baseline (Smith and Zachwieja, 1999). Furthermore, the potential for physical activity to attenuate the gain in visceral fat is evident in the obese as early as childhood.

Decreases in both total adipose tissue accumulation and its abdominal (visceral) deposition are achievable by both aerobic and resistive training, with significant changes in total body fat usually only in conjunction with an energy-restricted diet (Ballor and Keesey, 1991) or very large volumes of exercise (7 hours per week). Preferential visceral fat mobilization is often seen in response to exercise and dietary intervention, which means that small amounts of total body weight or fat mass (5%) may be associated with substantial changes in visceral fat (25% or more), with important metabolic implications for the prevention or treatment of the insulin resistance syndrome (Despres *et al.*, 2001).

Exercise and diet in combination are the most effective nonsurgical treatment for obesity, and this approach is uniformly advocated by international consensus panels (Grundy *et al.*, 1999). The advantages of adding exercise to diet alone include greater weight loss, preservation of fat-free mass, and resting metabolic rate, improved fitness levels, correction of metabolic abnormalities associated with visceral obesity, and better long-term adherence to dietary modifications producing sustained weight maintenance. Therefore, robust exercise plus diet appear to represent an optimal evidence-based treatment for obesity.

Relationship between Exercise Intensity and Changes in Body Fat

In general, weight loss parallels energy expenditure via exercise, whether achieved by greater volumes, intensities, or durations of the exercise prescription. There is no evidence yet from well-designed studies that low-intensity exercise is effective for reducing abdominal fat. Most robustly designed studies have used moderate- to high-intensity aerobic interventions. An overall higher-intensity stimulus can be delivered via intermittent intensities with resistance or interval

training, a prescription which may be effective and more easily tolerated by "at-risk" populations than sustained, intense exercise.

Relationship between Exercise Modality and Changes in Body Fat

There is no evidence that aerobic training is better than resistance training for reducing abdominal fat. Both resistance and aerobic exercise, at doses resulting in a sustained negative energy balance for several months, will generally result in significant reductions in fat mass when sensitive measurement techniques (generally not anthropometrics) are used. Resistance exercise may be more suitable as a fat reduction strategy for older obese individuals who have cardiovascular disease, arthritis, osteoporosis, or mobility disorders, who may not tolerate moderate- to high-intensity aerobic training, or who may need the added benefits of resistance training for maintenance of muscle and bone mass. Importantly, energy restriction results in significant losses of muscle and bone, and the addition of resistance training to hypocaloric dieting has been shown to prevent such adverse body composition changes (Ballor *et al.*, 1996), while aerobic exercise alone does not. Combined aerobic and resistance training has demonstrated a superior effect to aerobic training alone on trunk fat for older men. More well-designed studies are needed, particularly in overweight older adults, to explore the relative benefits of these modes of exercise for optimizing body composition.

Role of Exercise in Muscle Mass Preservation with Age

An increase in muscle mass, in contrast to changes in fat and bone, is only achievable to a significant degree with progressive resistance training or generalized weight gain from extra energy and protein consumption (McCartney *et al.*, 1995), and has a potential role in prevention of diabetes (Tuomilehto *et al.*, 2001), functional dependency (Chumlea *et al.*, 1997), and falls and fractures (Lauritzen *et al.*, 1993), as well as being important in the treatment of chronic diseases and disabilities which are accompanied by disuse, catabolism, and sarcopenia. For some diseases, like type 2 diabetes mellitus, there are potential advantages to both minimizing fat tissue as well as maximizing muscle tissue, since these compartments have opposite and likely independent effects on insulin resistance in the elderly (Despres, 1998). Muscle wasting or atrophy from any cause will exacerbate problems related to the extent and rate of the peripheral disposal of glucose into skeletal muscle, which is essential for maintenance of euglycemia in response to normal metabolism, meals, or other stressors. There is evidence from a variety of epidemiological and experimental studies that muscle weakness, decreased muscle mass, decreased activation of glycogen synthase, and alterations in numbers of Type IIb skeletal muscle fibers are related to, and may precede, insulin resistance, glucose intolerance, and type 2 diabetes expression. Thus, the typical alterations in body composition with aging (decreased muscle mass and increased visceral adiposity) are potentially independently related to the development of impaired glucose homeostasis in older adults.

Exercise to Maintain or Increase Muscle Mass

Appropriate progressive resistance training programs of 3–6 months' duration can be shown to increase muscle strength by an average of 40–150%, depending on the subject characteristics and intensity of the program, and to increase total body lean mass by 1–3 kg, or muscle fiber area by 10–30% (Fiatarone *et al.*, 1994; Pyka *et al.*, 1994). Thus, even if some of the neural control of muscle and absolute number of motor units remaining is not affected by exercise, the adaptation to muscle loading, even in very old age (Fiatarone Singh *et al.*, 1999) causes neural, metabolic, and structural changes in muscle which can compensate for the strength losses, and in some cases the atrophy, of aging. Generally, strength gains after exercise far exceed, and are not directly correlated with, changes in muscle size, due to the importance of neural adaptation in this process.

Predictors of Muscle Hypertrophy After Exercise

There is some controversy as to whether or not there are significant gender differences in the functional or hypertrophic response to resistance training in the elderly. Some studies have found women to have smaller gains in muscle strength and power (Jozsi *et al.*, 1999) or hypertrophic response (Ivey *et al.*, 2001) to training, while others have found no differences or even greater gains in women (Haikkinen *et al.*, 1998). It is likely that differences in training regimens (particularly related to intensity) and measurement techniques used to assess muscle mass, cross-sectional area, or volume may explain some of these discrepant results. Malnutrition, impaired protein synthesis rates, inflammatory cytokines, and depression are other factors that have been identified as detrimental to robust anabolic adaptations to resistance training in some studies.

High-velocity Resistance Training

A relatively recent area of investigation is that of power training (high-velocity resistance training), which has been proposed as a better way to target the selective fast-twitch fiber atrophy characteristic of aging muscle, as well as the earlier and more precipitous decline in muscle power and its associated disability, relative to muscle strength in older men and particularly women. Power training has been shown to be effective in both healthy (de Vos *et al.*, 2005) and frail elders (Fielding *et al.*, 2002), and results in muscle hypertrophy, strength and power gains, improvements in balance, and functional performance. Optimal training regimens for maximization of muscle power are still being defined.

PROMOTION OF PSYCHOLOGICAL WELL-BEING

Psychological well-being is vital to optimal aging, and is dependent on a host of factors, including genetic traits, social support systems, personality types, and the presence of positive and negative psychological constructs such as happiness, optimism, morale, depression, anxiety, self-esteem, self-efficacy, and vigor. Physical activity participation has been shown to be associated with more positive psychological attributes and a lower prevalence and incidence of depressive symptoms in cross-sectional and prospective epidemiological studies (McAuley and Rudolph, 1995) and experimental trials (Singh *et al.*, 2001, 2005). It is notable that effects are most significant in those with comorbid illness, such as cardiovascular or pulmonary disease (North *et al.*, 1990) or major depression (Blumenthal *et al.*, 1999; Singh *et al.*, 2001), attesting to the clinical relevance of this exercise adaptation.

The experimental evidence for exercise as an isolated intervention for the treatment of clinical depression in both younger and older cohorts is robust and consistent. Both aerobic and resistance training exercise produce clinically meaningful improvements in depression in such patients, with response rates ranging from 25 to 88%. In the studies that have addressed the issue of exercise modality, resistance training was found to be equivalent to aerobic training in young adults with depression (Doyne *et al.*, 1987), and yoga as effective as aerobic exercise. Blumenthal directly compared high-intensity aerobic exercise to antidepressant medications in older adults with major depression, and found the two approaches equipotent, with no added benefit of combined exercise and medication (Blumenthal *et al.*, 1999). Singh has compared high and low-intensity progressive resistance training to GP referral and care in older adults with major depression, and found that a clinical response (50% reduction in Hamilton Rating Scale for depression) was achieved in 61% of high-intensity training, 29% of low-intensity training, and 21% of the GP care group (Singh *et al.*, 2005). Similarly, low-intensity aerobic training in older adults with depression has been shown to be similar in efficacy to social contact, reducing depression scores by only 30% (McNeil *et al.*, 1991). Thus, the literature on exercise and depression suggests that it is effective in young and old, it is approximately as effective as antidepressants in clinical cohorts, that both aerobic and resistance modalities appear equally beneficial, and that optimal responses are seen with higher intensities of training.

EXERCISE AND COGNITIVE FUNCTION

There is a growing body of observational data and experimental evidence that physical activity can exert significant influences on a wide range of cognitive functions (Kramer *et al.*, 2004). The earliest lines of evidence were provided by cross-sectional studies of athletes or physically active individuals versus sedentary controls, with active or fit individuals demonstrating superior performance in tests of reaction time, motor control, or visual-spatial tasks. Changes in executive-control processes as well as changes in brain structures and functions most closely related to these processes are disproportionately affected by aging and exercise in some studies (Cotman and Berchtold, 2002; Kramer *et al.*, 2004). This has led to speculation that age-related cognitive dysfunction might be partially mediated by suboptimal and diminishing participation in physical activity across the lifespan. Virtually all of these studies have focused on cardiorespiratory fitness (maximal oxygen consumption) or aerobic exercise as the putative protective factor. However, approximately 50% of the variance in maximal oxygen consumption in children and adults is thought to be mediated by genetic factors rather than physical activity patterns (Fiatarone Singh, 2002), raising the possibility that shared predisposition to low fitness, vascular risk factors, and cognitive decline may explain these associations, rather than adaptation to an active lifestyle. In addition, changes in maximal oxygen consumption with aging are explained as much by losses of muscle mass (sarcopenia) as they are by losses of cardiovascular reserve (Fleg and Lakatta, 1988), suggesting that nonaerobic activities could be just as important as aerobic activities for the prevention of cognitive decline.

More recently, well-designed prospective cohort studies that have controlled for many known risk factors for cognitive dysfunction have in large part supported cross-sectional associations between physical activity patterns and risk of dementia (Laurin *et al.*, 2001). For example, in the Honolulu-Asia Aging Study (Abbott *et al.*, 2004), 2257 physically capable, cognitively intact men aged 71–93 were followed for 7 years for incident dementia. Walking significantly reduced the risk of dementia in a dose-dependent fashion, with a 1.8-fold increased risk for those who walked less than 0.25 m/day compared to >2 m/day, controlling for other possible risk factors.

Acute exposure to even one bout of aerobic exercise may result in improved cognitive test performance, as well as reduced depressive symptoms and anxiety. It is not known how long such acute bout effects persist, whether weight-lifting exercise has similar acute effects on cognition, or what proportion, if any, of the chronic exercise effects are explained by cumulative acute bout effects. Animal data demonstrate that voluntary wheel running (not stressful forced swimming) is a powerful means to enhance neural plasticity and function (Rhodes *et al.*, 2003), improving learning and memory, as well as increasing the availability of brain-derived neurotrophic factor (BDNF), formation of new neurons, and synaptic transmission in the hippocampus. Exercise also protects against the neurotoxicity of aging, stress, cortisol, or estrogen withdrawal in these animal models, and potentiates the beneficial effect of estrogen and antidepressants on hippocampal volume and metabolism.

The evidence from human trials is mixed, but three (Etnier *et al.*, 1997; Colcombe and Kramer, 2003; Heyn *et al.*, 2004) recent meta-analyses have concluded that exercise improves cognitive function, with an average effect size of approximately 0.4–0.6. The systematic review by Colcombe and

Kramer (2003) suggests that exercise effects are strongest when aerobic and weight-lifting exercises are combined, and when the dose of exercise is adequate (at least 30 minutes per session, greater than 6 months in duration).

Potential mechanisms by which exercise could improve cognitive function include changes in fitness, increased cerebral blood flow, reduction in depression, increase in presence or activity of neurotrophic factors (BDNF, insulin-like growth factor-1, IGF-1), downregulation of neurotoxic factors (C-reactive protein, cortisol, interleukin-6 (IL-6), and other inflammatory cytokines, and prevention or better control of chronic disease (e.g. stroke, diabetes, cardiovascular disease). Considering the nonrobust nature of most of the interventions reported in Heyn's meta-analysis of cognitively impaired elders (Heyn *et al.*, 2004), it does not appear that increases in aerobic capacity are required for cognitive benefits to accrue, as was previously thought. Cognitive benefits seen after nonaerobic exercise also cast doubt on a central role for aerobic capacity. The other mechanisms noted above appear more likely at this time. Exercise does increase cerebral blood flow acutely, as do cognitive tasks, and increased frontal cortex capillary density has been observed in animal models after exercise training, suggesting a possible common pathway for improved brain oxygenation and, thereby, function. Many of the most promising mechanisms in animal models have yet to be confirmed in human studies. Further exploration of the potential mechanisms of benefit in this crucial domain of health and function is needed, including studies linking changes in cerebral blood flow, depressive symptoms, physical fitness or burden of chronic disease, and disability to cognitive changes associated with exercise participation.

DISEASE PREVENTION THROUGH EXERCISE

Both healthy and chronically ill older adults are candidates for preventive strategies that will lessen the burden of comorbidity, disability, and premature death caused by incident disease. Physical activity patterns may be influenced by aging and genotype, and physical activity in turn may influence physiological capacity, psychological health, dietary intake, other adverse behaviors, or risk factors for chronic disease. All of these are potential pathways by which exercise could ultimately influence the prevalence of chronic disease in a population. Other than genetic factors and environmental insults (pollution, asbestos, heavy metals, infectious agents, etc.), most of the major contributors to the development or severity of chronic diseases are in some way related to habitual levels of physical activity. Examples would include cardiovascular disease (Blair *et al.*, 1995), stroke (Hu *et al.*, 2000), type 2 diabetes (Tuomilehto *et al.*, 2001), obesity, hypertension (Pereira *et al.*, 1999), osteoarthritis (Ettinger *et al.*, 1997), depression (Blumenthal *et al.*, 1999), and osteoporosis. A notable exception to these patterns is the diseases of the central nervous system (CNS) (e.g. Parkinson's disease, other degenerative neurological diseases) that have not been substantively linked etiologically with exercise or physical activity.

While appropriate levels of physical activity may optimize such risk factor profiles, on the other hand, the presence of risk factors may lead to reduced physical activity and thus heightened risk of disease. For example, inactivity may lead to sarcopenia, followed by muscle weakness and further restriction in activity levels, subsequently contributing to the development of osteopenia and gait abnormalities, and finally hip fracture.

Although observational studies can never completely separate the effects of physical activity from genotype or other unmeasured characteristics of individuals who self-select an active lifestyle, the best studies attempt to control for demographic differences, other known risk factors for the incident disease, and eliminate early or occult disease at baseline if possible prior to analysis. So, for example, exercise reduces the risk of cardiovascular disease by approximately 50%, even after controlling for such risk factors as smoking, obesity, hypertension, and dyslipidemia.

Longitudinal cohort studies have generally confirmed the cross-sectional data linking exercise to reduced disease risk. Of particular interest are studies such as those by Blair *et al.* (1995), in which middle-aged sedentary adults with low fitness levels have become fit at follow-up, and have markedly reduced cardiovascular mortality compared to those remaining unfit or inactive. These findings suggest that preventive exercise prescriptions instituted in middle age or beyond may be as important as those initiated at younger ages.

Randomized clinical trial data is now available for prevention of some disease states (cardiovascular disease, diabetes mellitus, and falls) but not yet available for others (stroke, osteoporotic fracture, depression). Diabetes is clearly preventable in high-risk obese adults with impaired glucose tolerance randomized to exercise and diet, as shown in the Finnish Diabetes Study (Tuomilehto *et al.*, 2001) and the Diabetes Prevention Program (DPP) (Diabetes Prevention Program Research Group, 1999). Similar to Finnish subjects, DPP participants randomly assigned to the intensive lifestyle intervention of diet and exercise reduced their risk of incident type 2 diabetes by 58% by 3 years. Of particular interest is the finding that those over the age of 60 responded best, with a 71% reduction in incident diabetes in this time frame.

The major diseases and syndromes for which exercise may be beneficial as a preventive strategy are listed in Table 7, along with the postulated mechanisms of exercise benefit, and the specific modality of exercise most relevant for these outcomes.

EVIDENCE FOR THE ROLE OF EXERCISE IN THE TREATMENT OF DISEASE

Mechanisms of Benefit

There are many ways to conceptualize the integration of exercise into the treatment of established disease. For example,

Table 7 Potential mechanisms by which exercise can prevent disease

Disease or syndrome	Postulated mechanisms of exercise effect	Recommended exercise modality
Arthritis	• Decreased body weight • Maintenance of cartilage integrity • Maintenance of muscle and tendon strength	Aerobic exercise[a] Resistance exercise[a]
Cancer (breast, colon, prostate)	• Decreased body fat • Decreased estrogen levels • Altered dietary intake • Decrease in gastrointestinal transit time • Increased prostaglandin F_2	Aerobic exercise
Chronic renal failure	• Reduced risk of hypertension • Reduced risk of type 2 diabetes mellitus	Aerobic exercise Resistance exercise[a]
Congestive heart failure	• Decreased risk of ischemic heart disease • Decreased risk of hypertension • Decreased risk of type 2 diabetes mellitus	Aerobic exercise[a] Resistance exercise[a]
Coronary artery disease	• Decreased blood pressure • Decreased cholesterol, LDL • Increased HDL cholesterol • Decreased fibrinogen • Decreased total body fat, visceral fat • Decreased insulin resistance, hyperinsulinemia • Decreased cortisol levels, inflammatory cytokines • Increased adherence to smoking cessation, dietary behaviors • Decreased depression, anxiety • Improved endothelial cell function	Aerobic exercise Resistance exercise
Dementia	• Improved cerebral blood flow • Increased neurotrophic factors in CNS • Hippocampal neurogenesis	Aerobic exercise
Depression	• Increased self-efficacy, mastery • Internalized locus of control • Decreased anxiety • Improved sleep • Increased self-esteem • Increased social engagement; decreased isolation • Decreased need for drugs associated with depression (beta-blockers, alpha-blockers, sedative hypnotics) • Decreased body fat, improved body image	Aerobic exercise Resistance exercise[a]
Osteoporotic fracture	• Increased bone density • Increased tensile strength • Increased muscle mass • Improved gait stability and balance • Improved nutritional intake (energy, protein, calcium, vitamin D) • Reduced fear of falling, improved self-efficacy • Increased overall activity levels, mobility • Decreased need for drugs associated with postural hypotension, falls, hip fractures (antidepressants, antihypertensives, sedative-hypnotics)	Resistance exercise[a] Aerobic exercise[a] Balance exercise[a]
Stroke	• Decreased obesity • Decreased blood pressure • Decreased cholesterol	Aerobic exercise Resistance exercise[a]
Type 2 diabetes mellitus	• Improved insulin sensitivity • Increased GLUT-4 protein and translocation to membrane sites • Reduced visceral fat mass • Decreased cortisol response to stress • Improved dyslipidemia • Decreased blood pressure • Increased muscle mass	Aerobic exercise Resistance exercise (combined with diet and aerobic exercise)

[a]Indicates that the modality of exercise has been shown to affect the postulated mechanistic factors, but not yet shown to prevent the distal disease outcome.

traditional medical interventions do not typically address disuse syndromes accompanying chronic disease, which may be responsible for much of their associated disability. Exercise is particularly good at targeting syndromes of disuse, and may thus significantly impact on disability without altering the underlying disease itself in any primary way. Examples would include Parkinson's disease (Reuter *et al.*, 1999), chronic obstructive pulmonary disease (Cambach *et al.*, 1999), and chronic renal failure. Exercise may also lower the risk for recurrences of a disease, such as secondary events in patients with cardiovascular disease (U.S. Department of Health and Human Services, 1996) or prevention of recurrent injurious falls in an individual after a hip fracture. Some pathophysiological aberrations that are central to a disease are specifically addressed by exercise, which may therefore serve as an adjunct to standard care. For example,

losses of visceral fat achieved through resistive or aerobic training improve insulin resistance and complement dietary and pharmacological management of type 2 diabetes in the older adult with central obesity (Weinstock *et al.*, 1998). Exercises designed to stimulate skeletal muscle hypertrophy in congestive heart failure provide benefit that counteracts the catabolic effects of circulating cytokines in this disease (Anker *et al.*, 1998), and is not achievable with cardiac medications alone. Functional improvements in individuals with arthritis (American Geriatrics Society Panel on Exercise and Osteoarthritis, 2001; McCarthy and Oldham, 1999) who are given quadriceps exercises improve joint stability and may thus add to the benefits of anti-inflammatory and analgesic medications. It is not possible in this chapter to review every disease in which exercise has beneficial effects, and therefore we will use type 2 diabetes as one example of the diseases outlined in Table 8.

Exercise in the Treatment of Type 2 Diabetes

The prevalence of type 2 diabetes appears to be rising precipitously, linked to the rise in obesity throughout the world (Shaw *et al.*, 2000). The vast majority of these individuals have scope for lifestyle modification, in particular, suboptimal levels of physical activity. Cardiovascular disease accounts for one-half of the mortality in older type 2 diabetics (Tan *et al.*, 2004), emphasizing the complex clinical syndrome represented by this cohort.

The value of tight regulation of glucose in type 2 diabetics has been convincingly demonstrated in the UK Prospective Diabetes Study, among others (American Diabetes Association, 2005). This is particularly important in the elderly, who may have glucose intolerance and then diabetes for many decades, and are therefore at extremely high risk of end organ damage due to glycosylation of body proteins. Although glycemic control has been proven to be highly effective in controlling diabetes, the deleterious effects of central obesity and lack of exercise can undo the benefits of proper medical management, and therefore may hasten the emergence of disease complications in susceptible individuals with insulin resistance. Weight loss diets are clearly central to the management plan of obese type 2 diabetics, and may be aided by the use of metformin as an appetite suppressant or acarbose as a means to decrease the extent of carbohydrate absorption. However, the difficulty of long-term weight management via

Table 8 Exercise and disease treatment

Disease state	Exercise of choice	Considerations
Arthritis	Aerobic	Low impact
	Resistance training	Sufficient volume to achieve healthy weight if obese
Chronic insomnia	Aerobic	Exercise 4–6 hours before desired bedtime to maximize effects
	Resistance training	
Chronic obstructive pulmonary disease	Aerobic	Resistance training may be more tolerable in severe disease; combined effects complementary if feasible
	Resistance training	Time exercise sessions to coincide with bronchodilator medication peak
		Use oxygen during exercise as needed
Chronic renal failure	Aerobic	Exercise reduces cardiovascular and metabolic risk factors, improves depression
	Resistance training	Resistance training offsets myopathy of chronic renal failure
Congestive heart failure	Aerobic	Resistance training may be more tolerable if dyspnea severely limits aerobic activity
	Resistance training	Cardiac cachexia targeted by resistance training
Coronary artery disease	Aerobic	Complementary effects on exercise capacity and metabolic profile from combined exercise modalities
	Resistance training	Resistance training may be more tolerable if ischemic threshold is very low due to lower heart rate response to training
Depression	Aerobic	Moderate- to high-intensity exercise more efficacious than low-intensity exercise in major depression
	Resistance training	Minor depression may respond to wider variety of exercise modalities and intensities
Hypertension	Aerobic	Small-moderate reductions in systolic and diastolic pressures seen
	Resistance training	Larger changes if weight loss occurs
Obesity	Aerobic	Sufficient energy expenditure to induce deficit
	Resistance training	Resistance training maintains lean tissue (muscle and bone) better than aerobic training during weight loss
Osteoporosis	Aerobic	Aerobic exercise should be weight bearing
	Resistance training	High impact, high velocity activity (e.g. jumping) potent if tolerable; avoid if osteoarthritis present
	Balance training	Resistance training effects are local to muscles contracted
		Balance training should be added to prevent falls
Peripheral vascular disease	Aerobic	Vascular effect is systemic, upper limb ergometry may be substituted for leg exercise if necessary
		Resistance training has positive but less robust effect on claudication
		Need to exercise to the limits of pain tolerance each session to extend time to claudication
Venous stasis disease	Aerobic	Local muscle contractions stimulate return of fluid via lymphatic system
	Resistance training	Utilize lower body training, elevate legs when possible

dietary restriction is well known in the clinical setting, due to a variety of factors that impede such behavioral change in older adults. In addition, weight cycling due to repetitive attempts at sustained weight loss leads to losses of lean tissue (muscle and bone) and decreases in metabolic rate, thus worsening the energy balance equation in the end, and making dietary management more and more difficult. Therefore, the standard care of obese type 2 diabetics leaves the majority of them suboptimally managed in relation to their primary metabolic derangement: *insensitivity to the action of insulin.*

All consensus panels recommend aerobic exercise as part of the management plan in type 2 diabetes. Moderate- or high-intensity aerobic exercise of 3–4 hours per week results in improved insulin sensitivity and glucose homeostasis, assists in attainment or maintenance of lower body weight, reduces visceral fat depots, modestly improves blood pressure and lipids, and lowers the risk of cardiovascular morbidity and mortality.

However, the clinical management of the obese elderly patient with this disease is often complicated by increasing insulin resistance and resultant polypharmacy, as well as multiple other comorbid health conditions that impede compliance with both diet and aerobic exercise and reduce quality of life. For example, it would not be unusual for an older diabetic to present with obesity, osteoarthritis, ischemic heart disease, hypertension, gout, hyperlipidemia, peripheral vascular disease, sleep apnea, peripheral neuropathy, a gait and balance disorder, functional impairment, renal disease, postural hypotension, bladder dysfunction, retinal disease, and depression. Such *disease clustering* makes the application of standard dietary and exercise recommendations as well as intense pharmacological management a challenge to practitioner and patient alike. It is not surprising that aerobic exercise recommendations, endorsed by all international consensus panels, are often difficult or impossible to implement in such patients. In particular, obesity, osteoarthritis, amputations, visual impairment, foot problems, fall risk, orthostatic hypotension, peripheral vascular disease, and a low threshold for ischemia may make aerobic exercise at the volumes and/or intensities shown to produce metabolic benefits in clinical trials unrealistic in practice.

An alternative approach to aerobic exercise recommendations for diabetics is the use of progressive resistance training. Insulin resistance is worsened by loss of muscle mass, decreased glucose transport into skeletal muscle and subsequent glycogen storage, catabolic/inflammatory mediators, inactivity, visceral fat, and related inflammatory cytokines such as IL-6 and C-reactive protein. The specific indications for resistance training in older diabetics include its ability to combat age and diabetes-related sarcopenia, to prevent loss of muscle and bone mass and reduced resting metabolic rate which otherwise accompanies hypocaloric dieting, to increase glucose uptake and storage in skeletal muscle, to reduce visceral fat depots, to reduce C-reactive protein, as well as its beneficial effects on resting blood pressure, functional status, mobility, sleep, and depressive symptoms. The effects on muscle mass are unique to high-intensity resistance training, and clearly distinguish it from aerobic exercise. For this reason, some experts are currently recommending its addition to recommendations for aerobic exercise and dietary modification (Sigal *et al.*, 2004). A review of the randomized controlled trial evidence upon which such recommendations are made is presented in Table 9. Although there is strong preliminary evidence that weight lifting exercise improves metabolic control and cardiovascular risk factors in type 2 diabetes, there have been only two published, randomized controlled trials of resistance training as an *isolated* intervention to augment usual care in type 2 diabetes (Castaneda *et al.*, 2002; Baldi and Snowling, 2003) to date.

Exercise to Counteract Iatrogenic Disease

Finally, exercise may counteract undesirable side effects of standard medical care, a use of exercise that is just emerging in the literature. Such use of exercise would include resistance training for patients receiving corticosteroid treatment to counteract the associated proximal myopathy and osteopenia (Storer, 2001), neutralizing the adverse effects of energy-restricted diets in obesity (Ballor *et al.*, 1996) or protein-restricted diets in chronic renal failure (Castaneda *et al.*, 2001), for example.

Osteopenia associated with corticosteroid usage appears to be completely eliminated by concurrent progressive

Table 9 Randomized controlled trials including resistance training in type 2 diabetes

Author	N (age)	Duration of training (months)	Resistance training intensity	Other additional intervention	Significant improvement in insulin sensitivity or glucose homeostasis
Dunstan *et al.* (2002, 2005)	36 (60–80 years)	12 (6 months supervised)	High	Moderate weight loss program	Yes, for supervised phase but not home-based, free-weight phase
Balducci *et al.* (2004)	120 (60.9 years)	12	Moderate	Aerobic at 40–80% HR	Yes
Baldi and Snowling, 2003	18 (46.5 years)	2.5	Moderate	None	Yes
Cuff *et al.* (2003)	28 (60.0 years)	4	Low	Aerobic at 60–75% HR	Yes
Loimaala *et al.* (2003)	50 (53.3 years)	11	High	Aerobic at 65–75% HR	Yes
Attema *et al.* (2002)	85 (age not reported)	6	High	Aerobic at 75% HR	Yes
Castaneda *et al.* (2002)	62 (66 years)	4	High	None	Yes
Dunstan *et al.* (1998)	27 (51 years)	2	Moderate	Low-intensity cycling between each set	Yes

resistance training, which should be recommended for all such patients (Braith *et al.*, 1996). Although bisphosphonates have also been shown to be very effective for corticosteroid osteopenia, they do not address the coexisting steroid myopathy, as does resistance training, and are therefore an insufficient antidote for corticosteroid side effects. An excellent target group for such health promotion efforts would be older men with steroid-dependent chronic lung disease (Storer, 2001), in whom pulmonary cachexia, malnutrition, tobacco use, and steroid myopathy and osteoporosis combine to produce profound wasting, osteoporotic fracture, and impaired exercise tolerance. Aerobic training will improve functional status in this clinical cohort, but is insufficient to address the musculoskeletal wasting.

EXERCISE AND THE PREVENTION AND TREATMENT OF DISABILITY

There are many ways in which physical activity may influence the development and expression of disability in old age. These theoretical relationships are now borne out in many epidemiological investigations, and provide the rationale for both the experimental studies and exercise recommendations that are found in many recent reviews of this topic (Andrews, 2001). For example, 1097 participants from the Established Populations for Epidemiological Studies of the Elderly (EPESE) study sites who were not disabled at baseline were analyzed for factors related to disability-free survival until death in old age (Leveille *et al.*, 1999). Physically active adults were more likely to survive to age 80 or beyond, and had approximately one-half the risk of dying with disability compared to their sedentary peers.

The most obvious conclusion from a review of the literature in this area is that there is a great deal of overlap between the identifiable risk factors for disability and the consequences or correlates of habitual inactivity. At the most basic level, shared demographic characteristics between those at risk of disability and those more likely to exhibit sedentary behavior include advanced age, female gender, non-Caucasian ethnicity, and lower educational level and income. Psychosocial features common to both cohorts include social isolation, low self-esteem, low self-efficacy, depressive symptoms, and anxiety. Lifestyle choices more prevalent in disabled and/or inactive adults include smoking and excess alcohol consumption. Body composition changes associated with both functional decline and inactivity include sarcopenia, obesity, visceral obesity, and osteopenia. Exercise capacity is typically reduced in both conditions in all domains, including aerobic capacity, muscle strength, endurance and power, flexibility, and balance. Gait instability and slowness, as well as impaired lower extremity function and mobility characterize both disabled and inactive populations. Since most studies have not assessed the full complement of factors known to be associated with disability, and many have made observations at a single point in time, it is not possible to say with certainty how all of these complex relationships fit together, which relationships are causal, and which risk factors are independent of each other.

In addition to the associations above, chronic diseases associated with inactivity, such as obesity, osteoarthritis, cardiovascular disease, stroke, osteoporosis, type 2 diabetes, hypertension, and depression are all risk factors for disability as well. In some cases, data linking inactivity to disability-related diseases is available from cross-sectional or prospective cohort studies as well as experimental trials (e.g. diabetes (Miller *et al.*, 1999), cardiovascular disease (Posner *et al.*, 1990)), and in other cases from epidemiological data alone (colon and breast cancer (Thune *et al.*, 1997)). Disability is complex and not fully explained by deficits in physical capacity such as strength and balance, and other pathways may be operative, including sensory function, glycemic control, psychological constructs, and other aspects of health status.

Recent prospective and experimental studies have strengthened the hypothesized causal relationship between sedentariness, functional limitations, and disability in older adults. Miller has reported results from 5151 participants in the Longitudinal Study of Aging (Miller *et al.*, 2000), and shown that physical activity results in a slower progression of functional limitations, and thereby slower progression to ADL/IADL disability were observed at 6 months of follow-up after the intervention ended. In the largest reported randomized controlled trial of exercise and disability to date (Fiatarone Singh *et al.*, 2004), 704 residents of nine different nursing homes were randomized into resistive exercise, nursing rehabilitation, or control conditions. After 17 months, residents in both intervention homes had significantly less decline in ADL functioning than those in control homes.

A review of studies targeting disability in disease-specific populations such as depression, cardiovascular disease, stroke, chronic lung disease, and arthritis is beyond the scope of this review, but there is evidence that exercise is beneficial in all of these conditions as a primary or ancillary treatment. The largest body of data exists for older adults with osteoarthritis, which is the commonest condition related to disability in the elderly (McCarthy and Oldham, 1999). Five of the 11 randomized controlled trials reported up to 1999 demonstrated improvements in disability scores relative to controls in trials from 4 weeks to 18 months in duration. Weight-bearing functional exercises, walking, and resistance training were used in various combinations in these studies, and there is no clear indication of the superiority of one modality over another in the reduction of pain and disability from osteoarthritis. It is likely that the disability reductions in arthritis are due to the impact of exercise on a variety of factors, including muscle strength, gait and balance, body weight, pain, comorbid disease expression, self-efficacy, and depressive symptoms, among others.

Table 10 Exercise recommendations for optimal aging and prevention and treatment of disease in older adults

Modality	Resistance training	Cardiovascular endurance training	Flexibility training	Balance training
Dose				
Frequency	2–3 days/week	3–7 days/week	1–7 days/week	1–7 days/week
Volume	1–3 sets of 8–12 repetitions, 8–10 major muscle groups	20–60 minutes per session	Major muscle groups 1 sustained stretch (20 seconds) of each	1–2 sets of 4–10 different exercises emphasizing dynamic postures[a]
Intensity	15–17 on Borg Scale (70–80% 1RM), 10 seconds/repetition, 1 minute rest between sets	12–13 on Borg Scale (40–60% heart rate reserve or maximal exercise capacity)	Progressive neuromuscular facilitation (PNF) technique[c]	Progressive difficulty as tolerated[b]

[a]Examples of balance enhancing activities include T'ai Chi movements, standing yoga or ballet movements, tandem walking, standing on one leg, stepping over objects, climbing up and down steps slowly, turning, standing on heels and toes, walking on compliant surface such as foam mattresses, maintaining balance on moving vehicle such as bus or train, and so on. [b]Intensity is increased by decreasing the base of support (e.g. progressing from standing on two feet while holding onto the back of a chair to standing on one foot with no hand support); by decreasing other sensory input (e.g. closing eyes or standing on a foam pillow); or by perturbing the center of mass (e.g. holding a heavy object out to one side while maintaining balance, standing on one leg while lifting other leg out behind body, or leaning forward as far as possible without falling or moving feet). [c]Proprioceptive neuromuscular facilitation involves stretching as far as possible, then relaxing the involved muscles, then attempting to stretch further, and finally holding the maximal stretch position for at least 20 seconds.

SUMMARY AND DIRECTIONS FOR FUTURE RESEARCH

There is sufficient data from both epidemiological studies and experimental trials to warrant the training of all physicians, including geriatricians in the basics of exercise prescription for health-related and quality of life benefits, as outlined in Table 10. Screening for sedentariness should take place at all major encounters with health-care professionals, given its role as a potent risk factor for all-cause and cardiovascular mortality, obesity, hypertension, insulin resistance, cardiovascular disease, diabetes, stroke, colon cancer, depression, osteoporosis, recurrent falls and disability, among other conditions. Exercise recommendations should be integrated into the mainstream of other health-care recommendations, rather than being marginalized as at present. Exercise advice should be specific in terms of modality, frequency, duration, and intensity, accompanied by practical implementation solutions and behavioral support systems for monitoring progress and providing feedback. Ultimately, the penetration of these recommendations into the most inactive cohorts in the community, who have the most to gain from increases in levels of physical activity and fitness (Blair and Garcia, 1996), will depend on a combination of evidence-based guidelines coupled with health professional training and behavioral programs (King *et al.*, 1991; Dunn *et al.*, 1999) tailored to age-specific barriers and motivational factors.

KEY POINTS

- The reduction in exercise capacity typical of the older adult is largely explained by reduced muscle mass and function, decreased maximal heart rate and cardiac output, and impairment of central and peripheral nervous system processing, recruitment, and conduction velocity.
- Aging and a sedentary lifestyle or disuse syndromes have very similar effects on a multitude of physiological changes attributed to chronological age which reduce exercise capacity.
- Habitual physical activity increases average life expectancy by approximately 2 years, but the mechanism of this effect is likely multifactorial and not precisely defined.
- Prevention of many of the typical changes attributed to biological aging is possible with chronic participation in physical activity, particularly alterations in body composition: decreased muscle mass, decreased bone mass and strength, increased adipose tissue mass and its central deposition.
- Prevention and/or treatment of many of the most common chronic diseases which afflict older adults, including obesity, cardiovascular disease, type 2 diabetes, hypertension, osteoarthritis, osteoporosis, stroke, peripheral vascular disease, and depression are possible with targeted, robust doses and modalities of exercise.

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13

Transportation, Driving, and Older Adults

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INTRODUCTION

The importance of transportation to health and social inclusion has been underrecognized in both the medical and the gerontological literature. Transportation is a crucial factor in maintaining older adult independence and the automobile is the most important source of transportation for older people. Not only is social connectedness a major priority for older people but problems with transportation have been recognized as barriers for access to health care for older people (Okoro *et al.*, 2005). Concerns over access to adequate transportation among older people have been voiced by a number of international agencies, including the Organization for Economic Cooperation and Development (2001 OECD) and the Conference of the European Ministers for Transport (CEMT, 2001). This has been augmented by major national reviews which have also emphasized the need to adapt transportation systems to the needs of older people (Committee for the Safe Mobility of Older People, 2004).

However, the major emphasis of much of the medical literature on transportation and aging is disproportionately skewed toward risk and crashes. This is particularly unfortunate, as older adults are the safest group of drivers (Fain, 2003), and even the often-quoted increased crash risk per mile is an artifact due to limited exposure or fewer miles driven per year. A number of studies have shown that the apparent increased crash risk disappears when one controls for mileage (low mileage is intrinsically risky) (Hakamies-Blomqvist *et al.*, 2002). However, a major issue for older adults is an increase in crash fragility. Whether as car occupants (Braver and Trempel, 2004) or as pedestrians, older people are more likely to suffer serious injury or death than younger people given the same crash severity. In traffic terms, older adult fragility exposes weaknesses in the design of the traffic environment. This clearly needs a societal response, in particular attention to in-car safety measures, which recognize the altered physiology and increased frailty of older people. A good analogy can be made with the danger posed by air bags for children who are front seat passengers: the response was not to stop children riding in cars, but rather to adapt an injury control measure (putting the children in the back seat, making occupants use seat belts).

For pedestrians, several responses are possible. Possibly the most important of these is to ensure that we do not unnecessarily turn older people into involuntary pedestrians through inappropriate driver screening programs: there is evidence that this phenomenon underlies the negative impact of medically screening older drivers in Finland and Australia (Hakamies-Blomqvist *et al.*, 1996; Langford *et al.*, 2004a; Langford *et al.*, 2004b). Other approaches include radically modifying traffic speed, the time needed for pedestrians to cross busy intersections, better organization where vulnerable road users (pedestrians and cyclists) share the road with vehicular traffic, and educating other road users to exercise caution in environments shared with older pedestrians.

Illness and Transportation

The most important impact of age-related illness on transportation is likely to be a reduction of personal mobility. This has been demonstrated for people with dementia (Taylor and Tripodes, 2001), but happens with other illnesses as well. Older people report that health is the commonest reason for driver cessation (Persson, 1993; Rabbitt *et al.*, 1996; Hakamies-Blomqvist and Wahlstrom, 1998; O'Neill *et al.*, 2000), and it should be of some concern that they rarely discuss this radical decision with a health-care provider (Johnson, 1995). Physicians dealing with older people need to be aware of these limitations and to be able to support their patients to maintain their independence.

The issue of crash risk has been overstated but sadly forms a negative public backdrop to our professional practice: a recent study of British and Irish media showed an overwhelmingly negative portrayal of older drivers, despite

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their excellent safety record (Martin *et al.*, 2005). Physicians must not allow a negative but inaccurate popular perception interfere with their task of assessing, treating, and advising older people in relation to their independence. This extends to the interpretation of studies on crashes: for example, certain illnesses are more common in older people who have crashes (McGwin *et al.*, 2000). However, since older people have less crashes in the first instance, the likelihood of effective public health interventions to further reduce this low rate are unrealistic and may cause further problems recognized with screening of older drivers.

Clearly for individual patients the maintaining of autonomy must be balanced with public safety to an extent consistent with that applied to the rest of the population. Age-related visual and cognitive diseases, in particular macular degeneration, dementia, stroke, and Parkinson's disease (Wood *et al.*, 2005), are likely to be the conditions most often associated with mobility and safety problems. Our main ethical prerogative is to preserve a sense of dealing with the issue in a hierarchical fashion common to good practice for all health-care conditions. This emphasizes in turn the World Health Organization's approach of health gain, health maintenance, compensation, and finally palliation (World Health Organization, 2001).

The Older Drivers Project, an initiative between the American Medical Association and the US National Highway Traffic Safety Administration has reaffirmed this principle, stating that a primary objective of its approach involves helping older drivers stay on the road safely to preserve their mobility and independence (Wang and Carr, 2004). The Older Drivers Project recommends that this can be accomplished through three methods: (1) optimizing the driver, (2) optimizing the driving environment, and (3) optimizing the vehicle. In this approach, driving cessation is recommended only after the safety of the driver cannot be secured through any other means. An algorithm to assess older drivers as recommended by the AMA (American Medical Association) is described in Figure 1 (American Medical Association, 2003).

Clinicians may be reluctant to address the driving issue in the office practice setting. There is a clear need for education in the assessment of mobility and driving: the good news is that such education appears to be effective (Byszewski *et al.*, 2003). Evaluating driving skills should not be viewed differently from the evaluation of risk for falls or other risk for injuries in older adults. Clinicians should consider the recommendation for driving retirement in older adults in a similar way to the decision that a previously ambulatory patient is now wheelchair bound for life: efforts should be made to preserve mobility when possible. Definitive guidelines on how clinicians can intervene effectively to ensure adequate mobility, driving safety, or effect driving cessation in impaired older adults still are needed, but current evidence and available resources indicate a general approach to this issue. There is an increasing body of evidence on the subject and some helpful guides.

Of particular importance has been the recognition that a relatively wide number of interventions can improve driving ease and safety (Table 1). It is also quite remarkable that most reviews on medications and driving emphasize possible negative effects on driving, rather than reflecting that anti-inflammatory, anti-Parkinsonian, and antidepressant medications might actually improve driving ability and comfort! The possibility that cholinesterase inhibitors might improve or maintain driving skills in dementia has not yet been tested, but remains an interesting area for future research.

WHAT WE NEED TO KNOW TO ASSESS OUR OLDER PATIENTS?

Physicians assessing older people for transport/driving capability need to know:

1. How do the older adults meet their transportation needs?
2. What intrinsic factors contribute to driving ability and how can we measure them?
3. What common illnesses in late life can affect the driving task?
4. What, if any, interventions should office-based clinicians pursue?
5. What is the physician's responsibility with regard to driver licensing and insurance authorities?

Taking a Driving/Transportation History

Although it may seem obvious that transportation should figure in a comprehensive assessment, this is not necessarily the case. An extreme example of this is the failure by the referring physician to advise on driving restriction for a significant number of people *referred* to a syncope clinic (MacMahon *et al.*, 1996). It is also likely that many patients do not obtain formal advice or assessment about driving after stroke (Fisk *et al.*, 1997). As there is potential to improve driving and transportation options, there is also a need to discuss restrictions or planned withdrawal from driving for many patients.

What Factors are Important in Driving Assessment?

The most major advance in this area has been the understanding that a purely cognitive model of driving ability does not adequately reflect the complexity and hierarchical nature of the driving task. Psychometric approaches have generally been disappointing for a number of reasons (Ranney, 1994), and efforts to find a best cognitive battery resemble the alchemist's search for transforming base metal to gold rather than a carefully thought out scientific endeavor.

The most common model for driver assessment would involve a combination of physician, occupational therapist, neuropsychologist, specialist driving assessor and social worker. Not all levels will be required by all patients: a patient with severe dementia clearly cannot drive, and

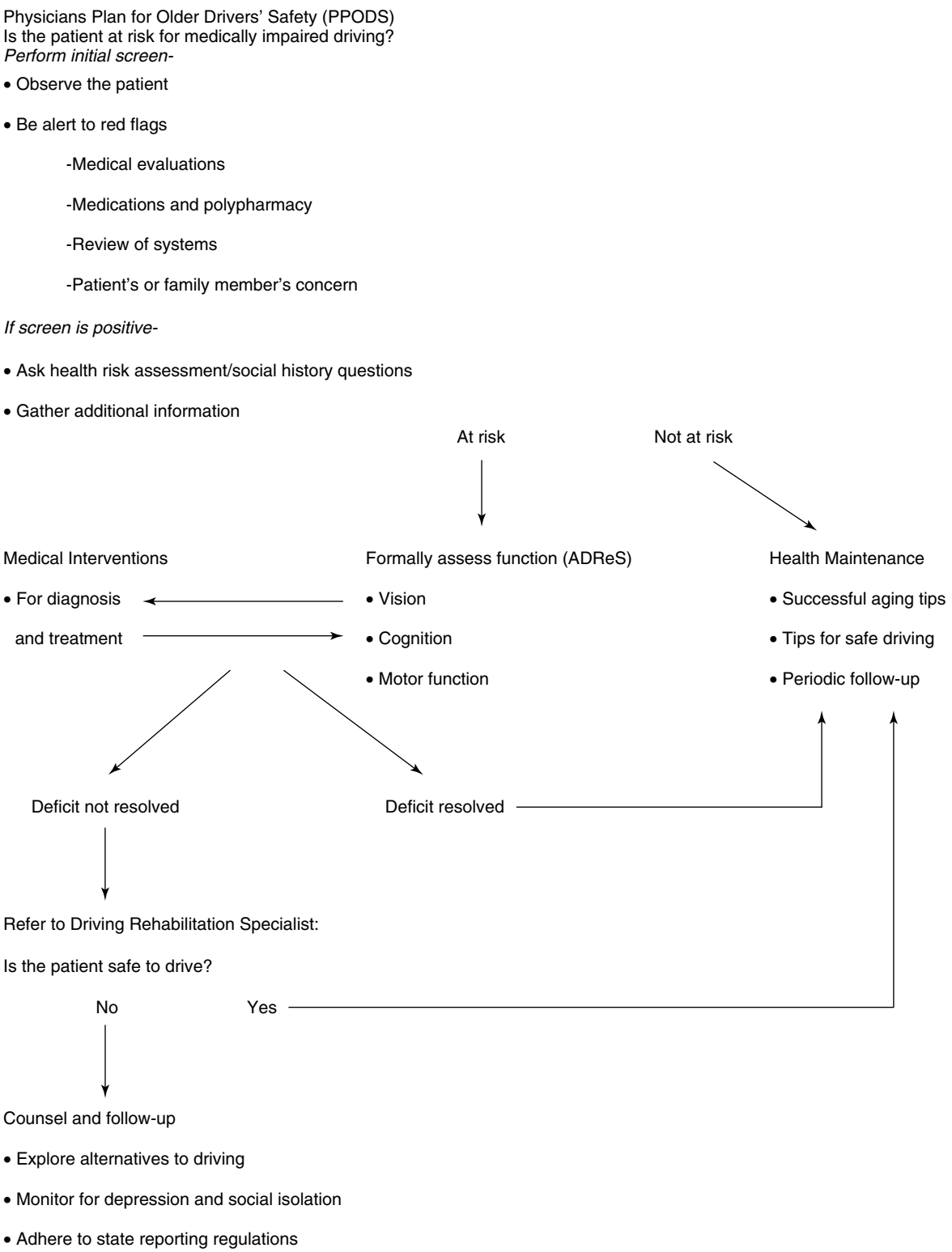

Figure 1 PPODS Chart

referral to the social worker to plan alternative transportation is appropriate. Equally, a mild cognitive defect may only require a review by the physician and occupational therapist. The overall interdisciplinary assessment should attempt to provide solutions to both maintaining activities and exploring transport needs. However, even in a skilled rehabilitation setting, the predictive value of team assessments may be low for diseases such as stroke (Akinwuntan

Table 1 Schematic outline of driving assessment

History
Patient, family/informant
Driving history
Examination
Functional status
Other illnesses and drugs
Vision
Mental status testing
Diagnostic formulation and prioritization
Disease severity and fluctuations
Remediation
Reassess
±In-depth cognitive/perceptual testing
±On-road assessment
Overall evaluation of hazard
Strategic
Tactical
Operational
Advice to patient/carer ± DMV
If driving too hazardous, consider alternative mobility strategies

et al., 2002) and the on-road test is the current best assessment available.

The on-road test may be helpful, as it may demonstrate impairments to a patient or caregiver who is ambiguous about the patient stopping driving. At a therapeutic level, members of the team may be able to assist the patients in coming to terms with the losses associated with stopping driving. The occupational therapist may be able to maximize activities and function and help focus on preserved areas of achievement, while the social worker can advise on alternative methods of transport. This approach should save time and valuable resources for occupational therapy, neuropsychology, and on-road driver assessors.

In addition to the usual workup, the medical assessment should include a driving history from patient and ideally (with the patient's permission) from a carer as well. The physician needs to judiciously weigh the collateral history, taking into account whether or not the carer is also dependent on the patient operating a motor vehicle. Physicians should also inquire about new unsafe driving behaviors. These behaviors can be apparent in mild dementia and would raise concerns about continuing driving privileges. It is important to recognize that these behaviors represent a *change* from baseline. They include becoming lost in familiar areas, driving too fast, reacting too slowly, consistently making poor judgments, failure to notice street signs, having more accidents, receiving indecent gestures from other drivers, miscalculating speed and distances, new dents on the car, knocking off rear view mirrors, showing poor judgment when making turns, or impaired ability to recognize or understand road or traffic signs.

The interested clinician can check static visual acuity (Snellen chart), hearing (whisper test or handheld audiometry), attention and reaction time (Trails A or B), visual spatial skills (clock drawing task), judgment, insight, joint range of motion, and muscle strength (Underwood, 1992; Reuben, 1993; Marottoli *et al.*, 1994; Foley and Mitchell, 1997). Many of these tests were recently endorsed by the AMA for assessing and counseling older adult drivers and are available on their website along with evidence based medicine references. These tests are probably more important for gaining an overall perspective on the patient's abilities and disabilities, rather than relying overly on the performance of any one component (American Medical Association, 2003).

The next stage of testing includes evaluations from occupational therapists and/or neuropsychologists. None of the studies have been sufficiently large to have a reasonable predictive value or to determine cutoff points on neuropsychological test batteries. This situation is paralleled in Memory Clinics where there is a wide variation in test batteries used: it is likely that the important elements of successful assessment are choice of key domains, familiarity with a test battery, and the development of an understanding and close liaison between the physician and the occupational therapist and/or neuropsychologist.

A wide range of tests have been correlated with driving behavior but few have been sufficiently robust to calculate cutoff points for risky driving. All of these tests can be criticized for taking an overcognitive view of the driving task (De Raedt and Ponjaert-Kristoffersen, 2000). A comprehensive review of tests is available from the US National Highway Transportation Safety Administration (Staplin *et al.*, 1999), and a rather futile attempt has been made at a "meta-analysis" of neuropsychological tests (Reger *et al.*, 2004). The other interesting aspect is that there may be a disparity between scores on a test battery and the clinical assessment of the neuropsychologist. In a small paper by Fox *et al.*, the neuropsychology test scores and the neuropsychology prediction were not found to be significantly associated, suggesting that the clinicians made their decisions on items not formally measured in the neuropsychology test battery (Fox *et al.*, 1997). In conjunction with the clinical assessment and collateral history, these tests will guide the physician as to which patients require on-road testing, as well as those who are likely to be dangerous to test!

At the moment simulators of sufficient sophistication are not widely available but may represent opportunities for both driver rehabilitation (analogous to training airplane pilots) and assessment. The main benefit of large sophisticated simulators such as the Iowa simulator has been to try to develop and understand neuropsychological and behavioral test batteries in a safe and reliable method and to correlate them with unsafe driving behavior and crashes. The classic paper by Rizzo in 1997 revealed that 29% of AD patients experienced crashes in the simulator versus zero of 18 control participants (Rizzo *et al.*, 1997). The drivers with AD were also more than twice as likely to experience "close calls". There was also evidence that some drivers with mild Alzheimer's disease did not crash and showed fair control of their vehicles compatible with the idea that some patients with mild dementia should be allowed to continue to drive.

On-road driver testing is the gold standard and should be offered to all patients who are not clearly dangerous when driving. The assessor will require a full clinical report, and may choose to use one of the recently developed scoring systems for on-road testing of patients with dementia. At

least three different road tests have been devised specifically for dementia although the numbers put through these in published series are still relatively small with 27 patients in the Sepulveda Road Test (Fitten *et al.*, 1995), 65 in the Washington University Road Test (Hunt *et al.*, 1997) and 100 in the Alberta Road Test (Dobbs *et al.*, 1998). The tests should ideally involve some degree of cognitive loading, which will tend to bring out the degree and extent to which the older driver can manage complex situations safely (Uc *et al.*, 2004).

The quantification, operationalization, and validation of these road tests need to be done repeatedly in environments other than that of the originators of the test. Current reliability of standardized tests seems promising (Akinwuntan *et al.*, 2003). An additional spin-off may well be that just as the simulators may provide information on which behavioral or neuropsychological tests might be helpful in deciding which drivers are safe to drive, so too may road test schedules help in the development of neuropsychological tests. Psychological batteries have been developed from both the Sepulveda and Alberta Road Tests.

There are certain limitations with road tests. Expenses for driving evaluations may vary from $200–$500 and health insurance or government health providers may not cover the cost. In addition, they often occur in an unfamiliar environment and in an unfamiliar car. However, professional organizations representing geriatricians need to undertake advocacy to ensure that on-road testing is available, of a high standard, and affordable to our patients.

What Risks are Associated with Common Diseases of Later Life?

While early papers on dementia and driving emphasized the potential risks from those with dementia, subsequent research has not unequivocally shown that drivers with dementia pose a public health hazard. The precise contribution of the dementias to overall crash hazard is uncertain. Although Johansson suggested a major role for dementia as a cause of crashes among older drivers on neuropathological grounds (Johansson *et al.*, 1997a), subsequent interviews with families did not reveal significant problems with memory or activities of daily living (Lundberg *et al.*, 1999). The Stockholm group also showed that older drivers who had a high level of traffic violations had a high prevalence of cognitive deficits (Lundberg *et al.*, 1998). Retrospective studies of dementia and driving from specialist dementia clinics tend to show a high risk (Friedland *et al.*, 1988; Lucas-Blaustein *et al.*, 1988; O'Neill, 1993), whereas those which are prospective and which look at the early stages of dementia show a less pronounced pattern of risk. In the first 2 years of dementia the risk approximates that of the general population (Drachman and Swearer, 1993; Carr *et al.*, 2000). The most carefully controlled study yet of crashes and dementia showed no increase in crash rates for drivers with dementia (Trobe *et al.*, 1996). Likely causes for this counterintuitive finding include a lower annual mileage, using state records for crash data, and restriction of driving by the patient, family, and physicians.

Extrapolating from special populations may skew predictions of risk. For example, epilepsy, for which there are relatively clear-cut guidelines in most countries, would seem to pose a clear threat to driving ability as viewed from a clinic setting. Recent population-based studies seem to suggest that the increased risk is relatively low (Hansotia and Broste, 1991; Drazkowski *et al.*, 2003 #1819). In a population renewing their licenses in North Carolina, the lowest decile had a relative crash risk of 1.5 in the 3 years previous to the cognitive testing (Stutts *et al.*, 1998), A somewhat reassuring finding from this cohort is that those with the poorest scores for visual and cognitive function also drove less and avoided high-risk situations (Stutts, 1998). A reasonable conclusion from these studies is that dementia among drivers is not yet a public health problem. Although increasing numbers of older drivers may change this situation, it is also possible that "Smeed's law" will operate, whereby increasing numbers of drivers among a defined population are associated with a drop in fatality rates per car (Smeed, 1968).

Older drivers report less driving at night or during adverse weather conditions, and avoid rush hour or congested thoroughfares. Most importantly, cognitively impaired older adults who renewed their licenses appear to even further restrict their exposure, many to less than 3000 miles per year (Stutts, 1998). Demented drivers may further limit their exposure when compared to age-matched controls (Dubinsky *et al.*, 1992). The data on exposure will require some confirmation, since there certainly are questions raised regarding the accuracy of reporting mileage in any cognitively impaired group. However, decreased exposure may explain why many crash studies have not observed major differences in crash rates from controls when comparing rates on the number of crashes per year and not factoring in total mileage.

Polypharmacy is common in older adults and medication may be additive to crash risk in older adults with cognitive impairment. This is a complex area and it can be difficult to tell whether it is the illness or the medication, which is causing the problem. There are many medication classes that have been studied and noted to impair driving skills when assessed by simulators or road tests. These decrements may not translate into increased safety risk. These include, but are not limited to, narcotics, benzodiazepines, antihistamines, antidepressants, antipsychotics, hypnotics, alcohol, and muscle relaxants. Very few studies have focused on the older adult driver. However, long acting benzodiazepines have been associated with increased crash rates (Hemmelgarn *et al.*, 1997). Another report suggests that there may be a significant number of older adults driving while intoxicated or under the influence of other medications (Higgins *et al.*, 1996; Johansson *et al.*, 1997b). Clinicians should review medications closely with each individual and attempt to discontinue medications that have the potential to adversely affect cognition when appropriate. Screening for alcohol abuse or misuse is also reasonable.

What Interventions Can We Make?

Depending on the illnesses present, there is potentially a wide range of interventions that we can undertake (Table 2). Adaptation of the car, following advice from the occupational therapist, physiotherapist, or specialist driving assessor can improve driving comfort and safety. Follow-up review should be organized for those with progressive illnesses such as dementia and Parkinsonism. A review period of 6–12 months would seem to be reasonable with dementia (Duchek *et al.*, 2003) but patients and carers should be asked to seek earlier review if they perceive a significant decline in the status of the dementia or in driving abilities. Although some studies have concluded with recommendations that all older adults with dementia should refrain from driving (Lucas-Blaustein *et al.*, 1988), the majority of clinicians would likely base this decision on dementia severity (Dubinsky *et al.*, 2000) or a demonstration of impaired driving competence (Drachmann, 1988). The American Academy of Neurology guidelines (Dubinsky *et al.*, 2000), proposing that no one with a Clinical Dementia Rating Scale (CDR) of 1 should drive, have been superceded by research which judged 41% of those with a CDR 1 as safe (19% were considered to be marginal, and 41% to be unsafe) (Duchek *et al.*, 2003). This reinforces the need for a full assessment and appropriate follow-up.

Table 2 Sample diseases for which appropriate assessment and remediation may be of benefit

Neuropsychiatric	
Stroke	Driving-specific rehabilitation (van Zomeren *et al.*, 1987)
Parkinson's disease	Maximizing motor function, treatment of depression, assessment of cognitive function (Anonymous, 1990)
Delirium	Treatment and resolution
Depression	Treatment: if antidepressant, choose one with least potential of cognitive/motor effects (Rubinsztein and Lawton, 1995)
Mild Dementia	Assess, treat depression, reduce/eliminate psychoactive drugs, advice not to drive alone (O'Neill, 1996a)
Cardiovascular	
Syncope	Advice pending investigation: treat cause (O'Neill, 1996b)
Respiratory	
Sleep apnoea	Treatment of underlying disease (Haraldsson *et al.*, 1992)
Vision	
Cataract	Surgery, appropriate corrective lens and advice about glare (Monestam and Wachtmeister, 1997)
Metabolic	
Diabetes	Direct therapy to avoid hypoglycemia (Frier, 1992)
Musculoskeletal	
All arthritides	Driving-specific rehabilitation program (Jones *et al.*, 1991)
Iatrogenic	
Polypharmacy	Rationalize medications (Ray *et al.*, 1993)
Psychoactive medication	Rationalize, minimize (Ray *et al.*, 1992)

For the progressive neurological conditions, the physician needs to help the patient and their family prepare for eventual withdrawal from driving. Early and appropriate diagnosis disclosure is likely to be important here (Bahro *et al.*, 1995). A helpful description of this process is the modified Ulysses contract (Howe, 2000), named after the hero who made his crew tie him to the mast on the condition that they did not heed his entreaties to be released when seduced by the song of the sirens. It forms the basis of a useful patient and carer brochure from the Hartford Foundation which is also available online (Hartford Foundation, 2000).

The very act of highlighting the potential of compromised driving ability may have a therapeutic benefit, promoting an increased vigilance on the part of the patient and carers that their social contract for driving privileges is not the same as that of the general public. Support is given to this concept by the success of restricted licensing for people with medical illnesses in the state of Utah (Vernon *et al.*, 2002). While the effect might arise from the restrictions (avoidance of motorways, nighttime driving) it is also possible that the very act of labeling these drivers may heighten self-awareness.

A clear recommendation should be made to the patient and recorded in the medical record: this should include advice to inform their insurance company of relevant illnesses, as well as any statutory requirement to inform their driver licensing authority.

When driving is no longer possible, alternative options should be discussed with the patient. For the fortunate minority who have access to a paratransit system (tailored, affordable personal transportation systems (Freund, 2000)), the graduation may be more easy. For the rest, although public transportation systems (Roper and Mulley, 1996) may have reduced fares for senior citizens, the very disabilities that prevented driving also render such services suboptimal (O'Neill, 1997). Owing to restricted sites and cognitive limitations of our older drivers, these services are typically underutilized. State or local sponsored services may provide door-to-door transport for older adults in large vans, many of which are lift-equipped. Local communities, societies, retirement centers, or local church groups may use funds or volunteers to provide services to physician offices, grocery stores, and meetings. In our experience, transportation is often provided by family members once the older adult can no longer perform the task (O'Neill *et al.*, 2000).

What is the Physician's Responsibility with Regard to Driver Licensing and Insurance Authorities?

In general, the welfarist role of the physician extends to reminding the patient that most insurance companies require disclosure by the driver of "illnesses relevant to driving" when they arise. Two issues arise: the medical advisers of the insurance companies may not make calculations of insurance rates (or continued insurance) on the basis of reason and evidence but rather on ageist grounds and prejudice against disability. We may be unwittingly exposing the patient to this prejudice. The answer to this lies in continued advocacy

efforts by advocacy and professional groups at a societal level as well as support by the physician in individual cases if the assessment supports preserved driving skills. A second issue is whether it is sufficient to recommend disclosure to someone who will not remember this advice. However, the physician's role is primarily to ensure safe mobility. In general, it is reasonable to assume that removal of insurance coverage is a secondary matter in such cases. It is reasonable to share the disclosure information with the carers.

The actual process of breaking confidentiality in the event of evidence of hazard to other members of the public is almost universally supported by most codes of medical practice – but to whom this should be reported poses some ethical challenges. The traditional route of reporting to driver licensing authorities (DMV (US), DVLA (UK)) may have relatively little benefit – removal of a driving license is likely to have little impact on many drivers whose insight into deteriorating driving skills is poor. It is important that this disclosure has some likelihood of impact and results in the least traumatic removal of the compromised older driver from the road. In such instances, the family may be able to intervene in terms of disabling the car and providing alternative modes of transport. In our own experience, we rarely have to invoke official intervention, but find that a personal communication with a senior police officer in the patient's locality may result in a sensitive visit to the patient and cessation of driving.

Mandatory reporting represents a different ethical challenge. It is unlikely that it is of significant benefit and unless significant benefit can be shown in future studies, the profession should resist the introduction of such schemes. For individual practitioners in jurisdictions where such regulations exist, a twin-track approach is probably necessary – professional advocacy with lawmakers and a considered approach as to whether disclosure is in the patient's best interests on a case-by-case basis. If the physician is confident that the state or province has a mechanism for fair assessment and an enlightened approach to maintaining mobility, compliance is not difficult. If the assessment is cursory and aimed at unduly restricting mobility, physicians may be faced with a problem recognized with other laws, which may put patient's welfare at risk and where professional obligations may require noncompliance with an unfair law.

CONCLUSION

Transportation and driving assessment have become an integral part of the assessment of older people. Geriatricians, appropriately supported by their interdisciplinary team and specialist on-road assessment, can help support safe mobility and social inclusion in later life. There is a need for more research to further clarify the most appropriate and economical assessments and interventions which further this end (OECD, 2001).

KEY POINTS

- Driving is an important component of the health and well-being of older people.
- The most important priority for geriatricians is to preserve the same proportionality of mobility to safety for older people as society accords to other age-groups.
- Many age-related conditions affect comfort, ability, and safety of the driving task but these effects can be ameliorated by appropriate interventions.
- The most important factors in assessing fitness to drive are likely to be measures of function and driving behavior: cognitive testing is less clearly helpful.
- Eventual driving cessation with progressive neurodegenerative diseases will be aided by early diagnosis disclosure and discussion of eventual driving cessation, as well as the provision of suitable alternative transportation options.

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14

Smoking in the Elderly

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PREVALENCE OF SMOKING IN THE OVER-60s

The prevalence of smoking in Great Britain has declined overall since the early 1970s. In 1994, the proportion of smoking men was 28%. In 2002, it was back down to 27%, having reached a peak of 30% in 1996. The prevalence of smoking rises initially, then falls with age to reach 10% in men and 7% in women aged 75 and over. Figure 1 shows the difference in prevalence of cigarette smoking between the different ages in 2002 (National Statistics, 2003).

Figure 1 shows that the prevalence of smoking is greatest in young middle-aged people and that in the youngest age groups, women smoke more than men. This reflects a cohort effect; women smoked very little in the post-World War II period, but gradually increased the habit with time. In different socioeconomic groups, the prevalence of smoking in the professional groups has fallen much more rapidly than for people who are in semiskilled or unskilled employment.

When one examines the proportion of people who had ever smoked and those who have never smoked, figures show that a high proportion of people aged over 75 are exsmokers. It has been suggested that many people give up smoking as they reach retirement age, both because of the effects upon their finances and on their health. The highest proportion of people who have never smoked (54%) are females aged 75 and over. This figure has been constant for at least 10 years. This reflects the relatively stable attitudes of society in the 1940s to smoking among women when they were young.

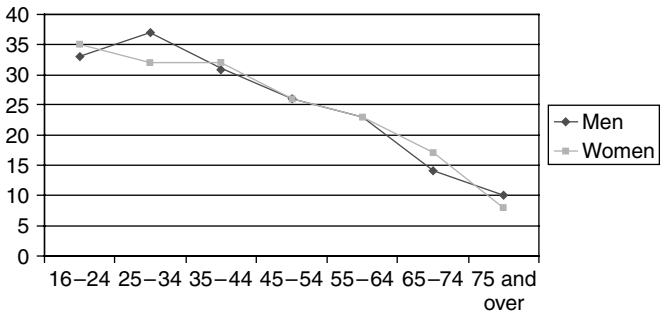

Figure 1 Prevalence of cigarette smoking by age in 2002

DISEASES ASSOCIATED WITH SMOKING IN ELDERLY PEOPLE

Heart Disease

Clear-cut evidence linking cigarette smoking to the development of ischemic heart disease has existed for many years. In the Multiple Risk Factor Intervention Trial (Neaton *et al.*, 1993) in the early 1990s, the risk of death increased steadily with cigarette consumption, reaching a plateau in those who smoked more than 35 cigarettes per day. The increased risk associated with cigarette smoking declined over the 12 years of follow-up. In addition, continued smoking after thrombolytic therapy was associated with a fourfold increase of reinfarction at 12 months (Rivers *et al.*, 1990).

More recently, a systematic review has shown that quitting smoking is associated with a substantial reduction in risk of all-cause mortality among patients with CHD (Critchley and Capewell, 2003). This risk reduction appears to be consistent, regardless of age, sex, index cardiac event, country, and year of study commencement (*see* **Chapter 46, Ischemic Heart Disease in Elderly Persons**).

The cardiovascular risk in older people who smoke is less well defined, possibly because they tend to smoke less than younger people. This contrasts with hypertension as a risk factor, where the risk increases steadily with age. The risk of cardiovascular disease in old people may be affected by a survivorship effect. In middle-aged people, smoking is such an important risk factor and heart disease is so common that the resulting high early mortality may appreciably reduce the numbers at risk in older people. In the Framingham study, men and women aged 65 to 94 who smoked were not at a significantly higher risk of coronary disease compared to

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nonsmokers. Diabetes was found to be increasing greatly in prevalence and operating more powerfully in women, countering their coronary disease resistance compared to men. It may be that insulin resistance promoted by abdominal obesity that has become so common in elderly people is to blame (Kannel, 2002). The older men in the Framingham study who smoked over 40 cigarettes a day had an increased risk. Other studies, admittedly some years ago, including the American Cancer Society Study and Canadian Veterans Study, found no excess risk in older smokers (Bush, 1991).

Stroke

Cigarette smoking is firmly established as a risk factor for stroke in older people (*see* **Chapter 71, Acute Stroke**), being associated with more than 50% of the deaths from cerebrovascular disease (Wilson, 1994). A meta-analysis of 32 separate studies provided strong evidence of an excess risk of stroke among cigarette smokers (Shinton and Beevers, 1989). A dose–response relationship was found between the number of cigarettes smoked and the risk of stroke. In the Framingham study, after a follow-up of 26 years, cigarette smoking was found to be a significant independent risk factor for stroke and specifically for brain infarction (Wolf, 1998). After cessation of smoking, risk of stroke decreased significantly within 2 years and reached the level of nonsmokers after 5 years. This rapid reduction in risk after cessation suggests that smoking plays a role in precipitating a stroke, possibly by increasing the fibrinogen level and promoting platelet aggregation.

Twenty-eight to sixty-eight per cent of the lacunar stroke patients in different studies were found to be cigarette smokers (Lodder *et al.*, 1990). Smoking therefore seems to be a nonspecific high-risk factor for lacunar infarction.

Effects on Bone

A meta-analysis of 29 published studies showed the importance of the relationship between smoking, bone mineral density, and risk of hip fracture (Law and Hackshaw, 1997). These studies reported the difference in bone density in 2156 smokers and 9705 nonsmokers according to age and that of 19 cohort and case-control studies recording 3889 hip fractures that reported the risk in smokers relative to nonsmokers.

The study showed that in premenopausal women bone density was similar in smokers and nonsmokers but in postmenopausal women bone loss was greater in current smokers than nonsmokers, diminishing by about an additional 2% for every 10-year increase in age, with a difference of 6% at age 80. In current smokers relative to non-smokers, the risk of hip fracture was similar at age 50 but greater thereafter by an estimated 17% at age 60, 41% at 70, 71% at 80, and 108% at 90. These estimates of relative risk by age, derived from a regression analysis of the studies of smoking and hip fracture, were close to estimates using the difference in bone density and the association between bone density and risk of hip fracture.

The estimated cumulative risk of hip fracture in women in England was 19% in smokers and 12% in nonsmokers up to age 85 and 37% and 22% up to age 90. Among all women, one hip fracture in eight is attributable to smoking. Limited data in men suggest a similar proportionate effect of smoking as in women. The association was not explained by smokers being thinner, younger at menopause, and exercising less or by the effect of smoking on estrogen secretion, but smoking may have a direct action on bone (*see* **Chapter 110, Epidemiology of Osteoporosis** and **Chapter 15, Alcohol Use and Abuse**).

Effects on the Mouth

Smoking has many negative effects on the mouth (Reibel, 2003). These include staining of teeth and dental restorations (*see* **Chapter 22, Oral Health**); reduction of the ability to smell and taste (*see* **Chapter 107, Smell and Taste**); the development of oral diseases such as smoker's palate, smoker's melanosis, and coated tongue; and possibly oral candidosis and dental caries, periodontal disease, implant failure, oral precancer, and cancer (*see* **Chapter 23, Oral Disease**). From a qualitative point of view, the latter is obviously the most serious tobacco-related effect in the mouth. Quantitatively, however, importance has been attached to periodontitis, which affects a large proportion of the population, and during recent years, more attention has been given to implant survival rates. All of these factors are increasingly important with age and therefore vital for elderly people.

Dementia

The EURODEM research group did a reanalysis of seven case-control studies, which included about 1700 patients in the early 1990s. This study suggested that the odds ratio associating a family history with a high prevalence of dementia tended to be *lower* for those with a positive smoking history (Van Duijn *et al.*, 1994).

However, researchers did further work to investigate the risk of Alzheimer's disease (AD) and smoking. They undertook a fuller meta-analysis of case-control and cohort studies (Almeida *et al.*, 2002). The authors systematically searched 21 case-control studies reporting data on 5323 subjects. As part of this study, they adjusted for confounding variables (such as age, sex, schooling, and alcohol use), and found that case-control and cohort studies produced conflicting results on the direction of the association between smoking and Alzheimer's disease.

They believed that survival bias, high mortality in smokers at earlier ages, and other methodological problems associated with case-control studies might explain the difference. There is still some debate about the possibility that smoking may actually mitigate against the onset of dementia on the basis of observations that nicotine improved performance on cognitively demanding tasks in normal

healthy adult human subjects (Wesnes and Warburton, 1984) and that nicotinic receptor binding sites were reduced in brains of patients with AD. This suggested that nicotine may be an effective therapeutic agent, or protective in AD, but the overall consensus presently is that smoking is associated with a higher prevalence of Alzheimer's disease.

Postmyocardial Infarction

A large systematic review (Critchley and Capewell, 2003) by Critchley looked at 20 studies. They showed a 36% reduction in crude relative risk of mortality for patients with coronary heart disease (CHD) who quit smoking compared to those who continued smoking. Results from individual studies did not vary greatly despite many differences in patient characteristics, such as age, sex, type of CHD, and the years in which the studies took place. The authors mention that few studies included large numbers of elderly persons, women, ethnic minorities, or patients from developing countries. Overall, they state that patients with CHD who stop smoking have a substantially reduced risk of all-cause mortality. This risk reduction appears to be consistent regardless of age, sex, index cardiac event, and country (*see* **Chapter 46, Ischemic Heart Disease in Elderly Persons**).

Blindness

Smoking is associated with several eye diseases, including nuclear cataract and thyroid eye disease, but the commonest cause of smoking-related blindness is age-related macular degeneration (Kelly *et al.*, 2004). Treatment is of only partial benefit so that identifying modifiable risk factors to inform efforts for prevention is a priority (*see* **Chapter 103, Disorders of the Eye**).

The authors cited above estimate that 53 900 UK residents older than 69 years may have visual impairment because of age-related macular degeneration attributable to smoking; of these, 17 800 are blind.

Observational studies show that smoking cessation reduces the development of macular degeneration, as former smokers have only a slightly increased risk of age-related macular degeneration compared to never smokers (Smith *et al.*, 2001). This reversibility is important for patients with macular degeneration in one eye, as a way of preventing involvement of the second eye.

POSITIVE EFFECTS

Parkinson's Disease

One of the consistent and perplexing pharmacoepidemiologic aspects of Parkinson disease is its negative association with cigarette smoking, especially in people with no family history of Parkinson's disease (Allam *et al.*, 2003) (*see* **Chapter 66, Parkinson's Disease and Parkinsonism in the Elderly**). This has led some investigators to conclude that some aspect of cigarette smoking may exert a neuroprotective influence concerning the development of Parkinson disease. Consequently, the effect of nicotine upon the tremor of Parkinson disease and upon neurotoxin lesion in animal nigrostriatal dopaminergic neurons has been studied, although without definitive conclusions. Some studies have questioned the notion of a protective effect because of the observation that the age at diagnosis of Parkinson disease in smokers is less and there is no observed dose–response relationship. However, twin studies have maintained the suggestion that smoking may be protective (Bharucha *et al.*, 1986).

VARIABLE EFFECTS

Asthma

Some work in Finland has shown odd associations between asthma and smoking. A survey in rural Finland used a standardized questionnaire to identify people with asthmatic symptoms (Isoaho *et al.*, 1994). The study showed that current asthma was rare in men aged 75 and above and absent in those who smoked. In contrast, current asthma was commoner in women smokers. It is possible that this finding was due to a high mortality at younger ages in male smokers. Alternatively, men who have smoked for many years may get other symptoms that mask their asthma. Having said this, the prevalence of asthma was said to be similar to that found elsewhere (*see* **Chapter 61, Respiratory Disease in the Elderly**).

STOPPING SMOKING

An important factor in helping elderly people fulfil their desire to stop smoking is the important effect that this can have on younger generations. In particular, grandchildren, who often have a close relationship with their grandparents, will be strongly affected by their attempts to discontinue smoking. Family attitudes are one of the strongest influences on children taking up and stopping smoking.

Time for Effects to Occur

It stands to reason that some time is likely to elapse before an exsmoker achieves the status of a nonsmoker. For cardiovascular disease, it has been said that the effects are very rapid. For other causes of death, especially lung cancer and bronchitis, the benefit of stopping smoking takes up to 5 years to appear. There are suggestions that exsmokers move

reasonably quickly toward the state of nonsmokers for bone density, pulmonary function, and muscle strength (Mellstrom and Svanborg, 1987).

METHODS OF HELPING PEOPLE TO STOP SMOKING

Following personal advice and encouragement to stop smoking given by physicians during a single routine consultation, approximately 2% of all smokers stopped smoking and did not relapse up to 1 year. This effect is modest but cost-effective: the cost of saving a life is about £900, an extremely cheap intervention by most measures.

Advice and encouragement are much more effective for smokers at special risk. In particular, 8% of pregnant women give up, and patients with ischemic heart disease are likely to respond in larger proportions, though the former is not relevant in the elderly population. Behavior modification techniques such as relaxation techniques, rewards, and punishment have an effect that is statistically significant compared to no intervention, but no greater than simple advice by a physician. Nicotine replacement therapy is effective in approximately 13% of smokers who seek help to stop. The effect is greater in those who are nicotine dependent.

Both sudden cessation and gradual reduction in smoking are similar in their efficacy on average. Physicians should take time to advise all their patients who smoke to quit. In general, smokers who are intent on stopping should be given additional support and encouraged to use nicotine replacement therapy, as long as this is not contraindicated.

Attempts to Stop Without External Help

Many smokers give up smoking on their own, but materials giving advice and information may help them and increase the number who quit successfully (Lancaster and Stead, 2002). This Cochrane systematic review was set up to determine the effectiveness of different forms of self-help materials, compared to no treatment and to other strategies; the effectiveness of adjuncts to self-help, such as computer-generated feedback, telephone hotlines, and pharmacotherapy; and the effectiveness of approaches tailored to the individual compared to nontailored materials.

The study included randomized trials of smoking cessation with follow-up of at least 6 months, where at least one arm tested a self-help intervention. Self-help was defined as structured programming for smokers trying to quit without intensive contact with a therapist.

The authors identified 51 trials. Thirty-two compared self-help materials with no intervention or tested materials used in addition to advice. In 11 trials in which self-help was compared with no intervention, the pooled effect just reached statistical significance. They failed to find evidence of benefit from adding self-help materials to face-to-face advice or to nicotine replacement therapy. There was evidence from 14 trials that personalized materials were more effective than standard manuals or no materials.

The reviewers concluded that self-help could increase quit rates compared to no intervention, but the effect was likely to be small. They found no evidence that self-help was better than advice from a health care professional or nicotine replacement therapy. There is evidence that materials that are tailored for individual smokers are more effective.

METHODS OF HELPING ELDERLY PEOPLE TO STOP SMOKING

In the past, publications on helping elderly people stop smoking tended to underplay its importance. This appears to have changed in the last few years as topics such as the importance of smoke pollution for children and nonsmokers have gained ground. In addition, the importance of smoking to diseases that are normally associated with elderly people, such as fractured head of femur, have made it clear that it is never too late to stop. Good evidence has also pressed home the importance of smoking cessation at any age, in relation to the big killers: CHD (Critchley and Capewell, 2003), COPD (chronic obstructive pulmonary disease) (Garcia-Aymerich *et al.*, 2000), and type II diabetes (O'Connor *et al.*, 1998).

There is still evidence, however, that primary care physicians, in particular, are still less likely to give advice to older people (Ellerbeck *et al.*, 2001). This is disappointing, especially when methods of assisting people stop smoking are becoming more effective.

The National Institute for Clinical Effectiveness (NICE) has guidelines for the use of smoking cessation therapies, notably the use of nicotine replacement therapy and the drug bupropion, said to reduce the craving for tobacco (NICE, 2002). NICE does not give any specific advice for elderly people using these therapies, but states: "People with conditions such as heart disease, overactive thyroid, diabetes, severe kidney or liver disease, and stomach ulcers are advised to use nicotine replacement therapy only after they have carefully considered the risks and benefits of the treatment and after discussion with a healthcare professional." In addition, "bupropion must not be prescribed for smokers who have a current seizure disorder (e.g. epilepsy) or any history of seizure. Smokers who are at risk of seizures must not be prescribed bupropion unless the benefits of smoking cessation are likely to outweigh the risks of taking the drug. There are other factors that may increase the risk of seizures in people taking bupropion, including taking other drugs that are known to increase the risk of seizures, alcohol abuse, or head injury. People with diabetes who are using glucose-lowering drugs or insulin and people who are using drugs to treat anorexia may also have a higher risk of seizures with bupropion". NICE does not recommend using both methods together.

The prevention of smoking in retired people is not fully researched. There appear to be only a small number of

randomized controlled trials on the effects of trying to reduce smoking in the community on a group of elderly people, and most of these were available some years ago. One, which looked at helping people stop smoking as part of a general health promotion approach gave generally negative results (Burton *et al.*, 1995).

Others were more effective. For instance, a US study tested the effectiveness of an office-based smoking cessation program tailored to midlife and older smokers, using a randomized controlled trial to compare usual care with physician-delivered brief quit-smoking advice and counseling for midlife and older smokers (ages 50–74) (Morgan *et al.*, 1996). Thirty-nine practices that managed to include five or more patients in the study were included in the study. Self-reported quit rates at 6-month follow-up were 15% for the Immediate Intervention group versus 8% of subjects in the Delayed Intervention group ($P < 0.005$). They concluded that smoking abstinence was significantly increased by training physicians and key office and clinical staff to intervene with older smokers. They state that brief interventions tailored to this age cohort can be successfully and efficaciously integrated into routine care.

Some years ago, we carried out a trial of assisting elderly people aged 60 and above to stop smoking in primary care (Vetter and Ford, 1990). Each member of the intervention group was invited by letter to come to see their general practitioner, who informed them of the importance of stopping smoking and of the availability of a nurse to help them stop. The subject was given the opportunity to discuss problems associated with stopping smoking with the practice nurse.

In contrast to the above studies, smoking abstinence was tested objectively by the use of a carbon monoxide monitor. There was a reduction in the proportion smoking in both groups, but the intervention group's reduction at 14% was greater than that of the control group (9%). Four per cent of the intervention group and 2% of the controls claimed to have stopped but had a positive reading on the carbon monoxide monitor. The difference between the groups in the numbers of validated nonsmokers was statistically significant. Figure 2 shows changes in breathlessness in the two groups. There was a statistically significant difference for an improvement in breathlessness in the intervention group compared to controls.

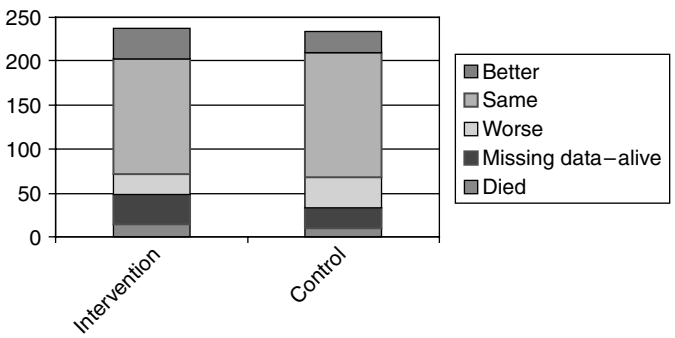

Figure 2 Changes in breathlessness after 6 months

KEY POINTS

- Smoking in elderly people shows a well-documented deleterious effect on health as in younger people.
- There are some minor differences in emphasis in old age.
- Some of these differences are likely to be due to a survival effect, given the high impact that tobacco use has on mortality.
- The most under-researched area is that of helping elderly people give up smoking.
- The small amount of research that is available suggests that such approaches have great potential.

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15

Alcohol Use and Abuse

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INTRODUCTION

Young adults are more likely than older adults to be drinkers, to drink heavily, and to report more alcohol-related problems (Grant *et al.*, 2004). Why, then, should physicians be concerned about alcohol consumption and problems in their older patients? No health-care provider in any health-care delivery system can responsibly and intelligently carry out the practice of geriatric medicine without a solid working knowledge of the patterns of alcohol use, abuse, dependence, and consequences among older patients. First, while the current magnitude of the problem may not be overwhelming, with the burgeoning of the elderly population, the burden can be expected to increase. Second, alcohol use and abuse are, in fact, significant health issues for older patients. Third, alcoholism is an eminently treatable disease with remission rates superior to many cancers. Intervention and treatment yield improved quality of life. Finally, all the recent media play regarding the cardioprotective effects of moderate drinking has undoubtedly attracted the attention of older individuals for whom heart disease is the number one killer. They may well ask the physician to articulate the risks and benefits of alcohol consumption for them. It behooves the physician to be able to respond intelligently.

In the twenty-first century, dramatic shifts will continue to occur in the age distribution of the world's population. In the more developed regions of the world, the population aged 60 and older currently constitutes 20% of their total population; by 2050, it will account for 32% (Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2005). In the United Kingdom, those aged 60 and older comprised 21% of the population in 2005; they will account for 29% of the population by 2050 (United Nations Population Division, 2005). Globally, the number of persons aged 60 and older is expected to nearly triple by 2050. In 2005, 86 million persons in the world were aged 80 or older. By 2050, this fastest growing segment of the population is projected to reach 377 million, increasing more than fourfold. The elderly population in developed countries has already surpassed the number of children and by 2050, there will be two elderly persons for every child (Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2005). This fastest growing group uses medications and other health services to a far greater extent and more often than any other segment of society. Elderly individuals fall prey to multiple chronic conditions; as a result, physicians see more individuals in the older population and see them more frequently, providing a welcome opportunity to discuss alcohol consumption and detect problems.

EPIDEMIOLOGY

Estimates of the magnitude of later life alcohol consumption and problems vary widely. In the field of studies on alcohol consumption, extreme variability of the definitions of terms such as "a drink", "abstainer", "moderate" drinker, "heavy" drinker, "harmful" drinking, "hazardous" drinking, "alcoholism", "alcohol abuse", and "problem drinker" is problematic both for those who conduct and those who read such studies. The term "Elderly" may also be variously defined, which further contributes to the wide range of prevalence estimates (Adams and Cox, 1995). In the United States, about half of those aged 65 and older report consuming alcohol (Moore *et al.*, 2002). In the United Kingdom, two-thirds of the men and nearly half of the women aged 65 and older reported consuming alcohol in the previous week (Rickards *et al.*, 2004). For most alcohol measures, prevalence estimates are progressively lower with increasing age; however, this does not hold for daily drinking. Older individuals consume less alcohol per occasion, but drink on more occasions (Adams and Cox, 1995). In the United Kingdom, 28% of men and 15% of women aged 65 and older reported drinking five or more times in the week prior to their interview and 21% of the men and 11% of the women reported drinking every day compared to 4% of the men and 2% of the women aged 16 to 24 (Rickards *et al.*, 2004).

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Best estimates of serious alcohol problems are those that measure alcohol abuse or dependence by utilizing rigid diagnostic criteria such as the International Classification of Diseases of the World Health Organization, or the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association. For example, among the US general population aged 65 and older, in 2001–2002, the 1-year prevalence estimates for alcohol abuse were 2.36% for men and 0.38% for women by DSM-IV criteria (Grant *et al.*, 2004). The 1-year prevalence estimates for alcohol dependence were 0.39% for men and 0.13 for women (Grant *et al.*, 2004). Although the DSM criteria have been invaluable in standardizing definitions of alcohol abuse and dependence, they yield extremely conservative estimates of the number of elderly who may get into trouble with alcohol use. Because of physical and psychosocial age-related changes, and other coexisting medical conditions and concomitant medication usage, older individuals may have problems caused by their drinking even though they do not meet diagnostic criteria for abuse and dependence. The alcohol use disorders identification test (AUDIT), a screening measure developed by the World Health Organization, identifies not only those who abuse and/or are dependent on alcohol but also those who may be hazardous drinkers because of the amount they consume (Coulthard *et al.*, 2002). In a survey of adults aged 16 to 74 in Great Britain in 2000, the prevalence of alcohol problems in the year prior to their interview was assessed using the AUDIT. Individuals who scored 8 or more on the AUDIT were classified as hazardous drinkers. Among men, 24% of those aged 65–69 and 14% of those aged 70–74 were classified as hazardous drinkers. Among women, 6% of those aged 65–69 and 5% of those aged 70–74 were so classified. Not unexpectedly, in this survey, the rates of the past 6-month's prevalence of alcohol dependence were much lower. Among the women aged 65–69, 0.7% met criteria for alcohol dependence, and among those 70–74, no cases were identified. Among the men, 2.9% of those aged 65–69 and 2.0% of those aged 70–74 were classified as alcohol dependent (Coulthard *et al.*, 2002).

At every age, men are more likely to be drinkers and to have drinking problems. The alcoholism rate is appreciably higher for elderly men than women, but because women live longer and seek medical care more often, the disparity in the patient population is not so great (Blow, 1998). Nevertheless, women alcoholics are more likely to go undiagnosed due to bias and social isolation. These rates vary widely depending on the definition of problem drinking and the population from which the sample is drawn. Among clinical populations, however, estimates of alcohol abuse or dependence are substantially higher because problem drinkers of all ages are more likely to present themselves in health-care settings. Rates of concurrent alcoholism range from 15 to 58% among older patients seeking treatment in hospitals, primary care clinics, and nursing homes for medical or psychiatric problems (Barry *et al.*, 2001).

Most older patients are not recognized as problem drinkers by health-care personnel. Since health-seeking encounters provide an excellent opportunity for the identification of and intervention for problem drinking, it is critical that physicians and other health-care providers take advantage of these opportunities. The presence of consequences, even if drinking levels are low, should drive the need for intervention. In the United States in 1999–2000, individuals aged 65–74 made an average of six ambulatory care visits per year while those aged 75 and older averaged eight visits (Burt and Schappert, 2004). In 2002, in the United Kingdom, the average number of National Health Service General Practitioner consultations was seven for those aged 65–74 and eight for those aged 75 and older (Rickards *et al.*, 2004).

Since heavy drinking is known to cause increased morbidity and mortality, it is not surprising that the prevalence of problem drinking is significantly higher in health-care settings. Alcohol abuse is a prevalent (14%) and important problem among the elderly in the emergency department setting and is not well detected by physicians there (Adams and Cox, 1995). Alcohol abuse was found to be less common among elderly trauma patients (falls and other injuries) than among their younger counterparts but very common (22%) among older patients with gastrointestinal problems (Adams *et al.*, 1992). The prevalence of alcohol-related problems among older hospital inpatients is even higher – 8–21%, with some estimates as high as 60% in certain select subgroups (Seymour and Wattis, 1992). Clearly, alcohol-related hospitalizations are common among older individuals. A landmark study of US national hospital claims data revealed that among patients aged 65 and older, alcohol-related hospitalizations occurred as frequently as those for myocardial infarction (Adams *et al.*, 1993). Psychiatric settings also show a high frequency of alcohol-related problems among older adults, ranging from 10% among the psychiatric outpatients to 23% of the elderly psychiatric inpatients (Adams and Cox, 1995). Among nursing home residents aged 65 and older, 2.8–49% have alcohol-related problems (Joseph *et al.*, 1995). Alcoholic dementia accounts for 10–20% of all admissions to US state mental hospitals (Smith, 1995). One study of elderly patients admitted to a US veterans nursing home reported that a quarter of these patients had active alcohol problems and nearly half were returned to independent living, suggesting that nursing homes serve as an important transition between hospital and home for older patients with alcohol problems, offering an ideal opportunity for identification and intervention (Joseph *et al.*, 1995). A quarter of elderly, cognitively impaired residents of long-term care facilities suffer from alcohol-related dementia (Carlen *et al.*, 1994).

SENSIBLE DRINKING GUIDELINES

In the early 1990s, advice about sensible drinking in the United Kingdom centered on the amount of alcohol consumed weekly, and advised that men consume 21 or fewer units per week and women consume no more than 14 units. Appreciating the potential harm that could be realized from consuming all 21 drinks on one occasion, the focus changed in 1995 to daily guidelines, which recommend a maximum

intake of 2–3 units per day for women and 3–4 for men, with two alcohol-free days after heavy drinking. Continued alcohol consumption at the upper levels is not advised (Prime Minister's Strategy Unit, 2004).

The standard definition of a unit of alcohol is that which contains 8 g of ethanol or 10 ml by volume. One unit is contained in half a pint of beer, a small glass of wine, and a single measure of spirits. Results from a national survey of drinking behavior and knowledge in the United Kingdom in 2004 revealed that the majority of respondents reported having heard of measuring alcohol consumption in units. Far fewer knew how to define a unit. Knowledge of the concept of units decreased with increase in age. Those aged 65 and older were least likely to report having heard of measuring alcohol in units. Likewise, 60% had heard of daily benchmarks but far fewer knew what they were (Lader and Goddard, 2004).

In a survey conducted in 2002, 16% of the men and 5% of the women aged 65 and older reported exceeding the daily number of units (more than four units for men and more than three units for women) on at least 1 day during the preceding week. In addition, 5% of the men in this age-group reported drinking more than eight units on at least one day and 1% of the women reported drinking more than six units on at least one day. In terms of weekly consumption, 15% of the men drank more than 21 units in the week and 3% drank more than 50 units. Among women, 7% reported totaling more than 14 units and 1% reported drinking more than 35 units over the course of the week (Rickards *et al.*, 2004).

AGE DIFFERENCES IN ALCOHOL EFFECTS

Increasing evidence suggests that the pharmacokinetic and pharmacodynamic effects of ethanol differ in older individuals compared with younger ones. Elderly people appear to be more sensitive to a given dose of alcohol. Between the ages of 25 and 60, the proportion of total body weight represented by fat doubles in men and increases by 50% in women, resulting in a corresponding decrease in total body water (Dufour *et al.*, 1992). Since alcohol is distributed in total body water, with a smaller volume of distribution, an alcohol dose identical to that given to a similar-sized younger individual of the same gender will produce a higher blood alcohol concentration in the older individual (Dufour *et al.*, 1992).

Research also suggests that mechanisms which are more complicated than simply differential volumes of distribution may contribute to differential sensitivity (Beresford and Lucey, 1995). Differential metabolism and intoxication were assessed in nonalcoholic younger and older individuals in three different metabolic settings using small doses of alcohol ($0.3\,g\,kg^{-1}$). This amount of alcohol resulted in considerable subjective feelings of intoxication in older subjects of either gender and the effects lasted longer (Beresford and Lucey, 1995). In addition, the elderly participants not only began with less perceptual motor capacity but also experienced a greater degree of impairment after ethanol intake and took longer to return to baseline functioning on some measures. While fasting markedly increased alcohol absorption for all study participants, the increased absorption in elderly women compared with younger women was particularly striking (Beresford and Lucey, 1995).

Although evidence is conflicting, some researchers suggest that, among young adults, gender differences appear to exist in ethanol metabolism by alcohol dehydrogenase (ADH) in the stomach, the so-called *first pass metabolism*, with the gastric ADH activity significantly higher in young adult men than in women. In elderly subjects, the gastric ADH activities were low in both sexes (Parlesak *et al.*, 2002). In addition, *Helicobacter pylori* infection is associated with decreased antral ADH activity. Eradication of the *H. pylori* normalizes ADH activity within 2 months (Kechagias *et al.*, 2001).

It was once thought that chronic heavy drinking accelerated the aging processes in the brain. The preponderance of scientific evidence now suggests that alcoholism does not cause premature aging. Rather, the effects of alcoholism are disproportionately expressed in older alcoholics (Oscar-Berman and Marinkovic, 2003). In other words, the aging brain is more vulnerable to the toxic effects of alcohol than is the younger brain, both acutely and with regard to reversibility of atrophic changes in the brain related to abstinence. Memory and executive skills appear to be resistant to recovery, or at least slower to recover with abstinence in older alcoholics (Munro *et al.*, 2000).

Not surprisingly, older subjects have been found to perform significantly worse in driving simulation than do younger subjects at the same alcohol dose (Beresford and Lucey, 1995), and have a dramatically higher risk of meeting the criteria for dependence at a given level of alcohol consumption than do younger individuals (Dawson and Archer, 1993).

MEDICAL CONSEQUENCES

Alcohol affects every organ in the body, manifesting itself in a wide array of pathology. For the elderly individual who already has reduced reserves because of normal aging and disease, the medical consequences of alcohol abuse are of paramount importance. They are important in their own right and provide clues to the diagnosis of alcoholism, and heavy alcohol consumption and alcoholism can cause symptoms that are also commonly seen in other conditions that beset the elderly.

In addition to alcohol dependence, alcoholic brain damage includes brain atrophy, dementia, and Wernicke–Korsakoff syndrome (Gambert and Katsoyannis, 1995). Peripheral neuropathy is frequently seen in clinical practice, where it is often first diagnosed as diabetic peripheral neuropathy (Smith, 1995). Alcohol disturbs normal sleep patterns and increases the risk of sleep apnea (Prinz *et al.*, 1990).

Alcoholic liver disease, primarily alcoholic hepatitis and cirrhosis, is a leading cause of death among alcoholics (Dufour *et al.*, 1993). Cirrhosis, secondary to hepatitis C

viral (HCV) infection is now the leading cause of adult liver transplants in the United States (OPTN, 2004). For people with HCV infection, alcohol consumption accelerates progression to cirrhosis and hepatocellular carcinoma (Lieber, 2001). For a variety of reasons, continued alcohol consumption is considered a major contraindication to treatment with current antiviral agents (Lieber, 2001). HCV infection is currently most prevalent among those aged 35–55 (CDC, 2004) but it does occur in older individuals also. In addition, as those currently infected age, HCV infection will become a greater problem in older individuals.

Heavy alcohol consumption is one of the leading causes of acute pancreatitis (Dufour and Adamson, 2003). Approximately three-quarters of the patients with chronic pancreatitis have a history of heavy alcohol consumption, and, while alcoholic liver disease and pancreatitis are much more likely to be encountered in younger patients, they do occur in the elderly (Dufour and Adamson, 2003). Alcohol use can cause esophagitis and gastritis, and exacerbate existing peptic ulcers (Smith, 1995). Alcohol-related testicular atrophy may contribute significantly to sexual problems in male alcoholics (Gambert and Katsoyannis, 1995). In women, it may cause premature menopause (Gambert and Katsoyannis, 1995).

Excessive alcohol consumption interferes with nutrition in many ways, including decreased budget for food, consumption of only empty calories available in alcohol, decreased appetite, decreased absorption of vitamins, amino acids and fats by a variety of mechanisms, and increased metabolic demand (Smith, 1995). Excess alcohol consumption is associated with iron deficiency anemia (gastrointestinal bleeding), macrocytic anemia, and coagulation defects. Alcohol-induced impairment of the immune system plays a role in increased vulnerability to tuberculosis and pneumonia (Gambert and Katsoyannis, 1995).

Hypertension is extremely prevalent among older people, affecting close to half of those aged 65 and older. Since hypertension is a major risk factor for stroke, myocardial infarction, and other vascular events, control of blood pressure is important (Adams, 2002). Alcohol consumption of above three drinks a day for men (1.5 oz ethanol or 36 g) and two for women is a major risk factor for hypertension (Zakhari and Wassef, 1996). Alcohol-related hypertension readily improves when alcohol consumption is decreased (Adams, 2002).

Cardiac manifestations include rhythm disturbances and alcoholic cardiomyopathy (Zakhari and Wassef, 1996). Extremely high levels of consumption are associated with an increased risk of coronary heart disease and ischemic stroke (Zakhari and Wassef, 1996). On the other hand, over 100 observational studies and more than 80 short-term metabolic studies have documented a strong association between moderate alcohol consumption and reduced risk of occurrence and death from myocardial infarction and ischemic stroke in both middle-aged and older men and women (Hines and Rimm, 2001). Experimental studies have found beneficial effects of alcohol on lipids, coagulation factors, and other cardiovascular markers. Genetic factors appear to modify the effects of alcohol on the risk for coronary heart disease, resulting in population variability in the amount of benefit (Hines and Rimm, 2001). Even low levels of alcohol consumption increase the risk of hemorrhagic stroke, especially in women (Scherr *et al.*, 1992).

Much remains to be learned about the relationship between alcohol consumption and diabetes mellitus. Light to moderate alcohol consumption appears to decrease the risk of developing type 2 diabetes in both men and women, with frequent (5 or more days a week) consumption conferring the most benefit (Conigrave *et al.*, 2001; Wannamethee *et al.*, 2003). Once diabetes has developed, alcohol consumption makes the control of blood sugar levels more difficult. Patients should be warned that hypoglycemia may occur several hours after alcohol consumption, and if likely to drink excessively, should be advised on how to modify their insulin doses and eating habits accordingly. The current recommendation of 2–3 units of alcohol per day should not be exceeded by diabetic patients (Gallagher *et al.*, 2001).

Alcohol abuse is associated with an increased risk of cancer of the liver, esophagus, nasopharynx, and larynx (Smith, 1995; Gambert and Katsoyannis, 1995). Some studies suggest that alcohol may play a role in cancer of the stomach, large bowel, and female breast (Smith, 1995; Gambert and Katsoyannis, 1995). Alcoholics with a variety of cancers have a poorer survival rate and an increased risk of developing a second primary than do nonalcoholics with the same cancer (Gambert and Katsoyannis, 1995). Chronic alcoholic myopathy causes muscle wasting and weakness. Even in the absence of muscle wasting, muscle strength is diminished (Smith, 1995). Aging is associated with a decrease in bone density in both men and women; however, the impact of alcohol on bone varies with dose and gender (Gambert and Katsoyannis, 1995). Male alcoholics are at greatly increased risk for osteoporosis. In addition, drinking leads to poor mobility and increased falls, leading to an increase in fractures. In the elderly, fractures tend to heal more slowly and to be associated with more complications. However, research also suggests that moderate drinking in both older men and postmenopausal women actually increases bone mineral density and improves bone mass relative to that of nondrinkers (Turner and Sibonga, 2001). Likewise, studies indicate that among healthy, mobile, independent, community-dwelling older individuals, alcohol may not play as big a role in falls (Nelson *et al.*, 1992; Sheahan *et al.*, 1995) as in more impaired individuals (Carlson, 1993).

ALCOHOL–MEDICATION INTERACTIONS

An older patient need not be alcohol dependent to get into trouble with alcohol use. A prime example is alcohol–medication interactions. In the United States, those aged 65 and older use 30% of the prescription drugs sold and 40% of over-the-counter medications (FDA, 1997). One study of community-dwelling elderly showed that 75% of those interviewed took at least one prescription drug and 52% reported taking three or more (Adams, 1995). In another

community study, all of the elderly drinkers reported utilizing at least one prescription or over-the-counter medication associated with an alcohol–drug interaction, reinforcing the concept that the profile of the older person at risk for an alcohol–drug interaction is that of the older person who drinks (Forster *et al.*, 1993). Alcohol interacts with over 100 prescription and over-the-counter medications (Dufour *et al.*, 1992), including over half of the 100 most frequently prescribed medications (Weathermon and Crabb, 1999). Acutely ingested, alcohol impairs the clearance of some drugs by the liver. In contrast, chronic alcohol consumption induces the synthesis of enzymes, leading to enhanced metabolism and increased clearance of some drugs, including anticonvulsants, anticoagulants, and oral hypoglycemic agents.

Psychotropic drugs such as antipsychotics and antidepressants are frequently prescribed for older patients: benzodiazepines or other sedative hypnotics are the most commonly prescribed classes of these drugs. Antipsychotic drugs inhibit the metabolism of alcohol and may markedly enhance its effects on the central nervous system (CNS) in the elderly. Antidepressants exaggerate the response to alcohol and impair motor skills (Weathermon and Crabb, 1999). Depression of the CNS may range from drowsiness to coma. The alcohol interaction with benzodiazepine drugs, especially diazepam and chlordiazepoxide, is much greater in the elderly than in other age-groups. Commonly observed side effects include hypotension, sedation, confusion, and CNS depression that may progress to respiratory depression (Weathermon and Crabb, 1999). These effects are especially hazardous in a population with decreased agility and a greater danger of serious complications from falls and accidents. Since older individuals are more sensitive to the effects of psychotropics, it is wise to reduce the dosages of benzodiazepines, analgesics, and sedative hypnotics in the elderly and to discourage the concomitant usage of alcohol. As a general rule, elderly patients should be instructed to refrain from using alcohol while taking CNS depressants, including benzodiazepines, barbiturates, muscle relaxants, and antihistamines – both in prescription form as well as over-the-counter cold preparations or sleeping aids (Weathermon and Crabb, 1999).

Alcohol is a vasodilator that enhances the absorption of nitroglycerin. Use of alcohol when vasodilation by nitrates is needed may result in severe hypotension. β-Blockers may mask the signs of delirium tremens. Use of alcohol with digoxin produces increased effects of alcohol and may result in seizures. Alcohol in combination with heparin can cause increased bleeding. Alcohol with tolbutamide or chlorpropamide can cause an Antabuse-like reaction (Weathermon and Crabb, 1999).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most prescribed drugs worldwide when grouped by generic categories (Adams, 1995). Aspirin is the active ingredient in countless over-the-counter preparations. Aspirin and other NSAIDs with alcohol increase the possibility of gastritis and gastrointestinal hemorrhage (Adams, 1995). Acetaminophen in therapeutic doses can result in severe hepatotoxicity in heavy drinkers (Adams, 1995).

Herbal medications currently are widely used and many people assume that because these products are "natural", they are also safe to use. Unfortunately, this assumption is not always correct. Chamomile, echinacea, and valerian are commonly used as sleep aids, and like prescription and OTC products that produce sedation, these products may produce enhanced sedative effects in the CNS when combined with alcohol. In addition, liver toxicities caused by various natural products have now been identified and their combination with alcohol may enhance potential adverse effects. To date, limited scientific documentation of such interactions exists due to lack of scientific studies on the subject (Weathermon and Crabb, 1999).

BARRIERS TO DIAGNOSIS AND TREATMENT

Attitudes toward alcoholism and aging on the part of the patient, physician, family, and society still often represent formidable obstacles to identification, diagnosis, and treatment. "Enabling" is an activity that is meant to "help" the alcoholic, but this also shields them from taking responsibility or being held accountable for the consequences of their drinking. In a recent study of elderly alcoholics presenting to an emergency department, one-third were found to have active "enablers" who blocked intervention for the alcohol problem. One-fifth of these enablers were physicians (Tabisz *et al.*, 1993).

Busy physicians may not consciously erect barriers, but rather, may be reluctant to assume clinical responsibility for a patient who is both elderly and alcoholic. A recent study among house officers in a US hospital found that they accurately diagnosed alcoholism in only 37% of elderly alcoholic patients compared with 60% of their younger patients (Egbert, 1993). Similar results were found among house officers in three Australian hospitals (Whelan, 1995).

Health-care providers may be unaware of age differentials in the signs and symptoms of alcohol-related problems, or, if able to make the diagnosis, may hesitate to do so because they are unsure about how to address the problem in the elderly, or may be unfamiliar with treatment resources for the elderly in their community, or with specialists in geriatric medicine or addiction medicine, with whom they might have to consult (Gurnack *et al.*, 2002).

Alcohol problems in the elderly are easy to miss. In a population in which there is already an overabundance of conditions requiring immediate medical attention, health-care providers may simply neglect to factor alcohol into the diagnostic equation. History taking can be a challenge with confused patients. Older patients may have difficulties remembering past average alcohol consumption. Denial, a hallmark of the disease at any age, may be reinforced in many older individuals who believe that alcoholism is a moral weakness or a character flaw rather than a disease. Elderly women are especially prone to delay seeking treatment until problems are more severe (Dunne, 1994). Social isolation

makes it easy to hide alcohol consumption – nearly a third of community-dwelling elderly live alone (Egbert, 1993).

A trap for the physician and family to avoid is unwillingness to discuss the patient's drinking problems with the individual, because he or she "has only a few years left". This is a myth. Older recovering alcoholics report that they began to live fuller, more satisfying lives after they stopped drinking and thus avoided the tragedy of wasting their remaining precious years. By recognizing and appreciating the broad patterns of problem drinking in the elderly population, physicians will be better able to recognize and understand the individual cases that they encounter.

DIAGNOSIS

Alcohol dependence is a serious medical and psychiatric disorder characterized by narrowing of the drinking repertoire, priority of drinking over other activities, increased tolerance to alcohol, repeated withdrawal symptoms relieved by further drinking, subjective awareness of a compulsion to drink, and reinstatement of drinking after abstinence (Seymour and Wattis, 1992). Problem drinking is drinking that causes harm, but the patient does not meet enough criteria to qualify for a diagnosis of abuse or dependence. Dependence and other drinking problems can occur in older patients, especially women, with substantially less alcohol than in younger individuals. Even older patients who do meet diagnostic criteria for abuse or dependence may differ in their presentation of key symptoms. For example, tolerance is characterized by requiring greater amounts of alcohol to achieve the same effect. Because of the reduction in body water, the elderly alcoholic may honestly report consuming a relatively smaller amount of alcohol to achieve the same effect as previously achieved, although there is the same induction of liver enzymes that cause tolerance in younger individuals.

Likewise, a person who is retired, widowed, and no longer driving, will obviously not report work-related problems, marital problems, or legal problems, such as arrests for drinking and driving – classic indicators of alcohol problems in the younger person.

Elderly alcoholics fall into two groups: those whose alcoholism began early in life (early-onset alcoholism) and those whose alcohol problems began later in life (late-onset alcoholism). Once again, definitions vary, with age cutoffs for "late onset" ranging from age 25 to 60 with most studies selecting age 40, 45, or 50 (Liberto and Oslin, 1995). Some investigators prefer the term "recent onset". An 85 year old who began drinking abusively at age 55 would hardly be considered a recent-onset alcoholic, but would qualify as one of "late onset". The importance of this distinction lies in the amount of damage linked to the amount of alcohol over time, the implication being that the "recent-onset" problem drinker may have a better prognosis and that intervention may be more effective when the drinking pattern is still being formed and before the illness has robbed the drinker of necessary physical and social resources (Liberto and Oslin, 1995). One-half to two-thirds of the elderly alcoholics are early-onset alcoholics (Liberto and Oslin, 1995). Usually they are more identifiable because of previous treatment contacts or earlier dysfunctional behavior that brought them to the attention of others.

The etiology of late-onset alcoholism appears to be more related to specific situational factors, such as retirement, death of a spouse or loss of friends, rather than family history or genetic influences (Brennan and Moos, 1995). However, many individuals in this group may have had undetected/undiagnosed alcoholism or a pattern of heavy drinking for years, with recent life events causing the disease to become manifest. Problem drinking tends to occur later in elderly women.

Patients suspected of having an alcohol-related problem should have a complete physical examination with special emphasis on peripheral manifestations of alcohol excess and chronic liver disease (parotid enlargement, Dupuytren's contracture, spider nevi, gynecomastia, jaundice, etc. *see* **Chapter 33, Liver and Gall Bladder**), including a thorough neurological assessment to rule out nystagmus, cerebellar ataxia, and peripheral neuropathy. When indicated, selected laboratory tests should be done to support the preliminary diagnosis – liver function tests and blood alcohol concentration may be informative. A mental status examination is necessary to assess the reliability of self-reported consumption as well as alcohol-related brain damage.

A careful history of current and past alcohol, tobacco, and other drug use, including prescription and over-the-counter medications, is mandatory. Frequency of drinking, beverage type, quantity per occasion, spirits added to tea or coffee, and corroborative history from caregivers or family are critical. Attention to definitions is at the heart of communication between the doctor and patient. It is critical to know whether a beer now and then means a 12 oz can of beer or a 32 oz bottle of beer and whether a "glass of wine" is a full 16 oz tumbler rather than a 5 oz wine glass. Many older individuals may not consider taking a tot of whiskey or rum in coffee or tea to be "drinking" and may neglect to mention such consumption. Hence this should be explicitly inquired about (Naik and Jones, 1994). Patients who have alcohol problems are also more likely to use anxiolytics, hypnotics, and other psychoactive substances. Inquiries about diet and nutrition are also pertinent.

Several self-administered screening instruments are available to assist in the diagnosis. Screening questions that work in busy general primary care samples of older adults include questions on quantity and frequency of alcohol consumption, binge drinking, and the CAGE questions (Mayfield *et al.*, 1974). A brief four-item questionnaire, the CAGE, originally developed for screening for alcoholism in younger patients, has been found to have excellent sensitivity and specificity among older patients as well (Fleming, 2002). Since it takes less than a minute to administer, the CAGE can be woven into a standard brief clinical history (see Table 1) and, for this reason, is probably the most commonly used screening instrument. If at least two questions are answered

Table 1 CAGE questions (Mayfield *et al.*, 1974)

1. Have you ever felt you should **C**ut down on your drinking?
2. Have people **A**nnoyed you by criticizing your drinking?
3. Have you ever felt bad or **G**uilty about your drinking?
4. Have you ever taken a drink first thing in the morning (**E**ye opener) to steady your nerves or get rid of a hangover?

Source: Reproduced from American Journal of Psychiatry (Copyright 1974). American Psychiatric Association.

affirmatively, the probability of alcoholism is high; however, in the elderly, even one affirmative response is strongly suggestive (Blow, 1998).

The AUDIT developed by the World Health Organization, identifies not only those who abuse or are dependent on alcohol but also those who may be hazardous drinkers because of the amount they consume (Blow, 1998; Allen and Wilson, 2003). The Michigan Alcoholism Screening Test (MAST) is a 25-item instrument that provides a quantifiable screen of alcohol abuse, has excellent reliability and validity, and is a widely used instrument for screening for alcoholism in younger individuals; however, some of the items may not be relevant for older drinkers (Blow, 1998). A version of this instrument developed especially for use with geriatric patients (MAST-G) has several elder-specific items such as "After drinking, have you ever noticed an increase in your heart rate or beating in your chest?" and "Does alcohol make you so sleepy that you often fall asleep in your chair?" (Blow, 1998). This instrument is highly valid and reliable among older problem drinkers and can be given as a paper-and-pencil self-administered assessment or by interview and takes about 10 minutes to complete (Barry *et al.*, 2001). A short version of the MAST-G, the SMAST-G, has been developed for use in busy clinical settings where the length of the instrument and its administration time are major barriers to its use (Barry *et al.*, 2001).

While all very useful, none of these measures identify people who may be at risk of, or experiencing, adverse consequences as a result of their drinking in combination with their comorbidities (e.g. hypertension, depression, etc.) and concurrent medication use, and yet do not qualify as "problem drinkers" on the above-mentioned screening instruments. Such risks are particularly relevant to older individuals. The alcohol-related problems survey (ARPS) has been developed to fill this gap – to identify older persons whose use of alcohol alone or in combination with their comorbidities, medications, symptoms, and functional status may be causing them harm or putting them at risk for harm. The ARPS is a 10-minute paper-and-pencil questionnaire that contains 60 items and is completed by the patient alone or with family assistance. On the basis of their responses, patients are designated as harmful, hazardous, or nonhazardous drinkers. Respondents completing the shorter 32-item version, the shARPS, are dichotomized as either harmful/hazardous or nonhazardous drinkers (Fink *et al.*, 2002).

Clues to an alcohol-related problem unearthed in the medical history include falls, bruises, emergency department visits, hyperuricemia, gastrointestinal problems, hypertension, insomnia, malnutrition, unstable diabetes and depression, as are self-neglect, urinary incontinence, diarrhea, decrease in functional status or apparent dementia (Barry *et al.*, 2001).

Laboratory investigations showing a raised mean corpuscular volume (MCV) or unexplained liver function test abnormalities, including elevated gamma glutamyltransferase, should alert the physician to the possibility of alcohol abuse. Hyperuricemia, hypertriglyceridemia, and hypoglycemia may also be caused or exacerbated by alcohol abuse (Seymour and Wattis, 1992).

Differentiating alcoholism from other psychiatric disorders is challenging but necessary because of the frequent occurrence of other psychopathology, especially depression, among elderly problem drinkers, particularly those who are hospitalized. The primary care provider, with consultation when necessary, should be prepared to make a comprehensive psychiatric evaluation of the patient to determine whether one or more diagnoses are in order and to determine which is the primary condition

INITIAL TREATMENT APPROACHES

With older problem drinkers, it is generally recommended that the least intensive treatment options be explored first. These initial approaches, which can function either as a pretreatment strategy or treatment itself, are brief intervention, intervention, and motivational counseling. Brief intervention is recommended as the first step, supplemented or followed by intervention and motivational interviewing (Blow, 1998). Brief interventions are time-limited, patient-centered counseling strategies that focus on changing their behavior and increasing compliance. Brief intervention is not unique to the treatment of alcohol problems. These counseling strategies are widely used by health-care providers for changing behavior, and have been found to be effective in reducing overall drinking, episodes of binge drinking, and frequency of excessive drinking in older adults. The clinical elements of brief intervention for the prevention and treatment of alcohol problems vary across trials and clinical programs, but they all contain a number of common elements: assessment; direct feedback; contracting, negotiating, and goal setting; behavior modification techniques; self-help directed bibliotherapy; follow-up and reinforcement. The number and duration of brief intervention sessions have varied widely. The classic brief intervention performed by a physician or nurse typically lasts 5–10 minutes and is repeated 1–3 times over a 6–8 week period (Barry and Blow, 1999). Numerous trials on primary care patients, including older individuals, have demonstrated that brief intervention is effective in reducing alcohol consumption in hazardous drinkers (Adams *et al.*, 1996; Gordon *et al.*, 2003).

If the older problem drinker does not respond to brief intervention, two other approaches – intervention and motivational interviewing – should be considered (Blow, 1998). In an intervention, several significant people in a problem drinking patient's life confront the patient with their firsthand experiences of his or her drinking. The formalized

intervention process includes a progressive interaction by the counselor with the family or friends for at least 2 days before meeting with the patient. For older patients, no more than two relatives or friends should be involved along with the health-care professional. Having too many people present may be emotionally overwhelming or confusing for the older person. Also, inclusion of grandchildren is discouraged, because many older adults may resent their problems being aired in the presence of much younger relatives (Blow, 1998).

Motivational counseling acknowledges differences in the readiness to address problem drinking and offers an approach for "meeting people where they are", which has proven effective with older adults. An understanding and supportive counselor listens respectfully and accepts the older patient's perspective on the situation as a starting point, helps him or her identify the negative consequences of drinking, helps the patient shift perceptions about the impact of drinking, empowers the patient to generate insights about and solutions for the problem, and expresses belief in and support for the patient's capacity to change. Motivational counseling enlists patients in their own recovery by avoiding labels and confrontations, accepting ambivalence as normal, inviting clients to consider alternative strategies for solving problems, and placing the responsibility for change on the patient (Blow, 1998).

SHORT-TERM STABILIZATION AND MANAGEMENT

The medical consequences of prolonged or heavy alcohol use can be severe and may require immediate attention. Conditions such as internal bleeding, fractures, other trauma resulting from falls, ischemic incidents, and mental confusion are not unusual and may, in fact, be the presenting complaint. If the patient is intoxicated when initially seen, the first step is detoxification. An intoxicated patient cannot engage in meaningful discussion of rehabilitation. Intoxicated elderly patients who threaten suicide should be taken seriously and given a prompt psychiatric examination and probably hospital admission as the suicide rate in these individuals is alarmingly high (AMA, 1995).

Although outpatient detoxification is often effective and safe for younger alcoholics who have mild to moderate withdrawal symptoms and no accompanying serious diseases, detoxifying elderly alcoholics is best carried out in a hospital setting where doses of benzodiazepines and/or other medications can be carefully monitored and emergency medical care is readily available (Seymour and Wattis, 1992). Sedatives should be used just vigorously enough to relieve withdrawal symptoms and not so vigorously as to result in somnolence, otherwise pulmonary complications may ensue. Dangers associated with alcohol-withdrawal syndrome are predominantly those of seizures and delirium tremens. For elderly alcoholics with a history of previous episodes of withdrawal, the risk is especially high (Seymour and Wattis, 1992). Delirium tremens, characterized by disorientation and confusion, visual or tactile hallucinations, and autonomic hyperactivity, must be considered a medical emergency; the death rate is 10–15% in untreated cases (AMA, 1995). With many older patients taking diuretics, careful attention to hydration and electrolyte balance is important (Seymour and Wattis, 1992). Vitamin supplements, especially thiamine, initially given parenterally may need to be continued orally, particularly if the patient has peripheral neuropathy (Seymour and Wattis, 1992). Acute withdrawal often persists longer in older alcoholics. In addition, confusion may be more severe and prolonged after discontinuation of drinking (Oscar-Berman and Marinkovic, 2003). Careful attention must be given to the patient's cognitive state during this period. Patients who have been medically detoxified should not be screened for cognitive dysfunction until several weeks after detoxification is completed because a patient not fully recovered from detoxification may exhibit some reversible cognitive impairment (Blow, 1998). However, counseling, didactic sessions, and mutual help groups, which otherwise would be appropriate are not useful to the patient whose mental faculties are too impaired to participate meaningfully.

LONG-TERM MANAGEMENT

After emergency situations have been addressed and detoxification completed, the next step is to work with the patient and family to develop a long-term treatment plan. This rehabilitation phase begins with the physician presenting the patients with the facts about their drinking problem in a concerned, nonjudgemental manner. Whereas the negative aspects of uncontrolled drinking are generally obvious to others, the alcoholic usually perceives benefits from drinking. Frank, compassionate discussion often helps the individual to recognize the negative consequences of their drinking and makes them consider the need for treatment. Although this discussion may be painful for the patient and may occasionally result in the patient leaving the physician's practice, people in recovery from alcoholism often date the beginning of their remission from such a discussion.

In general, the ultimate goal of treatment is abstinence. The patient can be referred to an addiction program, an addiction specialist or Alcoholics Anonymous (AA) or other mutual help groups. Addiction programs usually provide group therapy and/or individual counseling, relapse prevention training and support from an AA group. Patients who perceive that many AA members are too young should be informed that one-third of all AA members in North America are over the age of 50 and that compatible groups are likely to be found. There are more than 3000 AA groups in the United Kingdom today. Information about AA in the United Kingdom for the health-care professional can be found on the Internet at http://www.alcoholics-anonymous.org.uk/prof/. Older individuals respond well to group therapies, especially when increased socialization is also encouraged. Currently, older patients are "mainstreamed" with patients of all ages and do just as well in treatment (Blow, 1998). While age-specific treatment is intuitively appealing, research to date does not

support the view that older alcoholics require age-specific treatment. Whether they would have better outcomes in such settings is under investigation. Some studies have indicated more favorable outcomes for elder-specific groups than mixed age-groups. Treatment programs that emphasize social relationships and positive aspects of a patient's life have demonstrated better outcomes for those aged 60 and older, than programs using traditional confrontation and focusing on past failures (Blow, 1998).

The prognosis for patients with late-onset alcoholism is usually better than for those with early onset (Brennan and Moos, 1995). Late-onset patients seem to comply more readily with treatment plans and remain in treatment longer (Brennan and Moos, 1995). Among the early-onset patients, those having more drinking problems, financial stressors, and those who sought professional help were more likely to quit drinking (Brennan and Moos, 1995). Among the late-onset individuals, social influences and physical health stressors were more important in predicting remission and abstinence (Brennan and Moos, 1995). Studies have shown that older alcoholic individuals demonstrate greater adherence with alcohol treatment visits and medication than younger ones, with a greater reduction in the rates of relapse (Oslin *et al.*, 2002). Prior to making a referral, the physician should become familiar with programs available in the community, or elsewhere if necessary, and determine their accessibility both in terms of distance and time. The longer the waiting period, the less likely the patient will show up for admission.

PHARMACOTHERAPIES FOR ALCOHOLISM

Advances in the neurobiology of addiction and methodologies of improved clinical trials have accelerated the evaluation of medications for alcoholism. Because of the complex nature of alcohol use disorders, no single treatment strategy has thus far proven fully effective. While the psychosocial treatments for alcohol abuse and dependence can be effective in reducing alcohol use and increasing health and well being, they are not always completely successful for all patients and can be costly (Litten *et al.*, 2005). In addition, medications are being increasingly used in the treatment of other addictive disorders such as buproprion for smoking cessation.

No discussion about the pharmacotherapy of alcoholism would be complete without acknowledging the historical and practical utility of aversive therapies. Disulfiram (Antabuse®) is an example of a medication that can increase the unpleasant actions of alcohol (nausea, vomiting, flushing) by inhibiting acetaldehyde dehydrogenase, an enzyme involved in alcohol metabolism, leading to the accumulation of acetaldehyde after alcohol is consumed. While the efficacy of this drug is variable, disulfiram is widely used throughout the world in both tablet and implant form. Data suggests that the drug is most effective in older, highly motivated individuals, and in those who are supervised during daily ingestion. Some clinicians advise against the use of disulfiram to help enforce abstinence in the elderly because of the increased potential for adverse cardiovascular effects. Because of the risk of hepatotoxicity, physicians review the signs and symptoms of hepatotoxicity and liver function tests at the onset of treatment and at regular intervals thereafter (Anton and Swift, 2003).

Acamprosate (Campral®) has been licensed for the treatment of alcohol dependence in France for over 10 years and in the United Kingdom since 1996. The drug is currently approved and available in 29 countries including the United States, where it was approved in 2004. Over 20 clinical trials have been conducted, and overall it was found that acamprosate is effective in increasing the rates of abstinence and treatment retention. Acamprosate may also decrease the frequency of drinking as well as reduce alcohol consumption if a relapse has occurred. Neither type nor intensity of any concomitant psychosocial intervention has been found to improve outcome over the use of acamprosate alone. A current favored explanation for acamprosate's effect in alcohol-dependent patients is that it reduces the tendency to relapse in situations that have been linked to the negative sensations associated with the absence of alcohol, the so-called *negative craving*. The use of acamprosate varies within and among countries of Europe. In a survey in Scotland, all the National Health Service units specializing in treating alcohol problems prescribed it. It is generally recommended that in order to achieve the greatest chance of an effect, acamprosate should be started as soon as the patient is near successful detoxification. If the patient manages to abstain, the drug should be continued for 1 year. Given that acamprosate also appears to have a small effect in reducing the drinking following a lapse, the drug should not be stopped if the patient lapses – if the lapses are less severe and less frequent than prior to treatment, the drug may be helping. Diarrhea is the most common side effect. Since acamprosate is not metabolized by the liver, it is not contraindicated in liver disease (Soyka and Chick, 2003).

Naltrexone (ReVia®) was first approved for alcoholism treatment in the United States in 1994. The medication is an opioid antagonist, which has reportedly been shown to decrease the positive reinforcing effects associated with alcohol consumption and the sensation of wanting to drink (craving). Results for naltrexone studies have been less consistent than those reported for acamprosate, and several European studies have been negative or partly negative. Several studies have indicated that cognitive behavioral therapy with teaching of coping skills leads to the best outcomes when naltrexone is used (Litten *et al.*, 2005). Studies have shown that naltrexone is well tolerated and efficacious in preventing relapse in older patients who drink following entry into alcoholism treatment (Oslin *et al.*, 1997). Side effects of naltrexone are generally moderate at the 50 mg dose used in most studies and include nausea, vomiting, diarrhea, headache, and fatigue. A recent report of interaction between NSAIDs and high-dose naltrexone (>100 mg) leading to hepatotoxicity is a cause for concern and patients should be cautioned. In general, clinicians should start naltrexone at $25\,\text{mg}\,\text{day}^{-1}$ for a few days and move the dose to 50 mg as tolerated (Anton and Swift, 2003).

Alcoholism is a chronic, relapsing condition like arthritis or diabetes. Elderly patients, like alcoholics of every age, may well have "slips" and return to drinking. The resultant guilt and shame may prevent their return to the physician. Missed appointments should therefore be routinely followed up by a nonjudgemental invitation to return for treatment. One study examining the outcomes at 1 and 5 years after treatment for alcohol use disorders showed that elderly patients had better outcomes than did young and middle-aged patients receiving the same levels of services (Lemke and Moos, 2003).

CONCLUSION

The cornerstone of prevention is the inclusion of an alcohol history in *every* history and physical examination. Primary prevention of alcohol-related problems and alcoholism among the elderly consists mainly of alerting patients to possible alcohol–medication interactions and other risk factors that can lead to late-onset alcoholism. Physicians are more likely to be involved in secondary prevention where the role is recognizing early warning signs in their patients and intervening at the onset of harmful drinking behavior.

Even in the absence of signs and symptoms of alcohol-related problems, physicians must provide education on the adverse effects of alcohol with age and must define and advise moderation.

All other things being equal, there is no evidence to suggest that older individuals are any more or any less able to cope with the stresses of life. Old age *per se* is not a contraindication to moderate alcohol consumption. In older individuals who have no medical conditions for which alcohol is contraindicated, particularly prior history of alcohol dependence, and who take no drugs (prescription or over- the- counter) that adversely interact with alcohol, the physician may feel comfortable affirming the acceptability of sensible drinking.

The operative word here is "sensible". What is sensible? In fact, what is a drink? Once again, definitional differences create confusion. In the United States and Canada, one "standard drink" is about 0.5 oz or 12 g of ethanol, 12 oz of beer, 5 oz of wine, or 1.5 oz of distilled spirits. In Australia and New Zealand, a drink is 10 g of alcohol. In the United Kingdom, the measure of consumption is the "unit of alcohol" (8 g of ethanol) – half a pint (284 ml) of beer, a glass (125 ml) of wine, a glass (50 ml) of sherry, or a single measure (24 ml) of spirits. The Royal College of Physicians, Psychiatrists, and General Practitioners have expressed concern that British drinkers, being unaware of the actual size of a "unit", may think they are following drinking guidelines but are actually consuming more than recommended. For example, cans of beer frequently exceed half a pint by as much as 40% but may be mistaken for a unit. Elderly drinkers need to know the serving size of a drink. Given the aforementioned changes in body water and lean body mass, a reasonable definition of sensible drinking for both elderly men and women is one drink or 1.5 units a day.

Patients should be counseled to avoid alcohol consumption immediately prior to going to bed in order to avoid sleep disturbances, cautioned against potential drug–alcohol interactions, and told to avoid alcohol consumption prior to activities such as driving. The decision to recommend a particular level of alcohol consumption in any given patient must, however, be carefully tailored not only to the individual's specific medical needs but also to their social and environmental circumstances as well.

Finally, at each stage in life sobriety has special rewards, and old age is no exception.

KEY POINTS

- Alcohol consumption is relatively common among older individuals; therefore, all patients should be screened for alcohol consumption and related problems.
- While most older drinkers have heard of a "unit of alcohol" and "sensible drinking guidelines", far fewer are able to define these terms. Therefore, health-care providers should view patient visits as opportunities for providing alcohol education.
- Polypharmacy is highly prevalent among older patients. Alcohol reacts negatively with over 100 prescription and over-the-counter medications. Therefore, alcohol–medication interactions are a very real possibility among older drinkers.
- Alcohol dependence is a highly treatable condition. Older individuals do as well or better in treatment than younger individuals.
- Current pharmacotherapies for alcoholism are effective for some patients but not for others. The fields of neurochemistry and medications development are very active and rapidly evolving. New, more effective medications will soon be on the horizon.

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16

On the Evolution of All-cause and Cause-specific Mortality in the Age Class 75–84 years: a Worldwide Overview

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INTRODUCTION

The mean age of most industrialized populations is increasing. This is essentially due to two independent facts: a decrease in birth rate and an increase in life expectancy. Actually, the segment of the population above the age of 75 years is the fastest growing. The decrease in birth rate is an exceptionally important problem, but is of social origin and beyond the scope of this study. In view of the important consequence of the increase in life expectancy, we will address the evolution of mortality specifically in the age class 75–84 years of the population worldwide.

METHODS

Data were provided by World Health Organization (WHO). Mortality data for all-cause (AC), total cardiovascular (TCV), total cancer (TCA) and residual (RES) (noncardiovascular, noncancer) mortality were obtained for 5 years classes within the age range 35–84 years. All data, including these from the 75–84 years age ranges, were age-standardized according to the old European population standard, which is equal for men and women. The data from the initial year 1970 or the earliest available year, till the last available year, about the year 2000, were analyzed. Only populations with acceptable population and mortality statistics and with a low mortality due to infectious diseases were included. The period is covered by ICD-9 and ICD-10 of the international classification of diseases (WHO, 1977). This is of lesser importance since only broad disease categories are used. The data were submitted to linear regression analysis with time and the intercept, slope, t-value and the yearly decline as a percentage of the initial value (intercept) are provided. The t-value of the equation depends to a great extent on the linearity of the occurring changes. During the period considered, some countries show both increase and decrease in mortality. Only the evolution compared to the starting value can thus be appreciated. For a limited number of countries (Japan, United States, and the mean of France, Italy, and Spain), Gompertz equations (Gompertz, 1825) and second-degree polynomial equations between mortality and age (Kesteloot and Huang, 2003) will be provided. This will allow us to situate the evolution in the 75–84 years age class within the frame of the changes over a wider age range. This study is an extension and upgrading of previous work in this field (Sans *et al.*, 1997; Kesteloot *et al.*, 2002).

RESULTS

In Table 1 the crude all-cause, total cardiovascular, total cancer, and residual mortality rates are provided for 45 countries in the age class 75–84 years for men, and in Table 2 for women. The countries are listed according to the lowest all-cause mortality. All-cause mortality is the most reliable index of mortality in developed countries since it does not need standardization. Of the 10 highest AC mortality rates for men, 8 are provided by Eastern European countries. For women, the ratio is 10 out of the 12 highest. The greatest degree of variation exists for total cardiovascular mortality rates. Countries with the highest all-cause and cardiovascular mortality rates have the lowest total cancer rates. Albania has a lower mortality than Canada for men, and a similar mortality to Denmark for women. Albania is the poorest country of Europe and Denmark the richest of the European

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Table 1 MEN – mortality 75–84 years per 100 000 – mean of 3 latest available years

Country	Myear	AC	TCV	TCA	RES
01 Japan	1999	6008	1892	1928	2188
02 Hong Kong	1998	6160	1764	1777	2619
03 Australia	2000	6207	2569	1859	1779
04 France	1998	6518	2233	1950	2335
05 Switzerland	1999	6658	2752	1880	2026
06 Austria	2001	6741	3522	1782	1436
07 Sweden	2000	6768	3328	1692	1748
08 Iceland	1998	6827	3205	1987	1635
09 United States	1999	6860	2929	1732	2199
10 New Zealand	1999	6986	3195	1983	1808
11 Spain	1999	7014	2423	1940	2652
12 Greece	1998	7060	3590	1753	1718
13 Italy	1999	7080	3024	2055	2001
14 Singapore	2000	7156	2768	1929	2460
15 Cuba	1995	7311	3547	1518	2245
16 Germany	2000	7345	3626	1904	1815
17 Norway	2000	7575	3446	1951	2178
18 Finland	2001	7683	3568	1787	2328
19 England and Wales	1999	7876	3436	2025	2415
20 Belgium[a]	1996	7947	3239	2422	2285
21 Costa Rica	1994	8190	3419	1985	2786
22 Netherlands	1999	8291	3189	2351	2752
23 Denmark	1998	8382	3478	2164	2740
24 N. Ireland	1999	8537	3827	2002	2708
25 Albania	2000	8717	5276	1135	2306
26 Argentina	1995	8782	4116	1675	2991
27 Scotland	1999	8883	4072	2297	2515
28 Portugal	1999	8939	3776	1821	3342
29 South Korea	2000	9094	2424	2042	4628
30 Lithuania	2001	9175	5702	2000	1473
31 Canada	1997	9269	3805	2512	2951
32 Poland	2000	9279	5061	2030	2188
33 Chile	1993	9486	3456	1957	4073
34 Czech Republic	2000	9505	5677	2333	1495
35 Ireland	1999	9613	4291	2193	3129
36 China (rural)	1998	9648	3939	1142	4567
37 China (urban)	1998	9660	4465	1821	3374
38 Estonia	2001	9782	6424	1951	1407
39 Romania	2001	9824	7260	1191	1373
40 Hungary	2001	9897	5687	2402	1808
41 Latvia	2001	10 069	6556	1874	1639
42 Bulgaria	2001	10 599	7860	1066	1673
43 Ukraine	1999	11 238	8296	1154	1788
44 Russian Federation	2001	11 664	8239	1586	1839
45 Belarus	2000	11 778	7724	1552	2502

AC, All Causes; TCV, Total Cardiovascular; TCA, Total Cancer; RES, Residual; Myear: mean of 3 latest available years.
[a]for AC: mean year = 1999.

Table 2 WOMEN – mortality 75–84 years per 100 000 – mean of 3 latest available years

Country	Myear	AC	TCV	TCA	RES
01 Japan	1999	3127	1215	810	1102
02 France	1998	3599	1322	847	1430
03 Australia	2000	3800	1713	955	1132
04 Switzerland	1999	3822	1696	901	1225
05 Hong Kong	1998	3851	1346	959	1547
06 Spain	1999	4093	1758	785	1550
07 Italy	1999	4161	2036	937	1189
08 Sweden	2000	4186	2022	972	1192
09 New Zealand	1999	4239	2016	1078	1145
10 Austria	2001	4322	2450	991	881
11 Norway	2000	4416	2014	978	1424
12 Iceland	1998	4449	2062	1122	1265
13 Finland	2001	4601	2254	905	1442
14 Belgium[a]	1996	4617	2145	1049	1424
15 Germany	2000	4631	2472	1038	1120
16 United States	1999	4645	2017	1041	1587
17 Netherlands	1999	4696	1904	1051	1740
18 Singapore	2000	4956	2266	1036	1654
19 Canada	1997	5065	2131	1273	1662
20 England and Wales	1999	5092	2256	1136	1700
21 Denmark	1998	5368	2186	1297	1885
22 Greece	1998	5383	3269	853	1261
23 Albania	2000	5386	3533	450	1403
24 Argentina	1995	5396	2760	896	1741
25 N. Ireland	1999	5418	2572	1131	1715
26 Portugal	1999	5521	2770	816	1935
27 Costa Rica	1994	5602	2380	1134	2088
28 Cuba	1995	5609	2995	814	1801
29 Lithuania	2001	5728	4224	866	638
30 South Korea	2000	5741	1888	799	3054
31 Scotland	1999	5897	2729	1398	1771
32 Ireland	1999	6057	2795	1228	2034
33 Chile	1993	6167	2424	1180	2563
34 Poland	2000	6251	3842	1005	1404
35 Estonia	2001	6281	4526	892	863
36 Czech Republic	2000	6505	4257	1245	1003
37 China (rural)	1998	6525	2769	608	3148
38 Latvia	2001	6576	4749	866	961
39 Hungary	2001	6604	4275	1219	1110
40 China (urban)	1998	6801	3395	929	2477
41 Romania	2001	7725	6227	705	794
42 Belarus	2000	7876	5631	623	1622
43 Russian Federation	2001	8231	6436	759	1035
44 Bulgaria	2001	8268	6516	651	1100
45 Ukraine	1999	8278	6794	522	962

AC, All Causes; TCV, Total Cardiovascular; TCA, Total Cancer; RES, Residual; Myear: mean of 3 latest available years.
[a]for AC: mean year = 1999.

Union. Countries from the Mediterranean region (France, Italy, Spain, Greece) have low AC and TCV mortality rates for both sexes.

The changes in mortality rates in the age range 75–84 years are given in Tables 3–10. In Table 3, the results of the changes in mortality rates for all causes during the last 20–30 years for men are presented. The countries are ranked according to the magnitude of the percental decline. With the exception of increases in Ukraine (NS) and Belarus ($p < 0.001$) mortality is decreasing everywhere. Note the limited decline in Denmark and Iceland. Belgium is doing better than the Netherlands. The worst results are once again obtained in Eastern Europe with the exception of the Czech Republic. In the best performing countries, mortality has almost been halved over a period of 30 years.

In Table 4, the same results are presented for women. Although the starting mortality is lower, the percental decline is even more impressive than for men. Denmark and Iceland are performing poorly, and Belgium is again performing better than the Netherlands. Of all Eastern European countries, over the last 16 years, Czechoslovakia is performing best for both sexes. In Tables 5 and 6, the changes in total cardiovascular mortality are given for men and women. The most impressive changes occur for

Table 3 MEN – linear equation of all-cause mortality rates 75–84 years per 100 000 versus calendar year

Country	*n*	LAY	*a*	*b*	*t*	*d*
01 Czech Republic	16	2001	13 157	−264.4	−20.45	−2.01
02 Singapore	32	2001	14 226	−252.1	−15.06	−1.77
03 Japan	31	2000	10 808	−175.2	−28.03	−1.62
04 Australia	31	2001	11 768	−184.9	−24.97	−1.57
05 Albania	15	2001	10 731	−165.4	−3.69	−1.54
06 Austria	33	2002	12 779	−188.6	−29.74	−1.48
07 France	30	1999	10 277	−142.1	−24.94	−1.38
08 Hong Kong	30	1999	9797	−134.9	−12.32	−1.38
09 Portugal	31	2000	13 611	−179.5	−11.03	−1.32
10 Spain	31	2000	10 620	−138.2	−19.72	−1.30
11 Germany	32	2001	12 692	−163.8	−22.76	−1.29
12 New Zealand	31	2000	11 519	−143.5	−17.27	−1.25
13 Italy	31	2000	10 934x	−134.0	−20.83	−1.23
14 Finland	33	2002	12 403	−149.0	−29.31	−1.20
15 Switzerland	31	2000	10 146	−121.7	−43.92	−1.20
16 England and Wales	31	2000	12 201	−145.8	−29.43	−1.19
17 N. Ireland	31	2000	12 808	−146.4	−15.14	−1.14
18 Belgium	31	2000	11 972	−132.0	−21.76	−1.10
19 United States	31	2000	9764	−101.2	−24.18	−1.04
20 Scotland	31	2000	13 001	−134.3	−16.73	−1.03
21 Sweden	32	2001	9948	−97.6	−18.58	−0.98
22 Estonia	18	2002	11 736	−112.0	−6.01	−0.95
23 China (urban)	13	1999	10 697	−76.9	−1.95	−0.72
24 China (rural)	13	1999	10 524	−74.0	−1.84	−0.70
25 Ireland	31	2000	12 167	−79.3	−9.00	−0.65
26 Chile	24	1994	11 639	−74.4	−5.92	−0.64
27 Norway	32	2001	9610	−58.7	−14.90	−0.61
28 Hungary	33	2002	13 022	−77.1	−7.86	−0.59
29 Argentina	21	1996	10 598	−55.9	−4.12	−0.53
30 Greece	30	1999	8421	−42.0	−10.40	−0.50
31 Canada	29	1998	9075	−45.1	−1.67	−0.50
32 Poland	31	2001	11 886	−58.3	−5.19	−0.49
33 Netherlands	31	2000	9736	−40.7	−10.01	−0.42
34 South Korea	17	2001	9954	−40.5	−1.06	−0.41
35 Latvia	23	2002	11 452	−45.6	−2.85	−0.40
36 Romania	33	2002	11 709	−44.2	−5.93	−0.38
37 Denmark	30	1999	9624	−31.0	−5.05	−0.32
38 Iceland	30	1999	7546	−20.2	−1.70	−0.27
39 Lithuania	18	2002	9420	−10.2	−0.65	−0.11
40 Bulgaria	33	2002	11 241	−11.0	−1.59	−0.10
41 Cuba	27	1996	7794	−6.7	−0.47	−0.09
42 Russian Federation	23	2002	11 925	−8.9	−0.60	−0.07
43 Costa Rica	26	1995	8527	34.8	1.12	0.41
44 Ukraine	16	2000	11 054	46.5	1.68	0.42
45 Belarus	17	2001	10 110	126.9	5.47	1.26

n determines the number of years preceding the latest available year (LAY);
a: intercept; *b*: slope; *t* : *t*-value; *d*: percental decrease per year.

Table 4 WOMEN – linear equation of all-cause mortality rates 75–84 years per 100 000 versus calendar year

Country	*n*	LAY	*a*	*b*	*t*	*d*
01 Japan	31	2000	7816	−172.9	−33.57	−2.21
02 Czech Republic	16	2001	8971	−177.9	−31.63	−1.98
03 Spain	31	2000	7977	−146.3	−25.44	−1.83
04 France	30	1999	6498	−114.0	−32.11	−1.76
05 Portugal	31	2000	10 348	−180.4	−16.31	−1.74
06 Switzerland	31	2000	7013	−121.8	−24.71	−1.74
07 Italy	31	2000	7963	−136.3	−36.39	−1.71
08 Belgium	31	2000	8475	−142.8	−36.60	−1.68
09 Austria	33	2002	8985	−150.9	−58.24	−1.68
10 Australia	31	2001	7320	−121.6	−18.95	−1.66
11 Albania	15	2001	6294	−103.4	−2.64	−1.64
12 Germany	32	2001	9007	−145.6	−60.11	−1.62
13 Finland	33	2002	8709	−138.3	−18.85	−1.59
14 Singapore	32	2001	8869	−131.2	−21.15	−1.48
15 Estonia	18	2002	8256	−119.7	−11.27	−1.45
16 China (urban)	13	1999	8024	−114.8	−6.25	−1.43
17 New Zealand	31	2000	7346	−103.3	−22.57	−1.41
18 Argentina	20	1996	7747	−108.1	−8.15	−1.39
19 N. Ireland	31	2000	8625	−118.0	−20.19	−1.37
20 Sweden	32	2001	6746	−91.6	−36.51	−1.36
21 Hong Kong	30	1999	6074	−77.0	−12.13	−1.27
22 Norway	32	2001	6773	−82.6	−27.10	−1.22
23 Ireland	31	2000	9050	−110.0	−21.39	−1.22
24 Netherlands	31	2000	6679	−81.2	−12.19	−1.22
25 Chile	24	1994	8885	−107.9	−7.36	−1.21
26 England and Wales	31	2000	7513	−89.4	−27.92	−1.19
27 China (rural)	13	1999	7346	−82.9	−5.11	−1.13
28 Costa Rica	26	1995	7815	−78.4	−5.39	−1.00
29 Scotland	31	2000	8122	−80.5	−21.04	−0.99
30 United States	31	2000	5986	−56.5	−10.42	−0.94
31 Canada	29	1998	5745	−52.4	−4.55	−0.91
32 Hungary	33	2002	9778	−87.3	−16.81	−0.89
33 Greece	30	1999	7269	−62.9	−15.38	−0.87
34 Iceland	30	1999	5705	−45.5	−4.60	−0.80
35 Lithuania	18	2002	6774	−53.8	−5.57	−0.79
36 Latvia	23	2002	8038	−59.8	−7.22	−0.74
37 Denmark	30	1999	6517	−48.0	−9.21	−0.74
38 Poland	31	2001	8463	−59.7	−9.97	−0.71
39 Romania	33	2002	10 203	−66.1	−10.19	−0.65
40 Bulgaria	33	2002	9670	−42.5	−7.73	−0.44
41 Cuba	27	1996	6069	2.3	0.16	0.04
42 Russian Federation	23	2002	7800	20.6	2.29	0.26
43 South Korea	17	2001	5493	35.9	1.50	0.65
44 Ukraine	16	2000	7793	55.6	2.66	0.71
45 Belarus	17	2001	6776	83.7	5.37	1.24

n determines the number of years preceding the latest available year (LAY)
a: intercept; *b*: slope; *t* : *t*-value; *d*: percental decrease per year.

both sexes in Japan and Australia. Belgium is performing better than the Netherlands and Estonia better than the other Baltic States. Greece is performing badly, especially when compared with France, Italy, and Spain, the other Mediterranean countries.

With total cancer mortality, the picture changes dramatically. In a great majority of countries, mortality increases (Tables 7 and 8). Japan, notwithstanding a dramatic decrease in stomach cancer mortality, is no longer the leader of the decline. The significant decreases in Hong Kong and Singapore in this older age class, especially in women, remain unexplained. In Tables 9 and 10 the changes in remainder mortality (noncardiovascular, noncancer) are given. This is an important category consisting essentially of chronic diseases (respiratory insufficiency, liver cirrhosis, and others) and acute causes of mortality (suicide, homicide, accidents, and others). Included also are unspecified causes of mortality. This rubric is often neglected but the death rates are more important than those for total cancer mortality. The changes are also impressive both for the decreases and increases. These changes are difficult to interpret. The United States, the Russian Federation, Denmark, and Canada have some of the highest increases. The question arises as to how many of these changes could be due to misclassification of TCV or TCA in this higher age class.

Table 5 MEN – linear equation of TCV mortality rates 75–84 years per 100 000 versus calendar year

Country	*n*	LAY	*a*	*b*	*t*	*d*
01 Japan	31	2000	5931	−149.1	−38.56	−2.51
02 Australia	31	2001	7312	−161.4	−32.23	−2.21
03 Czech Republic	16	2001	8225	−175.4	−16.19	−2.13
04 Spain	31	2000	5660	−116.6	−39.04	−2.06
05 France	30	1999	4684	−92.8	−33.19	−1.98
06 South Korea	17	2001	3691	−72.2	−3.12	−1.96
07 United States	31	2000	6203	−119.1	−35.01	−1.92
08 Italy	31	2000	6208	−113.4	−28.61	−1.83
09 Estonia	18	2002	8888	−158.5	−10.48	−1.78
10 N. Ireland	31	2000	7700	−134.3	−22.73	−1.74
11 Belgium	28	1997	5911	−102.8	−20.70	−1.74
12 Hong Kong	30	1999	3475	−60.0	−15.84	−1.73
13 Switzerland	31	2000	5527	−94.5	−27.96	−1.71
14 New Zealand	31	2000	6585	−111.7	−29.06	−1.70
15 Canada	29	1998	5558	−91.6	−7.58	−1.65
16 England and Wales	31	2000	6537	−103.8	−48.05	−1.59
17 Finland	33	2002	7268	−113.1	−34.19	−1.56
18 Scotland	31	2000	7550	−117.4	−30.54	−1.55
19 Argentina	20	1996	6180	−93.9	−8.57	−1.52
20 Austria	33	2002	7213	−107.5	−18.30	−1.49
21 Portugal	31	2000	6919	−101.6	−11.79	−1.47
22 Germany	32	2001	7078	−101.1	−12.92	−1.43
23 Sweden	32	2001	6151	−84.8	−18.61	−1.38
24 Ireland	31	2000	7119	−93.9	−17.49	−1.32
25 Denmark	30	1999	5847	−73.9	−17.73	−1.26
26 Netherlands	31	2000	5071	−60.8	−25.69	−1.20
27 China (rural)	13	1999	4326	−50.9	−2.62	−1.18
28 Norway	32	2001	5524	−62.1	−20.89	−1.12
29 Latvia	23	2002	8637	−94.1	−8.29	−1.09
30 Singapore	32	2001	4104	−44.5	−5.18	−1.08
31 Albania	15	2001	5752	−50.3	−1.46	−0.87
32 Hungary	33	2002	8065	−62.8	−12.90	−0.78
33 Chile	24	1994	4444	−32.8	−4.54	−0.74
34 China (urban)	13	1999	4851	−33.7	−1.87	−0.69
35 Iceland	30	1999	4321	−28.7	−2.95	−0.66
36 Lithuania	18	2002	6486	−41.0	−3.21	−0.63
37 Cuba	27	1996	4228	−20.4	−2.57	−0.48
38 Russian Federation	23	2002	8437	−17.4	−1.52	−0.21
39 Poland	31	2001	6433	−3.9	−0.30	−0.06
40 Romania	33	2002	7785	5.6	0.81	0.07
41 Costa Rica	26	1995	3490	13.9	0.98	0.40
42 Greece	30	1999	3523	15.4	3.14	0.44
43 Ukraine	16	2000	7540	49.3	1.58	0.65
44 Bulgaria	33	2002	6733	48.8	7.61	0.73
45 Belarus	17	2001	6482	54.8	2.12	0.85

n determines the number of years preceding the latest available year (LAY); *a*: intercept; *b*: slope; *t* : *t*-value; *d*: percental decrease per year.

Table 6 WOMEN – linear equation of TCV mortality rates 75–84 years per 100 000 versus calendar year

Country	*n*	LAY	*a*	*b*	*t*	*d*
01 Japan	31	2000	4538	−121.5	−41.10	−2.68
02 Australia	31	2001	5243	−122.3	−28.06	−2.33
03 Spain	31	2000	4781	−107.4	−48.37	−2.25
04 France	30	1999	3269	−73.2	−40.94	−2.24
05 Switzerland	31	2000	4305	−95.9	−40.71	−2.23
06 Argentina	20	1996	5099	−111.8	−11.47	−2.19
07 Italy	31	2000	5106	−111.2	−35.70	−2.18
08 Estonia	18	2002	6861	−149.2	−18.10	−2.17
09 Czech Republic	16	2001	6105	−129.8	−30.53	−2.13
10 Belgium	28	1997	4536	−92.2	−33.21	−2.03
11 Canada	29	1998	3864	−78.3	−14.46	−2.03
12 United States	31	2000	4250	−85.1	−22.43	−2.00
13 Finland	33	2002	5765	−115.4	−29.51	−2.00
14 N. Ireland	31	2000	5714	−112.0	−26.86	−1.96
15 New Zealand	31	2000	4716	−90.7	−37.34	−1.92
16 Netherlands	31	2000	3893	−72.8	−28.50	−1.87
17 Sweden	32	2001	4391	−80.2	−66.92	−1.83
18 England and Wales	31	2000	4667	−84.7	−51.90	−1.81
19 Ireland	31	2000	5655	−101.7	−28.86	−1.80
20 Germany	32	2001	5626	−100.7	−22.65	−1.79
21 Austria	33	2002	5701	−100.3	−32.89	−1.76
22 Norway	32	2001	4105	−70.4	−40.83	−1.72
23 Scotland	31	2000	5374	−91.0	−36.85	−1.69
24 Portugal	31	2000	5694	−96.2	−18.12	−1.69
25 Denmark	30	1999	4088	−67.8	−24.77	−1.66
26 China (rural)	13	1999	3144	−51.6	−3.15	−1.64
27 Chile	24	1994	3866	−55.4	−7.08	−1.43
28 Latvia	23	2002	6773	−96.2	−13.19	−1.42
29 Hong Kong	30	1999	2334	−31.5	−11.20	−1.35
30 Iceland	30	1999	3224	−43.5	−6.49	−1.35
31 China (urban)	13	1999	3885	−52.2	−4.39	−1.34
32 Lithuania	33	2002	5436	−65.9	−7.74	−1.21
33 Hungary	33	2002	6754	−70.4	−20.73	−1.04
34 Costa Rica	26	1995	3343	−34.6	−4.39	−1.04
35 Albania	15	2001	3690	−35.8	−1.21	−0.97
36 Singapore	32	2001	3190	−22.7	−3.35	−0.71
37 Cuba	27	1996	3708	−17.2	−1.89	−0.46
38 Romania	33	2002	7670	−27.0	−4.29	−0.35
39 Poland	31	2001	4968	−13.9	−1.86	−0.28
40 South Korea	17	2001	2147	−5.1	−0.29	−0.24
41 Russian Federation	23	2002	6374	−4.5	−0.56	−0.07
42 Bulgaria	33	2002	6605	3.0	0.74	0.05
43 Greece	30	1999	3528	3.1	0.68	0.09
44 Belarus	17	2001	5058	12.9	0.67	0.26
45 Ukraine	16	2000	6062	43.4	1.57	0.72

n determines the number of years preceding the latest available year (LAY); *a*: intercept; *b*: slope; *t* : *t*-value; *d*: percental decrease per year.

In Table 11, the summary mortality data are given for both sexes and in Table 12, the Pearson correlation matrix of the data. The most salient points are the following: All mortality rates are lower in women but the male/female ratio is lower than at younger ages. The ratio of the highest/lowest mortality rates is higher for women and highest for residual and total cardiovascular mortality. For both sexes, residual mortality is a major part of all-cause mortality, more important than total cancer mortality. The correlation matrix (Table 12) shows that for all mortality rates the correlations between male and female mortality are very high (all $p < 0.0001$). In both sexes, total cancer mortality correlates negatively with total cardiovascular mortality ($p < 0.001$). Residual mortality does not correlate significantly with total cancer mortality, but negatively, of borderline significance, with total cardiovascular mortality.

Mortality and Age

Age is the most important determinant of mortality. The relationship between mortality and age can best be expressed by Gompertz equations, ln mortality versus age or by second-degree polynomial equations, ln mortality versus age and age^2. The differences between Gompertz and polynomial

Table 7 MEN – linear equation of TCA mortality rates 75–84 years per 100 000 versus calendar year

Country	*n*	LAY	*a*	*b*	*t*	*d*
01 Austria	33	2002	2427	−17.6	−10.31	−0.73
02 Sweden	32	2001	1979	−11.4	−5.57	−0.58
03 Finland	33	2002	2210	−11.7	−6.35	−0.53
04 Switzerland	31	2000	2238	−7.2	−2.58	−0.32
05 Czech Republic	16	2001	2412	−6.0	−2.34	−0.25
06 Germany	32	2001	2179	−4.8	−3.37	−0.22
07 Ukraine	16	2000	1222	−2.5	−0.58	−0.20
08 Bulgaria	33	2002	1081	−1.1	−1.47	−0.10
09 Argentina	20	1996	1705	−1.1	−0.36	−0.06
10 Cuba	27	1996	1647	0.1	0.03	0.01
11 England and Wales	31	2000	2184	0.7	0.28	0.03
12 France	30	1999	2016	2.1	1.02	0.10
13 New Zealand	31	2000	1969	2.6	1.37	0.13
14 Australia	31	2001	1890	2.9	1.91	0.15
15 Scotland	31	2000	2297	5.1	2.53	0.22
16 Netherlands	31	2000	2337	7.9	2.53	0.34
17 United States	31	2000	1672	6.3	4.40	0.38
18 Chile	24	1994	1744	7.5	4.29	0.43
19 Hungary	33	2002	2155	10.6	6.31	0.49
20 N. Ireland	31	2000	1834	9.6	3.92	0.52
21 Russian Federation	23	2002	1474	7.7	3.42	0.52
22 Romania	33	2002	887	4.8	2.40	0.54
23 Belgium	28	1997	2256	14.2	4.08	0.63
24 Norway	32	2001	1675	11.6	7.97	0.69
25 Denmark	30	1999	1933	14.5	5.20	0.75
26 China (urban)	13	1999	1655	14.5	2.26	0.88
27 Italy	31	2000	1698	16.8	7.59	0.99
28 Singapore	32	2001	1550	16.7	3.62	1.07
29 China (rural)	13	1999	1009	11.4	2.17	1.13
30 Canada	29	1998	1712	19.5	2.93	1.14
31 Spain	31	2000	1482	18.2	19.26	1.23
32 Ireland	31	2000	1712	21.5	9.46	1.26
33 Japan	31	2000	1457	18.4	16.54	1.26
34 Iceland	30	1999	1428	19.1	3.59	1.34
35 Albania	15	2001	940	13.4	0.92	1.43
36 Greece	30	1999	1293	18.5	18.56	1.43
37 Poland	31	2001	1333	20.4	19.81	1.53
38 Portugal	31	2000	1247	19.3	16.78	1.55
39 Estonia	18	2002	1482	30.2	5.58	2.04
40 Hong Kong	30	1999	1162	25.3	12.88	2.17
41 Latvia	23	2002	1300	28.4	13.58	2.18
42 Costa Rica	26	1995	1489	38.8	4.56	2.60
43 Belarus	17	2001	1126	29.6	7.97	2.63
44 Lithuania	18	2002	1301	40.3	11.98	3.10
45 South Korea	17	2001	739	88.5	14.21	11.98

n determines the number of years preceding the latest available year (LAY); *a*: intercept; *b*: slope; *t* : *t*-value; *d*: percental decrease per year.

Table 8 WOMEN – linear equation of TCA mortality rates 75–84 years per 100 000 versus calendar year

Country	*n*	LAY	*a*	*b*	*t*	*d*
01 Argentina	20	1996	1062	−8.0	−5.71	−0.75
02 Sweden	32	2001	1151	−8.2	−7.62	−0.71
03 Switzerland	31	2000	1162	−8.2	−9.44	−0.71
04 Austria	33	2002	1293	−8.9	−18.37	−0.69
05 Belgium	28	1997	1220	−7.5	−14.38	−0.61
06 Finland	33	2002	1116	−6.8	−13.10	−0.61
07 Chile	24	1994	1335	−7.4	−3.21	−0.55
08 France	30	1999	983	−5.0	−22.85	−0.51
09 Germany	32	2001	1236	−5.7	−9.07	−0.46
10 Netherlands	31	2000	1184	−5.3	−10.91	−0.45
11 Ukraine	16	2000	564	−2.1	−1.06	−0.37
12 Spain	31	2000	849	−2.0	−5.06	−0.24
13 Czech Republic	16	2001	1268	−0.8	−0.41	−0.06
14 Japan	31	2000	831	0.2	0.40	0.02
15 Italy	31	2000	982	0.3	0.42	0.03
16 China (rural)	13	1999	604	0.3	0.13	0.05
17 Norway	32	2001	972	0.5	0.80	0.05
18 Hungary	33	2002	1266	0.7	0.79	0.05
19 China (urban)	13	1999	892	0.8	0.26	0.09
20 Bulgaria	33	2002	621	0.7	1.63	0.11
21 Cuba	27	1996	882	1.2	0.51	0.14
22 Denmark	30	1999	1210	2.3	3.24	0.19
23 Australia	31	2001	919	1.8	3.20	0.20
24 Costa Rica	26	1995	1183	3.6	0.90	0.30
25 N. Ireland	31	2000	1026	3.2	3.08	0.31
26 New Zealand	31	2000	991	3.2	3.37	0.32
27 Portugal	31	2000	759	2.9	3.86	0.38
28 Romania	33	2002	525	2.7	2.46	0.51
29 Iceland	30	1999	1004	5.3	1.28	0.53
30 England and Wales	31	2000	1019	5.6	9.15	0.55
31 Ireland	31	2000	1086	6.4	5.50	0.59
32 Poland	31	2001	797	5.7	10.71	0.71
33 Russian Federation	23	2002	671	4.9	6.79	0.74
34 Canada	29	1998	912	8.2	3.22	0.90
35 United States	31	2000	832	7.6	19.56	0.91
36 Scotland	31	2000	1070	10.1	12.46	0.94
37 Estonia	18	2002	746	9.5	4.17	1.27
38 Greece	30	1999	604	9.0	14.84	1.49
39 Albania	15	2001	331	4.9	1.14	1.49
40 Singapore	32	2001	746	12.4	7.52	1.66
41 Latvia	23	2002	647	10.8	9.38	1.67
42 Belarus	17	2001	504	9.2	5.42	1.82
43 Hong Kong	30	1999	657	13.3	12.11	2.03
44 Lithuania	18	2002	634	14.6	11.57	2.30
45 South Korea	17	2001	290	35.0	12.03	12.05

n determines the number of years preceding the latest available year (LAY); *a*: intercept; *b*: slope; *t* : *t*-value; *d*: percental decrease per year.

equations are minor concerning all-cause and total cardiovascular mortality, but the polynomial equations always give the most significant results. This is not the case for total cancer and remainder mortality. For those diseases the relationship between ln mortality and age are clearly not linear, and polynomial equations are vastly superior. The quadratic term of age in the equation is highly significantly negative for total cancer mortality and highly significantly positive for remainder mortality. The data are illustrated for both sexes separately in Figures 1–6 for Japan, the United States, and a combination of France, Spain, and Italy. Countries with an oriental-type diet, a Western-type diet and a Mediterranean diet are thus compared. The mirror image between total cancer and remainder mortality is notable.

DISCUSSION

The great differences in mortality rates existing between countries in the age class 45–74 years are also present in the age class 75–84 years. It is imperative to be able to identify the causes of these differences. Of all possible explanations – the level of medical care, genetics, smoking, pollution, stress, socioeconomic factors, obesity, food additives, and others – nutrition has been identified as the most plausible explanation

Table 9 MEN – linear equation of remainder mortality rates 75–84 years per 100 000 versus calendar year

Country	*n*	LAY	*a*	*b*	*t*	*d*
01 Czech Republic	16	2001	2519	−83.0	−11.91	−3.29
02 Albania	15	2001	4039	−128.5	−7.40	−3.18
03 Singapore	32	2001	8573	−224.3	−19.89	−2.62
04 Greece	30	1999	3605	−75.8	−17.58	−2.10
05 Austria	33	2002	3139	−63.5	−22.31	−2.02
06 Hong Kong	30	1999	5160	−100.2	−11.59	−1.94
07 Poland	31	2001	4120	−74.8	−14.24	−1.82
08 Romania	33	2002	3037	−54.6	−23.36	−1.80
09 Portugal	31	2000	5444	−97.3	−8.84	−1.79
10 Bulgaria	33	2002	3428	−58.7	−17.64	−1.71
11 Germany	32	2001	3435	−58.0	−23.24	−1.69
12 France	30	1999	3578	−51.3	−18.53	−1.43
13 China (urban)	13	1999	4191	−57.8	−2.84	−1.38
14 Japan	31	2000	3420	−44.5	−10.30	−1.30
15 Italy	31	2000	3028	−37.5	−16.74	−1.24
16 England and Wales	31	2000	3480	−42.6	−12.87	−1.22
17 New Zealand	31	2000	2965	−34.4	−9.09	−1.16
18 Spain	31	2000	3478	−39.9	−6.81	−1.15
19 South Korea	17	2001	5524	−56.9	−2.36	−1.03
20 Australia	31	2001	2566	−26.4	−9.74	−1.03
21 Belgium	28	1997	3756	−38.3	−10.35	−1.02
22 Chile	24	1994	5450	−49.2	−4.52	−0.90
23 Hungary	33	2002	2801	−24.9	−5.04	−0.89
24 Switzerland	31	2000	2381	−19.9	−4.61	−0.84
25 Finland	33	2002	2925	−24.2	−5.92	−0.83
26 Scotland	31	2000	3154	−22.0	−6.52	−0.70
27 China (rural)	13	1999	5190	−34.5	−1.10	−0.66
28 N. Ireland	31	2000	3274	−21.7	−4.32	−0.66
29 Iceland	30	1999	1796	−10.5	−2.70	−0.59
30 Lithuania	18	2002	1633	−9.5	−1.87	−0.58
31 Costa Rica	26	1995	3548	−17.8	−1.50	−0.50
32 Norway	32	2001	2410	−8.1	−5.60	−0.34
33 Ireland	31	2000	3335	−7.0	−1.90	−0.21
34 Sweden	32	2001	1818	−1.4	−0.90	−0.08
35 Ukraine	16	2000	2291	−0.3	−0.01	−0.01
36 Russian Federation	23	2002	2014	0.8	0.13	0.04
37 Netherlands	31	2000	2328	12.2	3.93	0.52
38 United States	31	2000	1889	11.6	6.88	0.61
39 Cuba	27	1996	1919	13.6	3.44	0.71
40 Estonia	18	2002	1365	16.3	1.71	1.19
41 Latvia	23	2002	1516	20.2	2.31	1.33
42 Canada	29	1998	1804	27.0	3.10	1.50
43 Denmark	30	1999	1845	18.3	10.79	1.54
44 Belarus	17	2001	2502	42.5	1.40	1.70
45 Argentina	20	1996	2277	42.9	7.82	1.89

n determines the number of years preceding the latest available year (LAY); *a*: intercept; *b*: slope; *t* : *t*-value; *d*: percental decrease per year.

Table 10 WOMEN – linear equation of remainder mortality rates 75–84 years per 100 000 versus calendar year

Country	*n*	LAY	*a*	*b*	*t*	*d*
01 Albania	15	2001	2273	−72.6	−6.51	−3.19
02 Czech Republic	16	2001	1598	−47.3	−14.88	−2.96
03 Singapore	32	2001	4933	−120.9	−21.28	−2.45
04 Greece	30	1999	3136	−75.0	−18.38	−2.39
05 Portugal	31	2000	3895	−87.0	−10.30	−2.23
06 Japan	31	2000	2447	−51.6	−14.94	−2.11
07 Austria	33	2002	1991	−41.6	−20.73	−2.09
08 Romania	33	2002	2007	−41.7	−20.98	−2.08
09 China (urban)	13	1999	3247	−63.4	−6.32	−1.95
10 Poland	31	2001	2698	−51.5	−11.14	−1.91
11 Hong Kong	30	1999	3082	−58.7	−12.26	−1.91
12 Bulgaria	33	2002	2443	−46.1	−15.45	−1.89
13 Germany	32	2001	2144	−39.2	−13.33	−1.83
14 Belgium	28	1997	2786	−50.4	−14.17	−1.81
15 France	30	1999	2246	−35.8	−17.20	−1.59
16 Spain	31	2000	2348	−36.9	−8.13	−1.57
17 Costa Rica	26	1995	3289	−47.4	−6.50	−1.44
18 Italy	31	2000	1875	−25.4	−16.45	−1.36
19 Chile	24	1994	3684	−45.1	−5.70	−1.22
20 Switzerland	31	2000	1546	−17.7	−4.77	−1.14
21 Hungary	33	2002	1758	−17.6	−6.97	−1.00
22 New Zealand	31	2000	1639	−15.8	−6.93	−0.96
23 Finland	33	2002	1828	−16.1	−4.18	−0.88
24 China (rural)	13	1999	3598	−31.6	−2.33	−0.88
25 Norway	32	2001	1696	−12.7	−6.69	−0.75
26 Ireland	31	2000	2309	−14.7	−6.14	−0.64
27 England and Wales	31	2000	1826	−10.3	−4.45	−0.57
28 Iceland	30	1999	1477	−7.4	−1.47	−0.50
29 N. Ireland	31	2000	1884	−9.2	−3.09	−0.49
30 Lithuania	18	2002	704	−2.5	−0.66	−0.36
31 Sweden	32	2001	1204	−3.1	−1.82	−0.26
32 Netherlands	31	2000	1603	−3.0	−0.74	−0.19
33 Australia	31	2001	1158	−1.1	−0.59	−0.10
34 Scotland	31	2000	1678	0.4	0.18	0.02
35 South Korea	17	2001	3056	6.0	0.40	0.20
36 Argentina	20	1996	1586	11.7	3.16	0.74
37 Ukraine	16	2000	1167	14.3	0.57	1.22
38 Cuba	27	1996	1480	18.3	4.57	1.23
39 Denmark	30	1999	1219	17.6	5.31	1.44
40 Canada	29	1998	969	17.7	4.69	1.83
41 United States	31	2000	903	21.1	13.47	2.33
42 Russian Federation	23	2002	755	20.2	4.83	2.67
43 Estonia	18	2002	649	20.0	3.85	3.08
44 Latvia	23	2002	618	25.6	5.03	4.15
45 Belarus	17	2001	1214	61.7	2.52	5.08

n determines the number of years preceding the latest available year (LAY); *a*: intercept; *b*: slope; *t* : *t*-value; *d*: percental decrease per year.

(Kesteloot, 1992, 1996). A look at the ranking of mortality in the 40 countries considered makes it clear that the level of medical expenditure cannot explain the ranking, for example, the ranking of the United States and Denmark. This is even more evident at younger ages (Kesteloot, 2001). The important changes in mortality rates cannot be attributed to genetic factors since the genetic constitution of a population does not change to any significant extent over a period of 40 years. Hong Kong has high levels of pollution and stress, but has a low mortality. Singapore, with the lowest levels of pollution in the world (The World Bank, 1998), has a high mortality. Obesity is increasing worldwide, but mortality is decreasing. Owing to the globalization of the world food market, the same additives are used worldwide. Socioeconomic factors cannot explain the differences, for

Table 11 Mean mortality rates, standard deviation (SD), minimum (L) and maximum (H) values and their ratio (H/L) and sex ratio (SR), $N = 45$

Cause	Sex	Mean	SD	Min	Max	H/L	SR (M/F)
AC	Men	8402	1506	6008	11 778	1.96	1.54
AC	Women	5457	1302	3127	8278	2.65	
TCV	Men	4179	1711	1764	8296	4.70	1.39
TCV	Women	3001	1466	1215	6794	5.59	
TCA	Men	1869	343	1066	2512	2.36	1.97
TCA	Women	950	208	450	1398	3.11	
RES	Men	2354	767	1373	4628	3.37	1.56
RES	Women	1506	543	638	3148	4.93	

Table 12 Pearson correlation coefficients and significance level of mortality rates from 45 countries, age-adjusted 75–84 years, mean of 3 latest available years

	AC-M	AC-F	TCV-M	TCV-F	TCA-M	TCA-F	RES-M	RES-F
AC-M	1.0000	0.9369	0.8649	0.8280	−0.2253	−0.2275	0.1352	0.0982
		0.0001	0.0001	0.0001	0.1368	0.1328	0.3760	0.5211
AC-F		1.0000	0.8963	0.9129	−0.4019	−0.2896	0.0201	0.0440
			0.0001	0.0001	0.0062	0.0536	0.8956	0.7742
TCV-M			1.0000	0.9809	−0.4260	−0.3801	−0.3417	−0.3531
				0.0001	0.0035	0.0100	0.0216	0.0173
TCV-F				1.0000	−0.4897	−0.4329	−0.3430	−0.3445
					0.0006	0.0030	0.0211	0.0205
TCA-M					1.0000	0.8267	0.0607	0.0416
						0.0001	0.6920	0.7860
TCA-F						1.0000	0.0314	0.0908
							0.8375	0.5529
RES-M							1.0000	0.9615
								0.0001
RES-F								1.0000

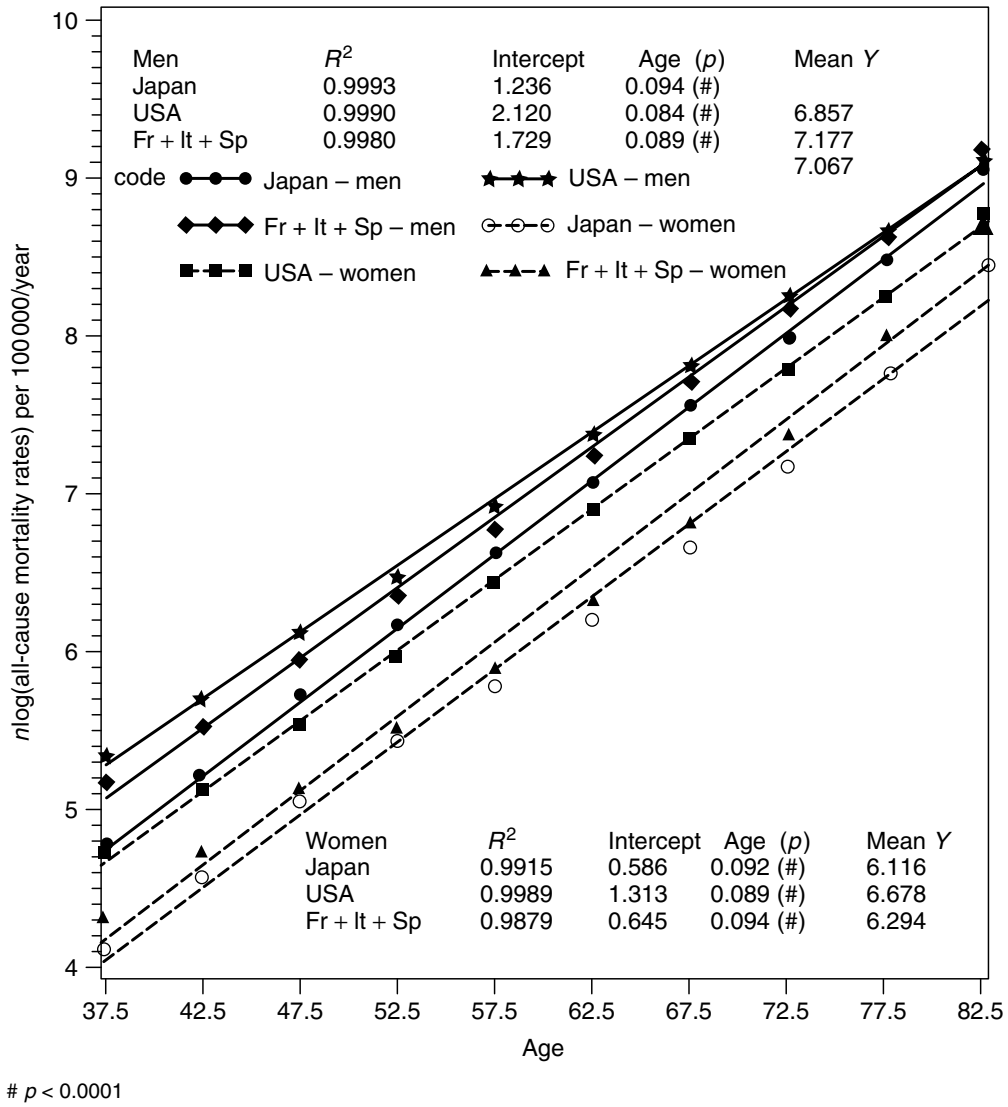

Figure 1 *n*log(ALL–CAUSE mortality rates) versus age for Japan, UnitedStates, and mean of (France, Italy, Spain), mean of 3 latest available years

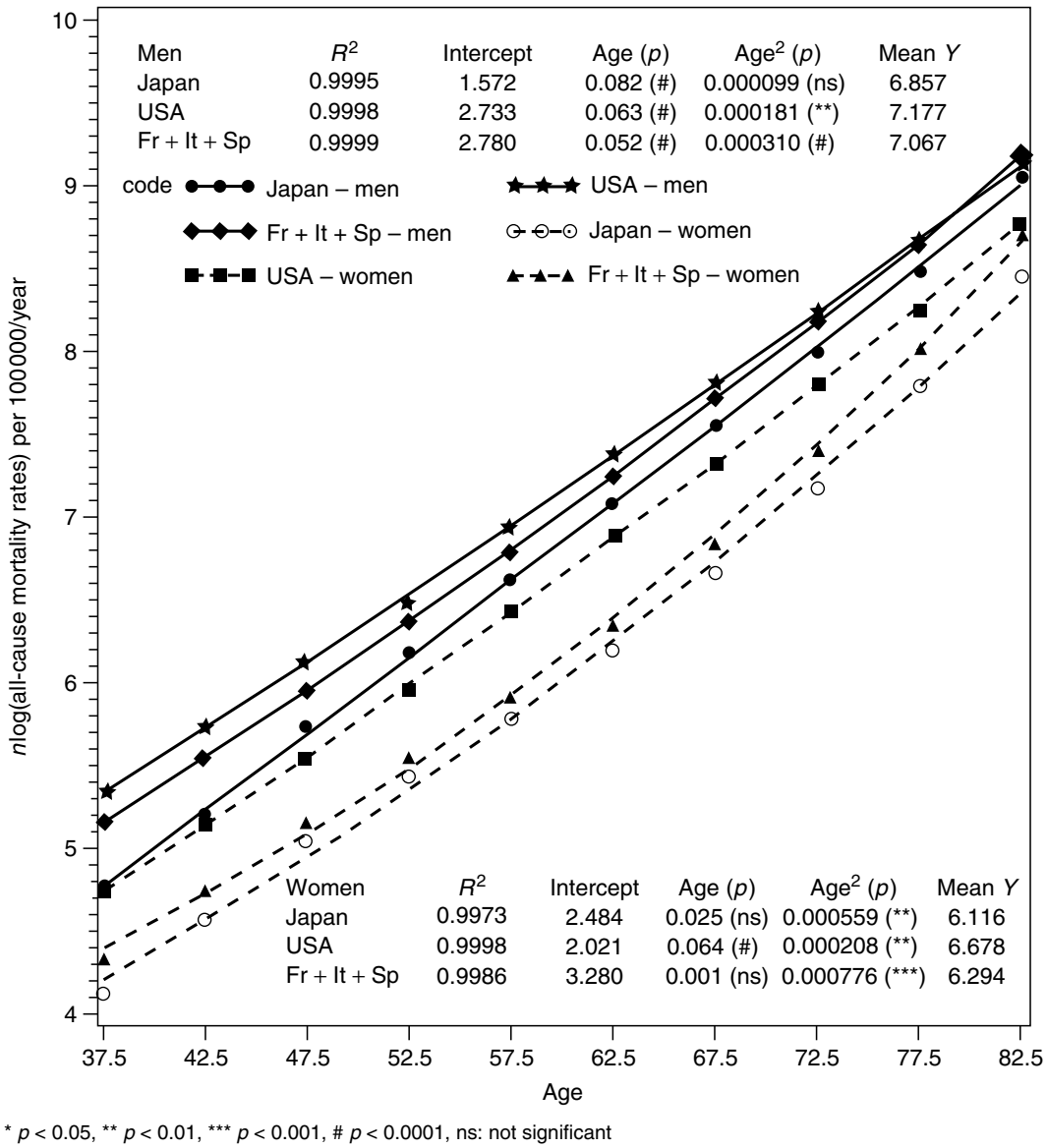

Figure 2 $n$log(ALL–CAUSE mortality rates) versus age, age^2 for Japan, United States and mean of (France, Italy, Spain), mean of 3 latest available years

example, the relative position of Albania and Denmark. Albania is the poorest country of Europe, and Denmark the richest of the European Union. Denmark has the highest mortality of the countries of the European Union in the year 2000 ($N = 15$). Much of the differences can be explained by smoking, especially for women; for example, the high smoking levels of Danish and Scottish women. Japanese men, however, have the highest smoking prevalence and level of cigarette smoking in the world, but a low mortality. Smoking is especially deleterious in combination with a high intake of saturated fat (Xie *et al.*, 1991). The ongoing changes in nutrition are impressive: a decrease in salt intake, especially in oriental populations; a decrease in the intake of saturated and trans-fatty acids, especially in Western populations; an increase of the intake of mono-, polyunsaturated, and omega-3 fatty acids; an increase in the consumption of fresh fruit and vegetables, and others. These changes should result in a better health at the population level.

The highly significant correlations between male and female mortality rates demonstrate that essentially the same causes of mortality are operative in men and women, but at lower levels in women (Kesteloot, 1987). The lower correlation for TCA mortality can be explained by differences in smoking habits between the sexes. A negative correlation ($p < 0.01$) exists between total cardiovascular and total cancer mortality. Several factors influence cardiovascular disease and cancer in the same direction, for example, salt, smoking, and saturated fat. As factors which could act in different directions, omega-6 polyunsaturated fat should be considered, protecting against heart disease, but possibly promoting some cancers, for example, colon

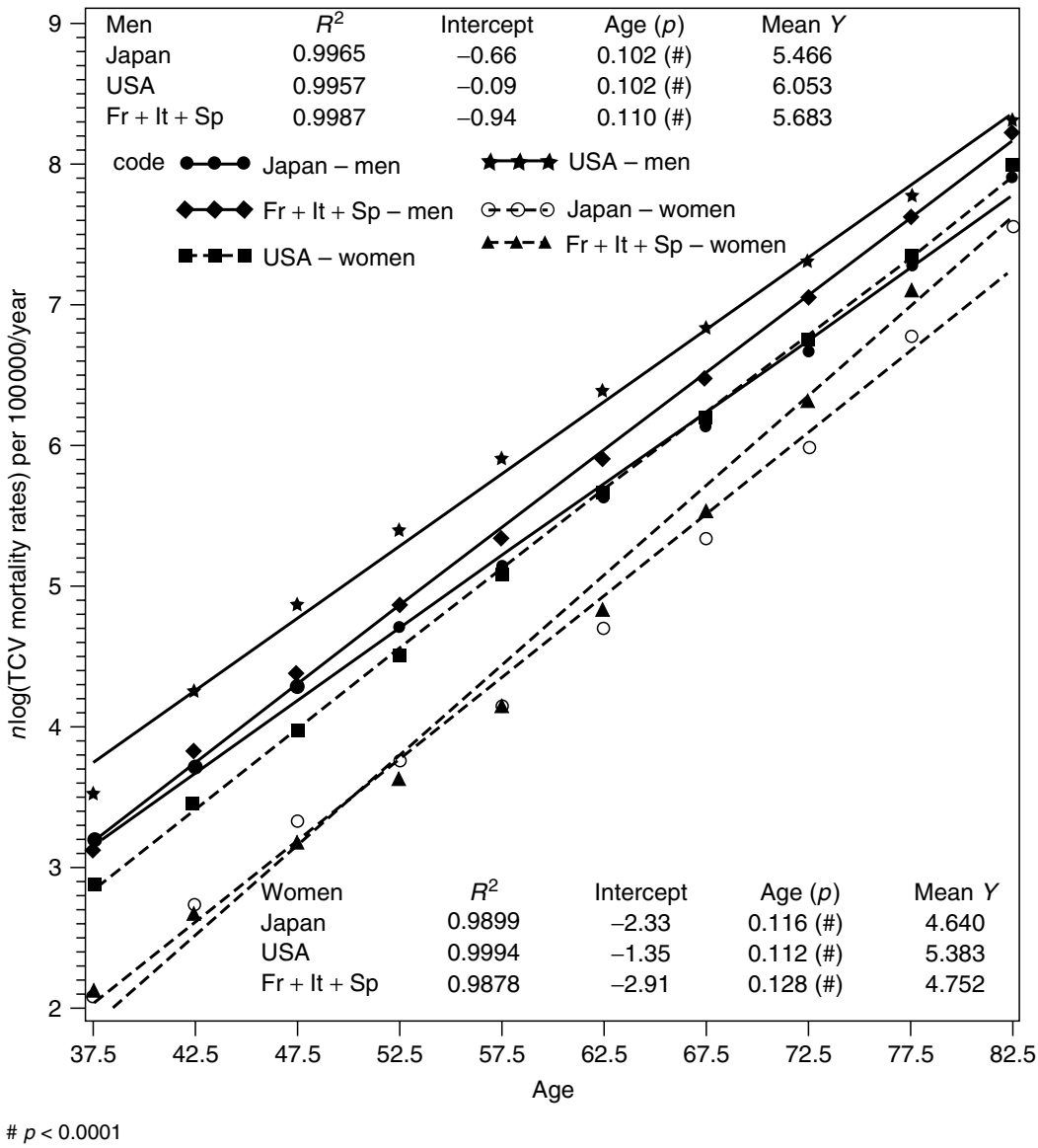

Figure 3 *n*log(TCV mortality rates) versus age for Japan, United States and mean of (France, Italy, Spain), mean of 3 latest available years

and breast cancer. An additional explanation could be that of an increase in cardiovascular mortality at the population level and because of life-style changes occurring earlier than an increase in cancer mortality, thus not allowing changes in cancer incidence to manifest themselves. This negative relationship should be further explored.

As can be seen from the equations relating ln mortality to age (Figure 1–6), the mortality rate in the age class 75–84 years is closely related to the mortality rates in the preceding age classes. The factors influencing mortality influence the total population between the ages of 35 and 84 years. Preventive measures should thus be directed toward the whole population. The extremely high R^2 of the correlation persists even when important mortality changes occur over a short period of time, for example, in the Russian Federation between 1985 and 1998 (data not shown).

The quadratic term of the polynomial equation is mostly positive, but negative in men from the United States for total cardiovascular mortality. The strongest quadratic term values are found in women, especially from France, Italy, and Spain. A more rapid increase in mortality occurs in women after the menopause. A negative quadratic term can be explained when the mortality level is high. Under such conditions, only the strongest individuals survive until the age of 75 years, and have a lower mortality rate later on. The relationship between ln mortality rate and age, age^2 is totally different for total cancer and remainder mortality. For total cancer, the quadratic term is always negative in both sexes, and highly significant in men (Kesteloot *et al.*, 1994). The possible explanations for this finding have been published before; briefly, the negative curvature could be due to a selective survival of cancer resistant

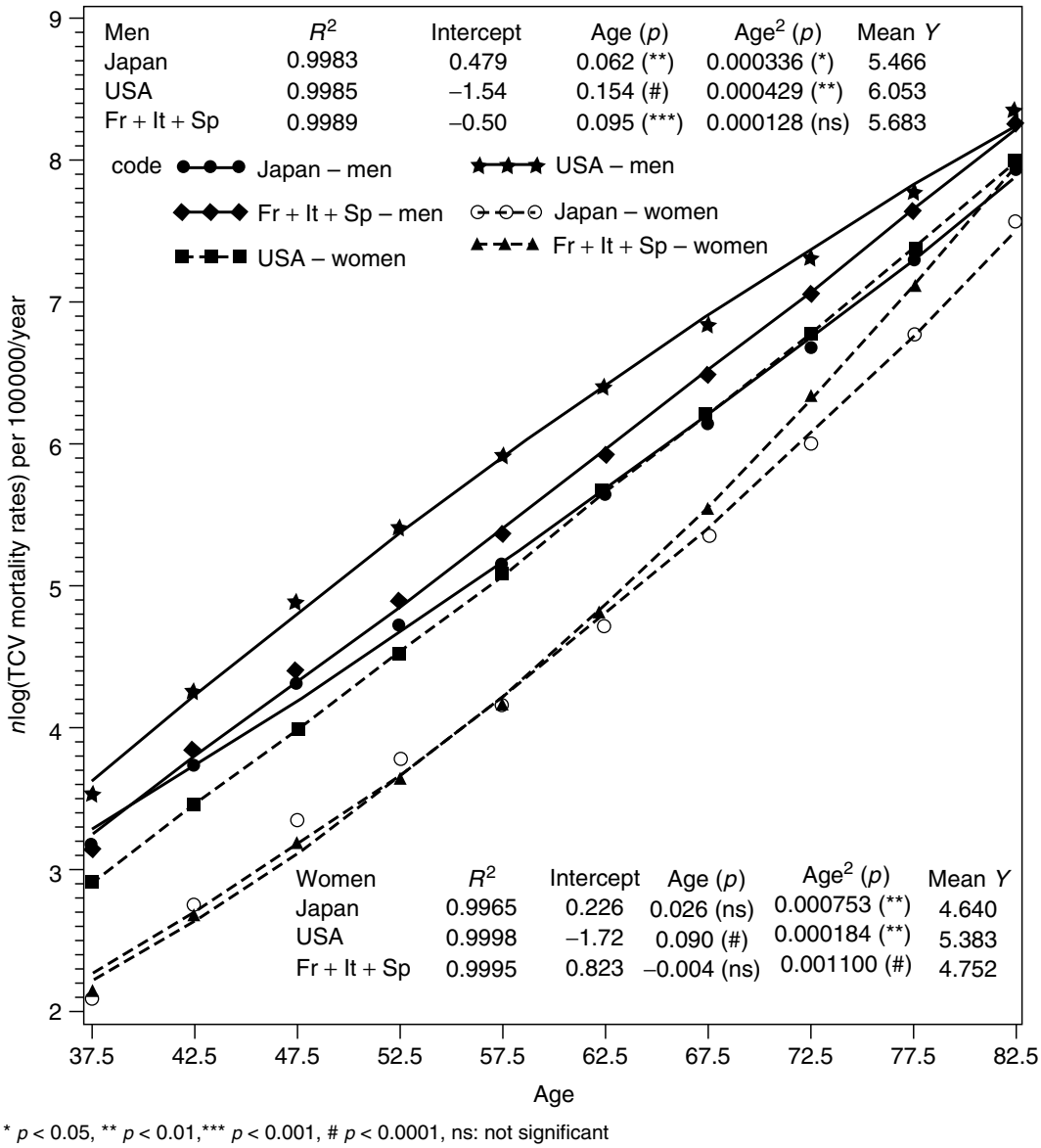

Figure 4 *n*log(TCV mortality rates) versus age, age^2 for Japan, United States, and mean of (France, Italy, Spain), mean of 3 latest available years

patients; to a slower growth of cancer at higher ages or to underdiagnosis of cancer at higher ages. The possibility of underdiagnosis and misclassification cannot be neglected since the evolution of remainder mortality is nearly a mirror image of that of cancer. As can be seen from the figures for all mortality causes considered, Japan has the lowest mean mortality rate (mean Y), followed by the Mediterranean countries and finally by the United States. One exception exists for total cancer in men where the United States is second.

In the United States for the year 2001, yearly mortality rates are available between the ages 1 and 100, separately for men and women and for Blacks and Whites (Arias, 2004). Within the age range 25–94 years and 35–94 years, all r^2, R^2 for Gompertz and second-degree polynomial equations were >0.99 and 8 out of 16r^2, $R^2 > 0.999$. The polynomial equations are always superior to the Gompertz equations and in the age range 35–94 years, slightly superior to the age range 25–94 years. A greater part of the mortality in the age range 25–34 years is not age related (accidents, suicide, and others) and this lowers the overall correlation coefficients. These findings largely extend the age range within which these equations are valid.

In summary, important changes in mortality are occurring in the age class 75–84 years. These changes are closely related to changes in mortality at younger ages. All-cause and cardiovascular mortality rates tend to accelerate at ages above 75 years, while the contrary occurs for total cancer mortality. The differences in mortality at older ages can best be explained by differences in nutrition. Much can be learned by comparing the mortality rates of different countries and the dynamics of the ongoing changes.

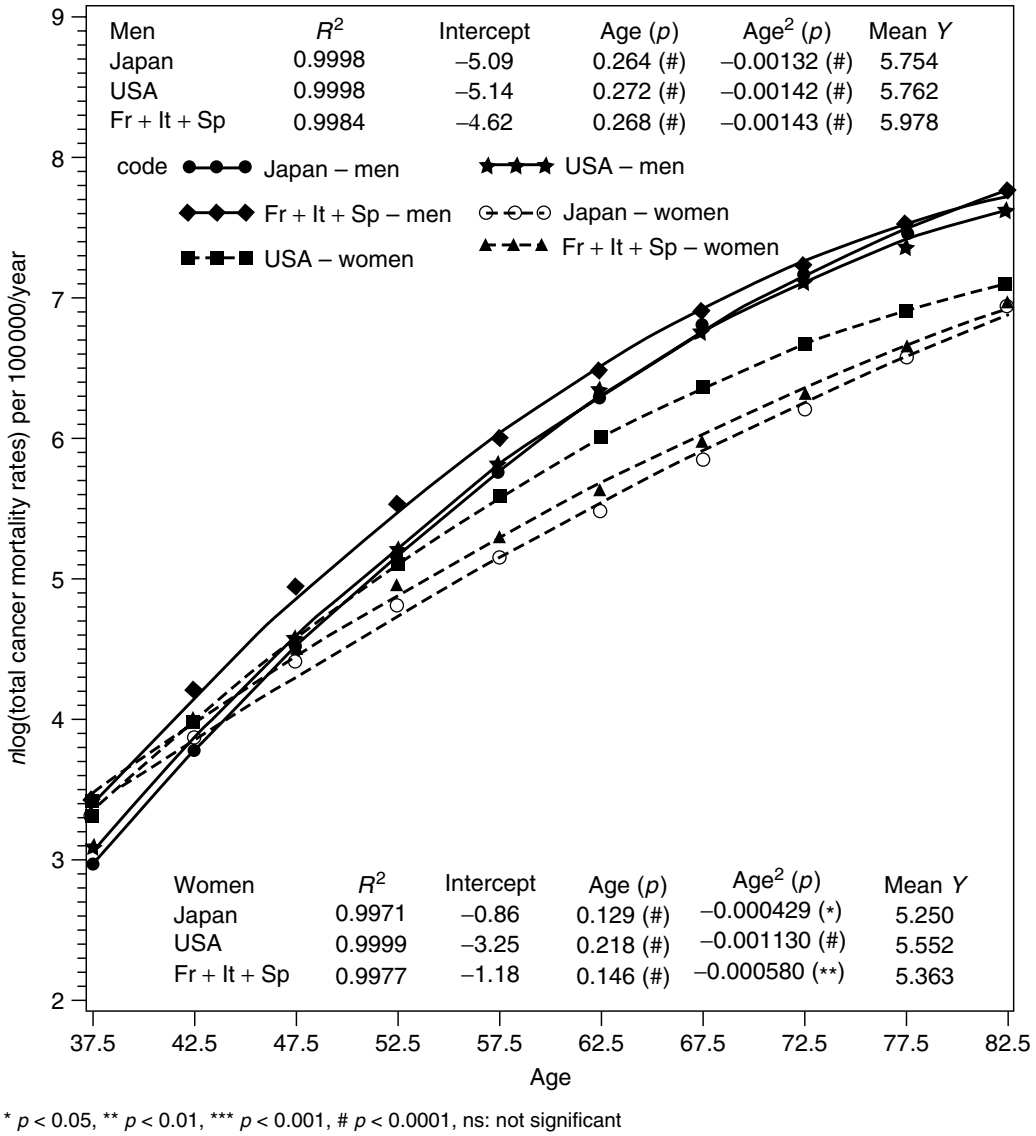

Figure 5 *n*log(total cancer mortality rates) versus age, age^2 for Japan, United States, and mean of (France, Italy, Spain), mean of 3 latest available years

KEY POINTS

- Mortality rate.
- Age class 75–84 years.
- Period 1970–1999.
- All-cause mortality.
- Cause-specific mortality.

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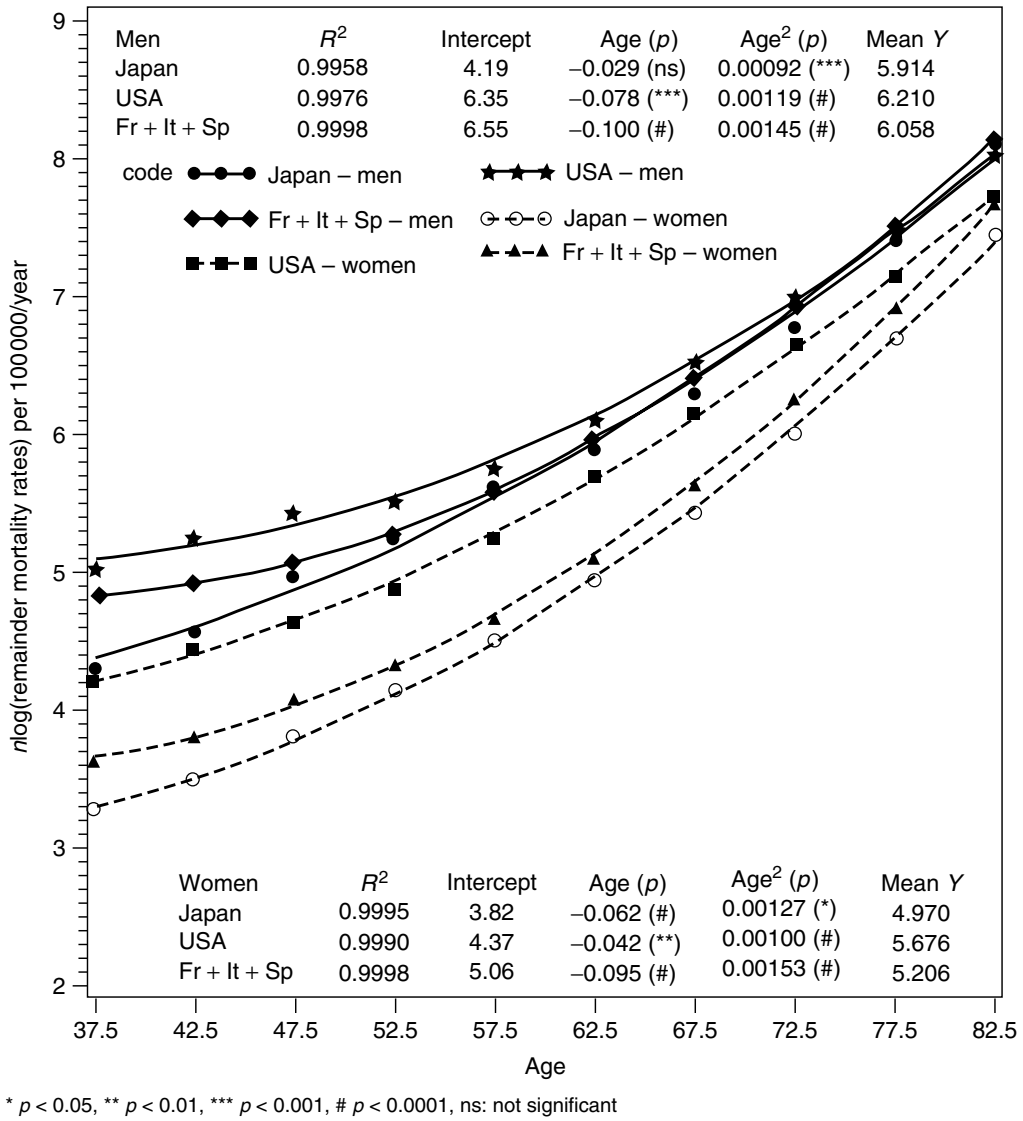

Figure 6 *n*log(remainder mortality rates) versus age, age^2 for Japan, United States, and mean of (France, Italy, Spain), mean of 3 latest available years

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17

Elder Abuse

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Based in part on the chapter 'Elder Abuse' by Gerald C. J. Bennett and Mark S. Lachs, which appeared in *Principles and Practice of Geriatric Medicine*, 3rd Edition.

'. . .there I met an old man who wouldn't say his prayers
so I took him by the left leg and threw him down the stairs'

Goosey Goosey Gander (nursery rhyme)

INTRODUCTION

Elder abuse is the long-lost grandparent of child abuse. With a legislative background of child protection at least in the industrial sphere and as a theme in the Victorian Novel, it seems surprising that child abuse within the home did not register in the medical literature until 1946 or into general medical consciousness until Kempe's book "the Battered Child Syndrome" in 1962. Less enshrined in popular culture, elder abuse was first described in similarly emotive terms as "Granny battering" by Baker and Burston in the mid 1970s (Baker and Burston, 1975; Burston, 1977).

Perhaps the cultural milieu with its intrinsic agism helped suppress this violence phenomenon. Even today, agism is not proscribed in the United Kingdom by an equal opportunities law. Section 47 allows people who, through age or infirmity, aren't able to devote to themselves or aren't receiving appropriate care to be forcibly removed to an institution. There is a fine for obstructing the process. It is to my knowledge the only instance where you can be arrested when you aren't criminal, mentally ill or infectious. Mobility allowance can only be claimed *de novo* by those below the age of 65 while those presenting to doctors with falls or immobility have diagnoses recorded for coding purposes as "senility". Within medicine, a wealth of literature attests to the disenfranchisement of older people from the best treatment. Who when looking at job applicants has not excluded some on the grounds that they were too old?

In the United Kingdom, the initial reports of violence toward older people were met with apathy and denial. Claims were repeatedly made by a social worker, Mervyn Eastman (1984) without effect, and even as late as 1991 the Secretary of State for Health was denying, on national television, that the problem existed. Only when faced with a press campaign, evidence from the Social Services Inspectorate, research from America, and powerful advocacy did elder abuse become recognized in 1993 as a bona fide social problem and manifestation of domestic violence. Thereafter, movement from this position has occurred and in 2000, the British Government published "No Secrets" – a report providing "Guidance on developing and implementing multiagency policies and procedures to protect vulnerable adults from abuse". Although not statute this at least provides a basis for critical appraisal of those areas that have not introduced appropriate practice.

By contrast in the United States, the challenge was immediately accepted and the subject rapidly gained academic respectability. In 1978, the House of Representatives Select Committee on Aging conducted an inquiry, which concluded that States should enact laws to address the problem. Some legislatures responded by giving elder abuse a notifiable disease status. The development of agencies with a specific remit and powers to investigate and intervene was driven by political acceptance and will. Adult protective services are now established in all states although their criteria for intervention and powers vary widely. They do share a mechanism for reporting and investigating elder abuse, which is linked to a social service provision to support the victim and prevent further harm. A broader remit covering vulnerable adults is usual although the definitions of abuse, criteria for engagement and character of interventions (e.g. civil or criminal) vary according to individual jurisdictions.

In the United States, self-neglect is included in this taxonomy, whereas in Europe this is seen as a separate issue although it is still the particular responsibility of local authorities.

Principles and Practice of Geriatric Medicine, 4th Edition. Edited by M.S. John Pathy, Alan J. Sinclair and John E. Morley.
 ISBN 0-470-09055-3

DEFINITIONS

Elder abuse is not a universally accepted term and some have used the terms "inadequate care" and "elder mistreatment" in recognition that a forensic approach may not be the most useful.

Similarly, a simple global definition, which is nontautological and utilitarian, is hard to come by. Individual organizations have tended to define elder abuse by their own criteria for intervention. Such an approach naturally causes problems not least for the scientific community wishing to standardize the terminology and thus generalize the significance of survey findings.

A reasonable stab at the problem was made by Action on Elder Abuse in 1994.

"Elder abuse is a single or repeated act, or lack of appropriate action occurring within any relationship where there is an expectation on trust, which causes harm or distress to an older person"

(Action on Elder Abuse, 1995)

DIMENSIONS OF ABUSE

More useful to practitioners perhaps are descriptions of the dimensions of elder abuse, where a systematic listing of the spectrum of phenomena allows an individual case to be recognized and categorized. These include:

- *Physical abuse*: inflicting physical harm or injury, physical coercion, sexual molestation, and physical restraint;
- *Psychological abuse*: inflicting mental anguish;
- *Material abuse*: illegal or improper exploitation and/or use of funds or resources;
- *Active neglect*: refusal or failure to undertake a care-giving obligation (including a conscious and intentional attempt to inflict physical or emotional stress on the elder);
- *Passive neglect*: refusal or failure to fulfill a care-taking obligation (excluding a conscious and intentional attempt to inflict physical or emotional distress on the elder).

PREVALENCE

Research into elder abuse was originally descriptive and based on the experience of interested workers and cataloguing referrals to responsible agencies. This naturally led to a distorted view of the subject. Random sample population surveys are better but are restricted by the capacity and willingness of those interviewed to disclose relevant information. As dementias may be particular stressors of dysfunctional relationships, these limitations may be significant. Even so prevalence studies do show some consistency. Rates are shown in Table 1.

These studies have been much more significant in elucidating the range and contexts of elder abuse. The seminal population-based random sample study from Boston (Pillemer and Finkelhor, 1988) had implications far beyond pure numbers. In a city where mandatory reporting, elder abuse teams, and structured interventions were already established, only 1 in 14 of the cases discovered were known to the responsible agency. This emphasized the fact that personal and institutional expertise is derived only from those that the individual or agency knows about. Thus physicians, for example, are more likely to see cases of serious physical abuse. Furthermore, themes from these studies have been expanded and used to integrate elder abuse more securely in the spectrum of domestic violence. So if the chief risk factor for being abused is the presence of a potential perpetrator, then it is not surprising that abuse by spouses turns out to be the most common form – a contrast with earlier reports suggesting that offspring were the most likely culprits. Presumably, dysfunctional marital relationships, where the currency of communication is aggression and violence, may not significantly change with aging. Encroaching disability leading to greater dependency, carer stress allied with the resultant inability of a person to leave the home, call the police or domestic violence unit leads to the special timbre that characterizes elder abuse. This makes it convenient for consideration as a discreet form of domestic violence.

It is not clear whether sex is an independent variable for victim or perpetrator. The Boston study found that men were more likely to be abused than women (although they suffered less psychological and physical harm), which may be a reflection of the number of relatively fitter women with power over older frailer partners.

Table 1 Comparison of rates and abuse by country

	Rates (%)				
Types of abuse	United States	United Kingdom	Canada	Australia	Finland
All types	3.2	–	–	–	6.7
Physical	2.0	2.0	0.5	2.1	
Verbal	1.1	5.0	1.4	2.5	
Neglect	0.4	–	0.4	1.4	
Financial	–	2.0	2.5	1.1	

Reprinted from *Forensic Medicine: Clinical and Pathological Aspects*, Bennett G and Rowe J, Copyright 2002, with permission from Cambridge University Press.

RISK FACTORS

Risk factors have been derived from in-depth exploration of those presenting to responsible agencies and thus may reinforce a tendency to miss those cases that do not present in the first place. The following are well recognized:

Functional impairment and chronic illness: may limit capacity to leave the situation, seek help, or defend oneself.

Home circumstances: the presence of an abuser being a prerequisite for abuse; those living alone may enjoy a degree

of protection. However, where there are few social contacts abuse is less likely to be identified or reported.

Cognitive impairment: dementia appears to be a risk factor for abuse presumably because of increased carer stress and disturbed behavior triggering antipathetic responses.

Stress: financial hardship and stressful life events may limit a family's caring capacity.

Abuser characteristics: the likelihood of abuse seems to be defined by characteristics of the abuser rather than those of the abused. Abusers are more likely to have personality disorders or a history of drug abuse or violent behavior. Financial dependence on the victim or for housing is often seen.

History of violence: domestic violence does not necessarily disappear with years. A history of violent conflict within a marital relationship predicts future abuse.

RECOGNITION

Recognition depends primarily on awareness and some knowledge of the subject – a prerequisite that cannot be taken for granted even amongst highly trained professionals (McCreadie *et al.*, 2000). However, this may be aided by the use of protocols that have been developed in the United States. These suggest that some consensus already exists, as there are many common components in these protocols (Mount Sinai Victim Services Agency Elder Abuse Project, 1988).

Certain features in the presentation should act as alerting calls to the clinician (Lachs and Pillemer, 1995). These include:

- Delays between injury or illness and seeking medical attention – examples include lacerations, healing by secondary intention, X-rays revealing healed but misaligned fractures, and decompensated chronic disease presenting in extremis where the carer has been monitoring the patient.
- Differing histories from patient and abuser – examples include different mechanisms of possible injury and a different chronology of injuries.
- Implausible or vague explanations provided by either party – for example, fractures that are not quite explained by the mechanisms of injury.
- Frequent Accident and Emergency Department attendance for chronic disease exacerbations despite a care plan and available resources – for example, chronic obstructive airway disease or chronic heart failure due to lack of medicines or their administration.
- The functionally impaired patient who arrives without the main carer – an example is a patient with advanced dementia who presents at the Accident and Emergency Department on his own.
- Laboratory findings inconsistent with the history provided – for example, subtherapeutic drug levels (e.g. Digoxin) despite carer-reported concordance. Toxicology may reveal that psychotropic agents have not been administered or that unprescribed ones have.

Characterization of psychological or perhaps material abuse in isolation from physical assault will not be revealed by a pattern of injuries and so requires a careful approach to the history and collateral history.

THE INITIAL ASSESSMENT

Although protocols undoubtedly help bring down barriers to recognition, like cognitive function testing, suspicion must be aroused to initiate their use although thereafter there should be an educational reinforcing effect on the clinician. Unfortunately, with little standardization and validation of these instruments, progress is limited and the differing needs of a simple alerting device and a more comprehensive elucidating protocol is as yet unrealized (Fulmer *et al.*, 2004).

The assessment may cover the following aspects:

1. Although adult protective services training has sometimes included courses on adversarial interviewing this probably is not appropriate for those working in the caring services. The victim should probably be interviewed alone, although a case can be made for the presence of someone to record the meeting so that the flow of information is not repeatedly halted by the necessity to write down names, times, places, and so on. As in geriatric medicine, history taking also subserves as the physical examination of intellectual function. Cognitive impairment (or the lack of it) and some assessment of its severity should be recorded. There needs to be direct enquiries about physical violence, restraints or neglect, and elucidating details about the precise nature, frequency, and nature of these events. This is easiest after sympathetic scene setting with exploration of the history of relationships, coping with previous life stresses, new problems intervening, and so on. Recording a day in the life of the subject starting at midnight and continuing for 24 hours will document the patient's functional capabilities and provide details of the care that is provided. Expanding this template over a week or so will usually give a good idea of the patterns of care taking place. When rapport is established, the use of escalating nonjudgmental questions is more likely to finesse a truthful response. It is easiest to write down in advance the questions that need to be answered and a form of words with which to introduce them.
   Questions like *What stresses did this situation place on you/your carer? How did you/your carer cope with this? Did you/your carer ever lose control? What happened then?* are better than unintroduced bald questions like *Did he/she hit you?*
   Writing down the full names, addresses, and contact details of all those entering the home will be essential at some stage.

2. *History from the alleged abuser*: the alleged abuser should also be interviewed alone and a similar approach is appropriate. Once again confrontation and accusation should be avoided in the information-gathering stage. Check the carer's understanding of the patient's physical or mental health (care needs, prognosis) and ask for the carer's explanations for the injuries or physical findings.
3. Other sources should also be interviewed if possible. Recent psychosocial factors (bereavement, illness, unemployment, and financial hardship) should also be enquired about. It must be remembered that the care workers visiting the home are the most likely to know what is happening, but because of their lowly status they are often the last to be asked.
4. *Behavioral observation*: Interactions between the subject and their carers and other contacts should be observed. Abuse can take place within relationships where actions of the victim are themselves abusive and hence trigger similar responses. The patient can be checked for any withdrawal or infantilism by the carer. Generational inversion where offspring take a parent-like approach to their own parents and insist on giving the history and making decisions for them is so common that specific safeguards may need to be taken.
5. *General appearance*: The patient's state of hygiene and nutrition, general cleanliness, and appropriateness of clothing must be observed.
6. *Skin/mucous membranes*: It should be noted that dehydration cannot reliably be diagnosed by skin turgor and that blood chemistry is a much better indicator. The patient must be examined for multiple skin lesions in various stages of evolution. Note bruises and pressure sores and record how such lesions have been treated. A body chart is useful and medical photography is even better provided informed consent can be obtained. Some elderly people bruise easily (senile purpura and the transparent skin syndrome/photoaging) even from normal caring activities. Pressure sores are one of the "geriatric giants" and hence in addition to implying neglect can indicate underlying disease.
7. *Head and neck*: Traumatic alopecia (distinguishable from the male pattern alopecia on a basis of distribution), scalp hematomas (raised, blood-filled bruises), lacerations, and abrasions must also be checked for.
8. *Trunk*: The patient should be examined for bruising, welts, and weals: the shape may suggest the implement used (e.g. a belt). Particular attention must be given to lesions in protected areas of the upper thighs, arms, and so on.
9. *Genitourinary*: The patient must be examined for rectal bleeding, vaginal bleeding, infestations, evidence of trauma, and pressure sores. Most clinicians have neither the expertise to collect samples in recent suspected rape nor the forensic support to process them (e.g. how many clinicians have combed pubic hair to find those shed by an attacker). The help of a forensic medicine specialist is essential here.
10. *Extremities*: wrist or ankle lesions suggest the use of restraints or immersion burns (glove/stocking distribution).
11. *Musculoskeletal*: The patient should be examined for occult fractures or pain and the gait must be observed.
12. *Neurological/psychiatric*: this needs formal examination to ascertain the site of any lesion. Anxiety and depressive symptoms need to be assessed. Where symptoms are indicative, formal testing using depression-rating scales should be carried out or the patient must be referred to a psychiatrist.
13. *Mental state*: formal testing should be carried out using the Folstein Mini-Mental State Examination. Cognitive impairment suggests that either delirium (acute confusional state) or dementia (chronic confusional state) is present. This then needs further assessment to rule out the treatable causes. Psychiatric symptoms may include delusions and hallucinations. Mental testing gives little indication of decision making capacity and this may need discrete assessment.
14. *Imaging*: Clinical indications will indicate this requirement.
15. *Laboratory investigations*: again the tests ordered will be indicated from the history and examination and may include drug levels, albumin, blood urea and electrolytes, hemoglobin, and occasionally toxicology. For those with extensive bruising, coagulation studies and platelets are useful. Unfortunately, diagnosis of scurvy is difficult not least because subjects have usually been fed prior to the institution of the studies.
16. *Social and financial resources*: The social networks (formal and informal) available to assist the patient must be documented and all available financial resources must be recorded. Those most vulnerable to financial abuse tend to be those living on modest incomes where a continuous small drain on the resources has a large effect. Overpayment for services is hard to judge and written records will probably not be available.

In England and Wales, those who have lost financial capacity as a result of dementia will almost certainly have inappropriate transactions taking place with regard to collecting pensions, managing bank accounts, and so on (Rowe *et al.*, 1993). In most cases, this is benign and a product of confused and confusing jurisprudence. This information may be crucial if interventions, which include alternative living arrangements and/or the provision of home services are considered later.

ONGOING INVESTIGATION AND INTERVENTION

Ongoing investigation and interventions should follow local agreements and policies. Most areas will have a lead agency defined and a management algorithm. The initial phase is information gathering.

For serious crime where assault or other major felony is indicated, involvement of the police is mandatory. Health

workers do not have the skills, resources, or probably the temperament to investigate significant crime. In the United Kingdom, local constabularies have domestic violence units who are a useful first port of call. In most areas, these officers do not investigate crimes. This has the advantage of allowing advice to be taken on how to use the law before embarking down that route. Further investigation in the United Kingdom requires arrest of the suspected perpetrator and a taped interview perhaps in the presence of a solicitor under the exigencies of the Police and Criminal Evidence Act; underlining the importance of previous screening by the domestic violence unit. A concomitant disadvantage is apparent when the officers who have been consulted and who are familiar with the case have to hand it on for investigation to a different team.

Wide experience of injuries from assaults including sexual ones is not usually the forte of geriatricians; so the skills of forensic medicine specialists should be actively sought.

There are other services with investigatory powers and their involvement may be required. For example, in the United Kingdom those who have lost financial capacity should have an appointee collecting and supervising their pension and benefits. The Benefits Agency has a duty to investigate the worthiness of the appointee and the appropriateness of their use of these resources.

Inevitably, collecting this information takes time. Pressure on beds notwithstanding, there are often requests for discharge both from the victims and the suspected abusers. Some households are dependent on the benefits and welfare payments received by the victim and so this pressure may be intense.

Most policies and guidelines are useful in identifying agencies and procedures to initiate investigation but thereafter the path tends to become less clear and the issues more fraught.

If the victim is significantly and cognitively impaired, it may be difficult not to compound abuse if they cannot give consent to photography or investigation. Even proceeding with the use of a duty of care mandate causes problems if he/she is not a competent witness. Where criminal charges may be brought, the testimony of the victim is an important factor and without this prosecution is difficult. Experience with domestic violence in younger people where a complaint has not been made has been addressed by emphasizing that public interest prosecutions, which do not have this prerequisite can be used. In practice, without a good witness this approach is nearly always ineffective.

In cases where serious physical assault is suspected, clinicians may find themselves in the invidious position of being informed that prosecution can only take place if an expert witness is willing to testify that the observed injuries could only have been precipitated by unlawful violence. As there are really no pathognomonic signs of assault on older people and even the most suspicious lesions may have benign explanations, this is a dangerous area. Expert prejudice has been held responsible for serious miscarriages of justice in child protection and has probably led to a backlash where clinicians are reluctant to go on record and voice their suspicions.

Where the victim has capacity it is unusual for them to be willing to testify against relatives or carers on whom they may be dependent. Indeed, pushing this issue raises the possibility of alienating the victim and further reducing the chances of effecting any significant change in their circumstances.

These problems notwithstanding, practical experience suggests that recourse to the criminal justice system should not be shunned. It clearly takes time for practitioners not least the police to develop expertise in these areas. In some cases, the process of arrest, caution, or a tape-recorded interview with the offer of a solicitor's presence may be the catalyst for changes in circumstances and behavior – the mere fact that the process has occurred deterring further abuse even when other factors are apparently immutable.

Many of these aspects will be discussed at meetings specially convened to decide which actions need to be taken. Such meetings need to be inclusive especially as the most useful witnesses are unlikely to be managers and senior professionals. Development of trust, communication, and working relationships between relevant agencies is important and only goes forward if those involved are willing and available.

All multidisciplinary meetings may suffer from decision making at the lowest common denominator. Obliging someone not present to make an intervention, which is of doubtful value, will not advance the cause. When abuse is characterized by sins of omission rather than commission or the abusers actions are a result of ignorance or frustration rather than malice, a less forensic approach may be appropriate.

Although triggering behavior from the victim is recognized as a precipitant, it is worth remembering that risk of abuse is better determined by the characteristics of the abuser than the dependency of the abused. Where there is a dysfunctional relationship, which has developed over years or decades, there can be little expectation that offering more domiciliary services will necessarily alter patterns of abuse. Indeed some interventions are probably ineffective. A study of older people on a respite care program in a community hospital showed that 40% were being abused (Homer and Gilleard, 1991). Such respite care did not significantly reduce anxiety, depressive symptoms, or carer strain (Homer and Gilleard, 1994).

If investigation often leads into a fog where doubt increases with time, practitioners are often left with no justifiable interventions. In contrast, failures of care as suggested by poor nutrition, repeated injury perhaps as a consequence of falls, inadequate care, and an inability to materially affect the situation with domiciliary services frequently leads to institutionalization. In fact, referral to the adult protective services is an independent risk factor for nursing home placement (Lachs *et al.*, 2002). This not only occurs in those who are neglecting themselves but also where mistreatment is suspected. It is perhaps a reflection of the difficulties presented by these cases and the level of development of responses that those victims of mistreatment should be removed from their homes to an institution. The irony presented by this approach where the victim is institutionalized rather than the

abuser in contrast to other jurisdictions must cause concern to practitioners.

This is just one of the varied outcomes where intervention may actually make things worse for the abused.

ISSUES AROUND COMPETENCE

While all would support an approach that offers empowerment and increases the choices available to victims a few caveats apply here. Assessing competence, for example, should be a rapier not a blunderbuss. Legally, competence is assumed and must be disproved. Naturally, this implies there is no such thing as global competence, and the ability to make decisions needs to be tested in the specific area in which there is doubt. So global assessments of mental function that merely measure the capacity to perform that test are not particularly useful. Thus, where financial capacity is in doubt questions about the abstract and symbolic fiduciary processes (such as what is a mortgage? what happens if in arrears?) as well as the subject's resources, claims on them, and the relative merits of these claims are essential. Although the precise constituents of a capacity have only been legally defined for testamentary capacity, there is good helpful literature available (British Medical Association/The Law Society, 2004).

Those with broad knowledge in this area are aware that this is as much a mask of ignorance. A subject living at home suffering repeated falls and unaware of these failings and his/her surroundings may be felt to be better off in residential care. Indeed, a common practice of dubious ethics is to use such lack of capacity to endorse such a move. What little science there is suggests that residential care is an independent risk factor for hip fracture so that the subject is more likely to suffer an injurious fall therein (although less likely to lie on the floor undiscovered) (Norton *et al.*, 1999). The ethical principle of the least restrictive intervention comes into force and is now a statute law in Scotland. It seems worrying that no controversy, legal cases, or campaigns have sprung up over this issue, which may be proscribing what is common practice.

If negative outcomes have been reported, is there positive evidence of benefit beyond the anecdotal or case series? Presumably due to serious methodological problems in a difficult area, there have been no well-conducted intervention trials for the prevention of elder abuse. The one study attempting to detect a difference between a group where an intervention had taken place and controls showed a greater reporting of subsequent abuse in the intervention group (Davis and Medina-Ariza, 2001). It was not clear whether this was a function of raised awareness in the group.

INSTITUTIONAL ABUSE

Tragic cases, subsequent media interest, public shock, and official inquiries that have surfaced in child protection are noticeable by their absence in the elder abuse field. By contrast, exposes of derisory care in institutions have reached the public agenda. Abuse naturally sits at the lower end of the spectrum of institutional care. This is care which may be done down for a price but which may not be up to a quality standard. Those charged with delivering care are likely to be relatively untrained, working unsociable hours in difficult conditions for close to the minimum wage. Even in hospitals the inverse care law applies with the most disabled people being afforded the least nursing by those with the least training. There are of course perverse incentives that may lead to institutional abuse. Perplexed people with dementia constantly wandering or calling out on a quest inexplicable even to themselves may be perceived as harrying. How much easier it is if they sprawl quietly sedated in a chair where the price of their consequent immobility is relative peace and an occasional need for help with going to the toilet or to bed. Sedative use has been consistently noted to be excessive in UK nursing homes and yet there is little or no evidence for its effectiveness, and much can be withdrawn with only beneficial consequences. This is one of the features of inadequate medical care for residents (Fahey *et al.*, 2003).

Physical restraint sits between the unethical and the illegal. Once again the evidence for effectiveness is absent but the adverse effects are well documented. Perversely, the counterintuitive nature of the science may result in public pressure to protect people while the expected interventions are harmful. Bed rails exemplify this as instruments that do not reduce falls from the bed but can result in serious injury and death (Parker and Miles, 1998).

The risk factors for abuse in institutions have been explored (Pillemer and Bachman-Prehn, 1991). These include exogenous factors from the cultural milieu to the legal framework, funding, and political aspects of the care system. The design and fabric of the buildings and their suitability for the task along with the organizational structure is influential. As might be expected, the staff providing the care is the most important factor. With younger people having more negative attitudes to aging, an immature, uneducated workforce laboring for little monetary reward and accorded low status is worrying. With such circumstances leading to demoralization and burnout, the ground becomes fertile for abusive practices to spring up. The characteristics of those residents are also a factor. It is more difficult to care for very dependent, demanding subjects who can offer little reward for caring acts.

Naturally then quality can be deduced from the absence of risk factors and the converse of this scenario (Gibbs and Sinclair, 1992). A well-designed unit with staffing appropriate in numbers and quality to the dependency of the residents is to be desired. Of course, the key element is the culture imbued from a clear and effective leadership that is eager to maintain high standards. Those high standards pertain to the treatment of staff. In abusive institutions, it is often a feature that the staff is being abused by their managers (e.g. in some residential homes care staff are also expected to cook, clean, and launder residents' clothing, etc.).

There is of course potential to improve institutional care through both formal and informal monitoring. The regular inspection of units by the responsible authorities or the funding agencies is usual.

AGENCIES RESPONSIBLE IN THE UNITED KINGDOM (*see* Chapter 161, Health and Care for Older People in the United Kingdom)

The Commission for Social Care Inspection (CSCI) has a remit to "*carry out local inspections of all social care organizations – public, private, and voluntary – against national standards and publish reports; register services that meet national minimum standards; carry out inspections of local social service authorities; publish an annual report to Parliament on national progress on social care and an analysis of where resources have been spent; validate all published performance assessment statistics on social care; publish the star ratings for social services authorities*" www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/SocialCare/NationalCareStandardsCommission#, 2005.

The Healthcare Commission (the Commission for Healthcare Audit and Inspection) carries a responsibility for health services "*The Inspectorate will: encourage improvement in the quality and effectiveness of care, and in the economy and efficiency of its provision; inspect the management, provision, and quality of health care services and tracking where, and how well, public resources are being used; carry out investigations into serious service failures; report serious concerns about the quality of public services to the Secretary of State; publish annual performance ratings for all National Health Service (NHS) organizations and produce annual reports to parliament on the state of healthcare; collaborate with other relevant organizations including the CSCI; carry out an independent review function for NHS complaints*".

Within hospitals the diversity of patient needs, specialties, morbidities, resources, staffing numbers and training, and so on virtually ensures that some patients will be inappropriately housed in inadequate facilities where there is neither the interest nor the knowledge to provide the best care. So the infantilized patient sedated in a bed with rails, wearing a diaper-type continence pad unable to reach fluids kept in a feeder cup may still be seen. A "nature trail" approach whereby markers of poor care are identified can be easily constructed as a training device. The patient walking down a ward exposed by an open-back gown, catheter bags on frames as clear stigmata of incontinence, locked doors, and so forth indicates an acceptance of poor quality care tantamount to abuse.

Doctors are powerful and frail people in the hospitals are vulnerable. It is easy to provide inadequate explanations of diagnostic or management plans, take consent that is barely "informed", or suggest solutions in a coercive manner. The traditional ward round where conversations can carry on at the end of the bed without the patient's involvement or where confidential matters can be easily overheard are still common practice. All geriatricians will be familiar with relatives who wish to know the patient's diagnosis before they do and then request that the victim is kept in ignorance. All geriatricians also know that collusion may prevent a complaint and its tedious ramifications.

It is beholding on all clinicians to be introspective about their practice with the idealism and humanity that brought them to medicine in the first place and to strip out the cultural education and conditioning that breeds tolerance of these wrongs.

USEFUL WEB SITES

www.elderabuse.org.uk
www.elderabusecenter.org
www.inpea.net

Acknowledgment

The chapter on elder abuse in the previous edition was written by Gerry Bennett and Michael Lachs of whose erudition I have borrowed freely. Gerry was pre-eminent amongst the UK claims makers and undoubtedly the most important person in promoting our understanding of the subject. That he did this with courtesy, quiet enthusiasm, and masterful persuasion is all the more remarkable. This was just one of the many achievements of his tragically short life.

KEY POINTS

- Elder abuse is common and is found in all societies which have been studied.
- Those presenting to responsible agencies are not representative of the spectrum of abuse.
- Abuse is better defined by the characteristics of the abuser than the dependency of the victim.
- Provision of more domiciliary services and support is unlikely to improve a dysfunctional abusive relationship.
- The effectiveness of intervention strategies has not been systematically studied although there is clear evidence that some may increase institutionalization of victims.

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18

Smart Homes

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INTRODUCTION

The adjective "smart" seems to be added to so many items of technology these days, primarily, it would seem, to try and persuade the public that such items are in a rather special category, and hopefully aid sales. Smart homes also sound somewhat pretentious but there is no doubt that this developing technology can provide many benefits to support elderly people and there is a growing body of experience which demonstrates its potential. This chapter looks at the ways in which smart homes can provide support based on the experiences of a number of groups. It considers the issues that have to be addressed if it is to be successful, as well as the community infrastructure needed to support the technology, and it concludes with a look at the future of this work.

WHAT IS A SMART HOME?

So what constitutes a smart home? The term smart homes has been confused by some to describe technology that relies on sensors in the home that can send messages to call centers. Such technology is really telecare and will be referred to as such in this chapter. The primary property that endows a house with the smart home label is its ability to support the user in an autonomous fashion. In other words, it can monitor the user's activities and the way they interact with appliances in the home, but it is also able to supply a response itself to support the user. So if a smart home detects a running bath being nearly full it will respond by turning off the taps rather than calling for someone to come and intervene.

What needs to be incorporated in a house to enable it to qualify for this lofty label? A smart home requires three facilities to be installed in order to operate (see Figure 1). First of all it requires sensors that can monitor the occupant's behavior and activities as described above, for example, by sensing water level in the bath. Secondly, it requires a series of support devices so that it can autonomously provide the backup needed to support the user, for example, means for automatically turning off the bath water. And thirdly, the particular feature that distinguishes a smart home, it requires a means whereby all the sensors and the support devices can talk to each other. This facility is achieved through the use of a communication bus, which is conventionally a form of wiring that enables messages to be sent. The communication bus is linked to a computer or other logic controller that can see all the information being provided by the sensors and make judgments about the user's behavior. If it decides some action is needed then it can initiate the activities of the relevant support device.

So there is nothing particularly complicated about smart technology. It has been around for a long time in installations in larger public buildings such as airports, hotels, and so on. In such buildings, the technology primarily enables environmental control to be provided autonomously so that the building is able to ensure appropriate temperatures and ventilation, and so on, are maintained automatically. The communication bus, a key feature of such installations, has been the subject of some standardization so that different manufacturers' components can talk to each other. Many of the components developed for these purposes, such as lighting controls, can be directly applied to usage in domestic homes (Figure 2).

One variable in this equation, which has a major impact on the suitability of smart home installations, is that the communication bus can exist in several forms. Traditionally it has been a separate form of wiring installed in the building that just carries the information, or telegrams as they are known, between the sensors and the support devices. However, it can be in the form of a radio link between all these devices, or carried as a signal superimposed on top of the mains power. As will be discussed later, these alternative forms have much potential for retrofit into people's own homes.

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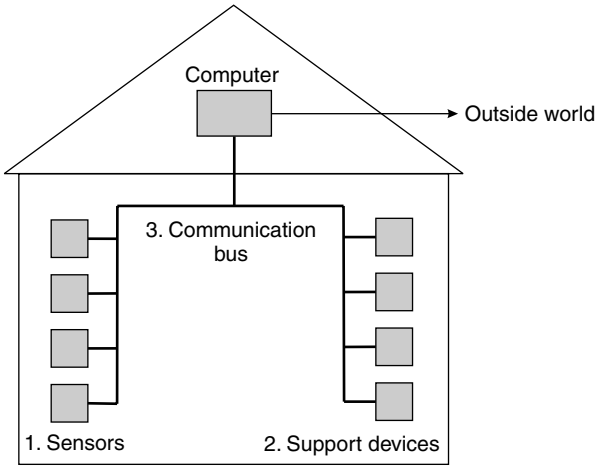

Figure 1 The components of a smart house system

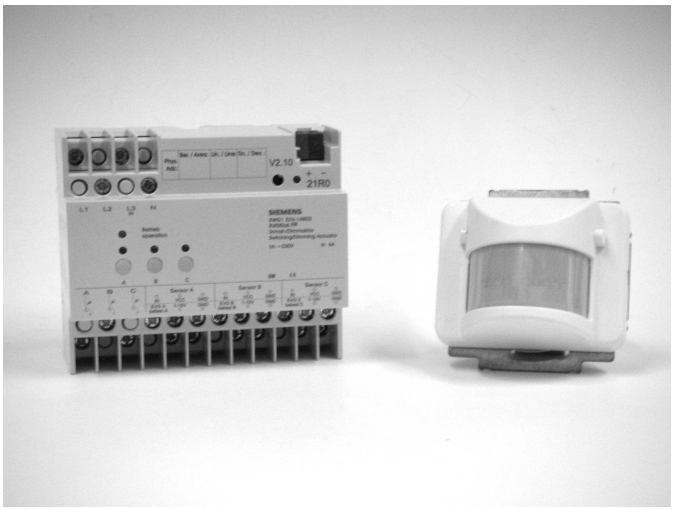

Figure 2 Some standard EIB (European Installation Bus) components; a light fader unit (left) and a passive infrared sensor (right)

APPLICABILITY TO ELDERLY PEOPLE

Given the ready availability of smart home components, a number of groups have explored the possibility of using them in a domestic setting to provide support that augments the help received from carers. A lot of work has been carried out to see if people with physical disabilities can be supported. The Joseph Rowntree Foundation (JRF) has provided a number of installations in York that aim to do just this, with a fair amount of success. The Edinvar Housing Association in Edinburgh has also completed some pioneering work to explore the potential of this technology. JRF has published a number of guides about the technology (Gann *et al.*, 1999; Pragnell *et al.*, 2000). The installations have primarily used commercial smart home components developed for public buildings and configured them in a form that enables their use in a domestic environment. A variation on this theme is the work developed at Brunel University through the Millenium Homes project (Lines and Hone, 2002). The main feature of the Brunel approach is the use of several items of purpose-designed technology to enable the home to give voice prompts to the user to check if they need outside support. This development is currently being further developed commercially, and several installations are in use. Some pioneering work in Norway has also explored the potential of this technology to support people with dementia (Bjoerneby, 1997).

The majority of these installations, unlike the Brunel work, have used the ready availability of smart home components to provide the technology that is used. For lighting and ventilation, these components are very appropriate. However, there are a number of situations where such technology is not so appropriate and where support devices need to be better tailored to the needs of the end user. A typical example is the use of commercially available technology to provide tap control. Several installations have used taps that are controlled through an infrared sensor. These are standard components that would be very useful for someone with poor hand function. All the user has to do is wave their hands in front of the sensor, usually mounted just underneath the tap, and the tap will turn on. Water will continue to be provided whilst the hands are in position. However, this operation is somewhat unnatural and for someone with a cognitive problem such taps would be totally confusing. These kinds of installations take a somewhat technology-led approach to their design. In other words, the installations start from looking at what technology is available and then configuring it in a form that seems to be close to providing the support needed. The work carried out on the Gloucester smart house project at Bath University explores these issues from a somewhat different perspective (Orpwood, 2001). This project is being run by the Bath Institute of Medical Engineering, and is aimed specifically at supporting people with dementia and uses a design technique that is very user-led. In other words, user needs are explored initially to provide a definition for the kind of problems that have to be supported by the technology. Having made these definitions, the design work then moves on to create purpose-designed devices that provide the care needed.

ENSURING USER FRIENDLINESS

There is a common perception that elderly people are inevitably going to be technophobic. Of course there is a spectrum of reaction to technology on the part of elderly people in the same way as there is for any other age group, and some elderly people are very excited and very proficient in using equipment such as computers. However, there is no doubt that interaction with sophisticated technology can cause a lot of anxiety, which may deter many people from using it. Consequently, when it comes to providing supportive technology for the majority of users it is preferable that the cognitive load on the user is kept as low as possible.

The technology should really provide support with as little intervention as possible from the user.

The problems of designing user-friendly installations are exacerbated when it comes to providing support for people with dementia. For such a user group, having to learn new skills or make sense of a new piece of technology is out of the question. The technology really does have to be invisible and just intervene and provide support when the house deems it to be necessary. Designing for such users is a useful discipline when it comes to ensuring user friendliness on the part of the smart house technology. For people with dementia, installations have to be provided where the technology is totally in the background, and where the home appears to be just the same as any other home, where the user does not have to learn any new skills, and does not have to interact with the new technology. But such installations are going to be very user-friendly for more cognitively able users as well, and will be suitable for those who are less able to cope with new technology. Design approaches that embody this approach have been published (Orpwood *et al.*, 2003; Orpwood *et al.*, 2004a).

The individual nature of so many problems that need to be dealt with has a big impact on the installation of smart home systems. As with all assistive technology, any means of tailoring it to the needs of the individual is going to make it more effective. Smart home technology is inherently flexible in that the way a system responds depends on the control software and this in turn can be quite easily configured for the individual. Ideally, installations need to be set up for an individual client by a nontechnical professional such as an occupational therapist (OT), and this in turn means that such configuring interfaces also need to be user-friendly.

SOME EXAMPLES OF USAGE

It is difficult to imagine how new technology can be supportive of someone but require little or no learning. A few examples would be useful. A situation that causes a lot of concern is the problem of an elderly person getting out of bed at night and finding the toilet. For someone who is a little unsteady on their feet, rising from lying down to standing is particularly dangerous. The problem is exacerbated by the fact that they are probably in a dark environment. How can smart home technology assist in this situation? First of all the house can know whether it is dark or not through ambient light sensors. It can also detect whether someone is in bed and about to get up by means of bed-occupancy sensors. These are usually either placed underneath the bed legs and detect a weight change (see Figure 3), or they lie across the mattress to sense the same changes. Sometimes pressure sensitive mats are used on the floor next to the bed, although experience has shown that some users will make a point of not treading on the mat once they have learnt that it is there. Given this information the house can ensure that when someone gets out of bed in the dark the bedroom lights are turned on, or a bedside lamp. To reduce the possibility of alarming the user the light can be activated through faders so that lights do not just suddenly come on. They fade up to quite a low level in a gentle manner (Figure 4). In this way, the user is provided with lighting to help them orientate more easily and move around without tripping or bumping into things. The process can also be reversed. If the user gets back into bed but forgets to turn off the light, the house can again detect that this has happened and can turn the lights off automatically.

This simple use of smart home technology can be taken further. The movements of an occupant about a room can be easily and reliably detected using passive infrared sensors (PIRs). These are the kind of sensors that are used in most home security systems and burglar alarms. If the user has got out of bed and begins to go out of the bedroom, the house lighting can be used to provide further support. It is

Figure 3 A bed-occupancy sensor that fits under a bed leg

Figure 4 An automatic bedside lamp in use

quite easy to arrange for lights to come on automatically as the user moves around the house, again ensuring they have illumination and help reduce falls. The work carried out for the Gloucester smart house for people with dementia goes one stage further and if the user goes to go out of the bedroom, the house makes an initial assumption that they probably want to go to the toilet. It then fades up the toilet lights and fades down the bedroom lights. In this way, it provides guidance to the toilet for the user. Finding the toilet at night can be a particular problem for people with dementia. When the user has finished in the toilet and begins to go out of the bathroom, the house reverses its response, fading up the bedroom light again and fading down the toilet one. In this way, the house can provide guidance to the user moving around the house in addition to providing illumination.

There are many other ways that smart house technology can provide support to the occupant (see Figure 5). Several examples are discussed later. A common usage is to provide safety and security support. The house can detect if something a little dangerous has been done, say in the kitchen, and then provide prompts and support. In a similar way, the use of other domestic appliances such as the bath and the kitchen sink can be backed up by keeping water temperatures safe and turning off taps as described above. For people with dementia, the house can keep an eye on wandering tendencies and try to discourage going out of the house and calling for help if it occurs. The house can also provide prompts for activities that need to be carried out such as taking medication, or provide a form of day diary to remind people of visitors or mealtimes or even a favorite TV program. In many ways the house acts like an extra carer, but one that acts for 24 hours a day without becoming tired or frustrated. But of course it can never supply the qualities of personal human care, and it is crucial that installers bear this in mind and do not just see smart homes as a cheap replacement for normal caring.

APPROPRIATE DESIGN

Simple application of smart home technology can in the ways illustrated provide a lot of support for the user. However, if it is to be effective it has to be designed from a close understanding of the issues that are likely to arise and the way that users are likely to interact with the technology. A very useful rule of thumb that was used in the development of technology within the Gloucester smart house project was to try to design new support equipment that reacted in a way that emulated the behavior of personal carers. The reasoning behind this approach was that in many circumstances a personal carer is likely to be the person who best understands what works in caring for the person they are looking after. If they have developed a strategy that works for them, it is likely that any new technology that reacts in a similar way is likely to be helpful. In the work carried out at Bath for people with dementia, the particular strategies found to work by carers were explored more systematically through a comprehensive survey of personal carers (Jepson and Orpwood, 2000). The survey showed there was a good consensus on the part of carers about the kind of strategies that worked for them. This understanding was a starting point for the new technology developed by the team for use in a smart home. During the design and development work, whenever a situation arose where it was not clear how the technology should react, it was found to be very useful to ask "What would the carer do in this situation?". In this way, the technology is being designed to act as a kind of invisible carer that is ever present, just looking over the user's shoulder, checking that things are okay, and just providing help when needed.

A good example of the use of the "carer emulation" approach is provided by the designs used to control a bath. It would be quite easy to install a bath water level sensor

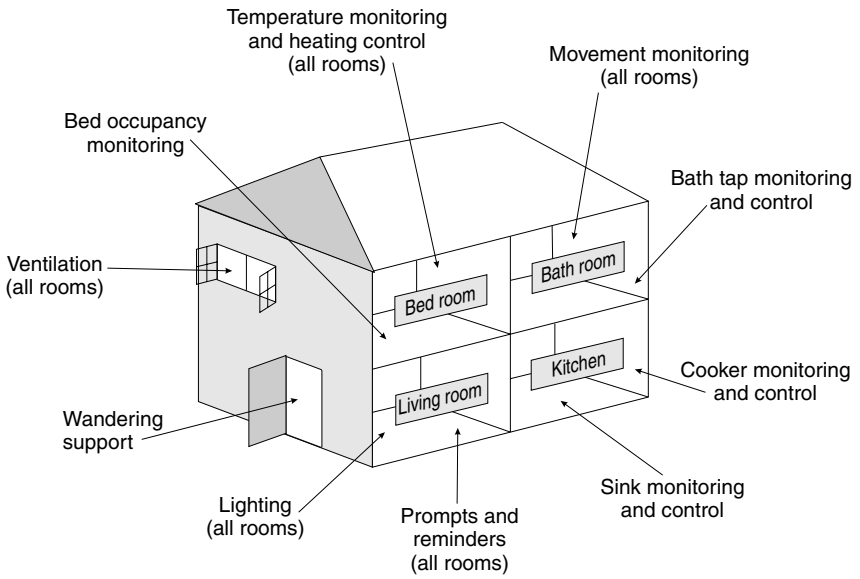

Figure 5 Possible support that can be provided with a smart house installation

that shut off the water supply when the bath was full. Such a facility would ensure that a forgetful user didn't flood the bathroom. However, if they came back to add some more hot water, or they let out the water and wanted to run a bath the next day, they would find the taps didn't work because the water had been shut off. This sense of the house taking control is something that the team were particularly keen to avoid. A key element in maintaining quality of life for someone with a cognitive problem is to enable them to feel they are still in control of their lives, and finding their house is taking that control away from them would be counterproductive. How would a carer react to the problem of someone forgetting they were running a bath? It was found that, in these kind of situations, where the carer would be monitoring the person they were caring for and intervening if they were forgetful, the carer would follow a simple pattern of behavior. They would first of all provide a reminder, "Don't forget you've got the bath running". If that didn't do the trick, they would then intervene to turn off the bath (or the cooker or other appliance). However, they would turn off the tap in the usual way, which would mean it could still be used subsequently. And thirdly, in many cases they would provide some sort of reassuring comment to the user, such as "I've turned off your bath. It's ready now", so that the user knew why something had happened.

If this threefold strategy is to be incorporated within the house, there is a need for some additional technology. There is a need for a means of communicating with the user, to provide prompts and reminders. There is also a need for a means of turning off the bath taps in such a way that the user can still carry on using it themselves. The communication issue is an important one that will be dealt with more fully below. Suffice to say here that the messages were conveyed by voice, and were provided through the radio. The means for shutting off the water was done by redesigning the taps (Figure 6). The taps had their insides removed and a new shaft was provided that was rotated when the tap was turned. The shaft was linked to a sensor that could monitor how far the tap had been turned. So all the new tap did was to sense how far the user had opened the tap. Depending on this information an electric valve would open to let the water through at an equivalent rate. If the house needed to shut off the water it could turn off the electronic water valve and then apply an electric brake to the tap shaft. In this way, as far as the user was concerned, the tap felt like it had been turned off. The house would then reset the rotation sensor back to zero. If the user subsequently came to operate the tap it would first of all feel like someone had turned it off, but it would also activate the sensor in the usual way and the electric valve would supply water. This novel tap design was not just an engineer's good idea about a new tap design, it was completely led by an understanding of the issues involved and the way that the user was likely to respond through emulating the reaction of carers.

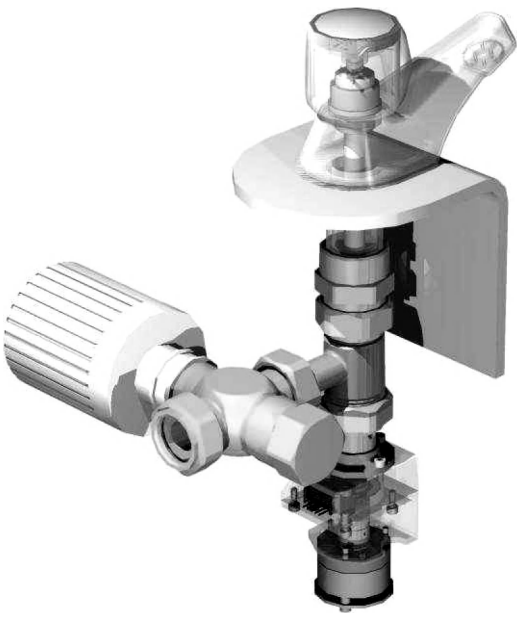

Figure 6 Diagram of the tap developed to enable the water supply to be turned off without taking control away from the user

Other techniques have been used to get a better understanding of what is needed for new designs where there is a very intimate interface with the user. A European Commission funded project, ENABLE, which evaluated the impact of assistive technology on people with dementia and their carers, placed a lot of emphasis on focus groups and other meetings with professional carers (Orpwood *et al.*, 2004b). These sessions were very useful to explore solutions in an interactive manner. The carer could highlight certain problem areas, the engineers could suggest possible design solutions, and the carers could reflect on these and suggest improvements or alternatives. Discussions such as these with professionals from different disciplines can be very constructive and fruitful. Another successful technique pioneered by researchers at Dundee University is the use of actors to provide a bridge between users and researchers (Marquis-Faulkes *et al.*, 2003). The Dundee team explored the issue of falls in the elderly. They used actors to simulate situations where falls occur. These were useful both to communicate with the user and get comments and feedback about situations and strategies, and also as tests for the sensing technology they were developing so that different categories of falls could be detected.

THE DIFFICULTY OF BEHAVIOR MONITORING

The main role of sensors in a smart home environment is to allow judgments to be made about user behavior. Some aspects such as whether someone has just come out of a toilet or not are fairly easy to sense and make judgments about. Most aspects though are surprisingly difficult to judge, even for simple behaviors, where complications can arise from inevitable variations in the way different people act. For example, the work described above on bed-occupancy systems showed that the house cannot just turn the light off as soon as someone gets back into bed. Users were found to

often sit on the bed before getting back in, perhaps to remove slippers or dressing gown. If the lights went out straight away it caused some confusion. A delay was introduced to ensure the user was fully back and settled in bed before turning off the lights. But even this required some careful setting up. The original delay used was five minutes but this proved to be too long and disruptive. If users knew the light would go off automatically many would tend to rely on that facility, or even feel that it must be used. Five minutes can seem to be a long time, lying in bed waiting for the lights to go off. The ENABLE project mentioned above tested a bedside lamp that had the facilities just described. It was interesting that although both people with dementia and their carers knew that the light could be turned off manually in the usual way, they felt they had to wait for it to happen automatically. These may seem like minor points in the use of such technology but they can be major factors in the confidence that their users have in them and therefore their acceptance.

Bed-occupancy sensors would superficially seem to be very straightforward. A weight sensor can tell the difference between whether someone is in bed or out of it. However, such a sensor will also be activated by someone turning over in bed, or moving from one side to the other. It also has to deal with situations that occur such as someone going to stand up from a bed, and then not quite making it and falling back onto the bed before finally getting to their feet. The algorithms (simple computer programs) that use the raw sensor data and make conclusions and judgments based on it have to deal with all these variants of user behavior (Figure 7). To ensure they are effective a lot of raw data has to be collected so that all the variations can be seen to enable an effective algorithm to be developed to deal with them.

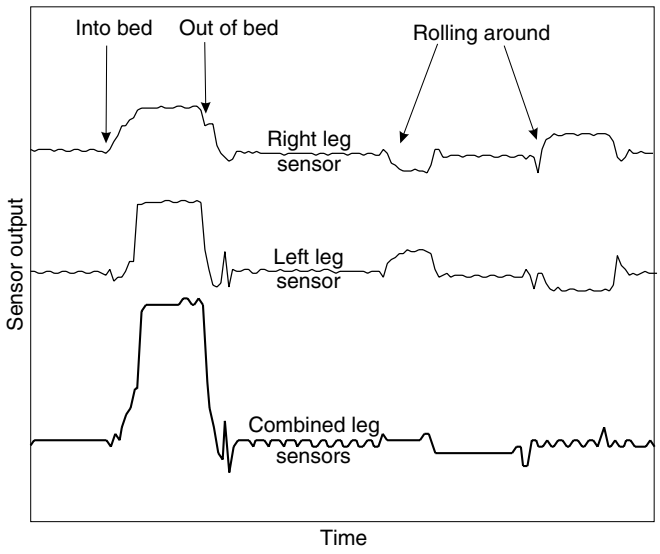

Figure 7 Raw data from a bed-occupancy sensor. The upper traces show the output from the sensors fitted to both legs at the head end of the bed, and the lower shows how the summed output can differentiate between getting in/out of bed and simply rolling around

If the house gets it wrong with a bed-occupancy sensor, it is not so crucial. If it gets it wrong with, say, a gas cooker monitor, then the outcome could be much more serious. Making judgments about human behavior based on simple sensor data is always going to be probabilistic. For example, with the gas cooker monitor developed for the Gloucester smart house, one of the sensors used was a simple infrared temperature sensor that was mounted at the side of the cooker and could detect the temperature of the pan or kettle. The data from the sensor was to be used to detect whether a pan had boiled dry or not. If a pan was boiling water, then its outside temperature would climb to close to 100 °C and stay there until it boiled dry, when the temperature would very rapidly increase. It would appear to be straightforward to detect this sudden temperature increase from the sensor data and initiate a response. However, users do not just leave a pan alone once it is in use on the cooker. They will very likely turn the gas up and down according to how the cooking was going. They may well move a pan around to different rings on the cooker. Such activities can make it very difficult to judge what is going on from the simple sensor data. A lot of cooking activities were monitored until it was felt that for about 80% of the time a pan could be reliably detected as having boiled dry. However, the other 20% of circumstances had to be dealt with in some way. It was decided to try and ensure that any errors were false positives. In other words, the cooker may on 20% of occasions turn off when it didn't really need to. However, these false-positive activations did prove to be quite irritating to users during evaluations. The exercise underlined the probabilistic nature of making judgments about user behavior. The level of errors could be reduced by incorporating information processing systems with learning capabilities, but it would still not reduce them to zero. Clearly in these kind of situations where there is potential danger there has to be some kind of backup. In the case of the cooker monitor, the device had a facility for shutting down the gas supply to the cooker if it continued to sense danger after responding to a danger signal. It also would call for assistance from outside the house in such situations. This is an important conclusion for smart house installations. Some aspects of the support they provide are quite safety critical. In these situations it must be recognized that the house may make a false judgment about the user's behavior and means for providing some kind of backup and a means for calling for outside assistance are essential.

THE IMPORTANCE OF COMMUNICATION

It has already been stressed that communication with the user within the smart house is important. Some systems such as the Brunel Millenium Homes project make much use of voice communication with users. The Bath work also places much emphasis on communication to guide and support the user. The smart house is an intelligent and autonomous care provider and like any other carer it needs to communicate with the person it is caring for. Voice communication is of

course very flexible and has the advantage that it reflects the kind of interactions provided by a human carer. But it does have some disadvantages. The communications it provides are transient. If the user is forgetful, then a message that encourages them, for example, to take some medication may be registered but then forgotten a few minutes later. For users with severe memory problems, such as those with dementia, this problem is exacerbated. In addition, the very fact that voice messages are very anthropomorphic means that users may well treat them emotionally and get angry or irritated when prompted to do something.

Some work has shown the usefulness of voice communication though. The Brunel team have had very positive responses to their system. The Bath group also have had some good responses even though their work was fairly exploratory because it was looking at voice communication with people with dementia. A lot of professional carers felt that this might not work because the person with dementia may well be made more anxious by the use of disembodied voices, particularly people with conditions such as Lewy body disease where they tend to hallucinate and hear voices anyway. The other concern raised was that if the voice was recognised, the person with dementia may well think the owner of the voice was in the building and go looking for them. To try and address the first concern, the designers made sure that any voice messages came from devices that normally had voices coming from them, such as the TV or the radio. The Gloucester smart house project modified radios so that they would be turned on and a message played when necessary, or played instead of the broadcast if the radio was already on. It was argued that the often reported anecdote that people with dementia will personalize the messages they hear from the radio or TV, and feel they are being addressed personally, might well mean they would take good note of any prompt or advice coming from these devices. It was also decided to use a voice that was a warm anonymous one.

Most of our experience of voice prompts has come from the use of a wander reminder for people with dementia. This device sits by the main door and if it detects someone in its vicinity at nighttime it plays a voice prompt that says something like "It is still nighttime Joan. I should go back to bed" (Figure 8). If the user still goes out of the house this is detected, an alarm is sent to a carer to alert them to the fact. Most of the users have been mild to moderate in their degree of dementia. The results have been very positive, with less wandering reported in most cases and no wandering in several. However, some carers have reported that the user just swears at the voice box! The fact that the voice was disembodied does not seem to have been a problem. It would appear that people are quite used to voices coming out of little boxes from their lifetime experience of radio, tape-recorders, and so on, and it seems quite normal. Interestingly, there was some evidence of habituation to the message and the carer was encouraged to change the message frequently. One unexpected outcome from these changes was that it was reported that users seemed to respond better to a voice they recognized. In all the cases so far, the new recording has been done by the personal carer, that is, the person that the user probably trusts. These observations are rather anecdotal at the moment but provide some interesting insight into an area that is an important research topic for smart home installations for elderly people.

Other means for communication are being explored. As mentioned above it would help to use messages that remain for a longer period for people with memory problems or who are a little forgetful. Simple hand written text messages are often used by carers of people with dementia. For example, carers might use Post-Its around the house to remind the user not to touch certain appliances, or to remind them to take medication, and so on. Automated text messages on a small screen on the wall, which can be activated by the house in appropriate situations, are being explored. A further development of this idea that has been successfully tested is the use of simple pictures or graphics in addition to the written message. There is scope for providing these messages on the TV where simple animation or even small video clips can be used.

Figure 8 A wander reminder fitted near an exit door

QUALITY OF LIFE ISSUES

It has been commented that smart home technology has primarily been used to support safety and security issues, and not very much for other activities such as leisure (Marshall, 2001). The technology is ideal for monitoring activities such as cooker, fire, and tap usage, to ensure appropriate temperatures and ventilation, to help prevent wandering or disorientation at night, and so on. The impact that it has on quality of life is less clear, and yet as far as the users themselves are concerned, it is maintenance of or improvement in their quality of life that is all important. Are there ways in which this technology can have an impact on quality of life?

There are a large number of quality of life measures now available, including measures for people with dementia

(Brod *et al.*, 1999). The ENABLE project used a measure of the impact of technology on quality of life as one of its main outcomes. Recently some work has started in the United Kingdom to explore whether it is possible for smart home technology to have an impact as well. This is a collaborative venture with the main academic partners coming from Liverpool, Sheffield, and Bath Universities. The project aims to tease out those aspects of the lives of people with dementia that have an impact on quality of life and then provide designs of smart home technology and built environments that can help improve on them. The work is in an early stage but already it is clear that there are a number of issues that are important. A key issue of course is that of independence, and for the user to have a sense of being in control of their lives. It is for this reason that so much emphasis had been placed in the Gloucester smart house project on empowering the user and not letting the house take control away from them. Another crucial issue is the importance of reducing social isolation. Are there ways in which smart home technology can enable people to feel part of wider society, and still be able to maintain contact and socialize with friends, family, and carers? There is some indication from other work that even simple phone or video conference chats can be of benefit (Monk and Watts, 2000). The often reported habit of TVs being left on in an otherwise empty home to provide a sense of social involvement gives an indication of the complex way that people can interact with technology. Many issues that have an impact on quality of life are very personal to the individual. There can often be some barrier for a given individual that prevents him/her from doing something that may not seem that important to an outsider, such as being able to cook a simple meal for oneself. If such barriers can be identified and removed through the use of some technology, it could provide a big increase in their personal quality of life.

LINKS WITH THE OUTSIDE WORLD

As was mentioned above, the major factor differentiating smart home technology from telecare systems is its ability to act autonomously. However, there is an important need for communication with the outside world. Already mentioned is the need for backup in the event of an emergency. The house needs channels of communication that can alert the carer and others to the fact that the house is not able to cope on its own. The Bath work, for example, used an SMS link to call for assistance. If the gas cooker monitor decided that there was still some danger despite it having turned off the cooker knobs, then it would shut down the gas supply and send a text message to the mobile phones of several carers, advising them to come and check, and to turn the gas back on again. This system worked very well. Such links could be provided via landline phones and perhaps to a call center. It would also be possible to send messages via a web server to appear on a remote monitor. Installations in a sheltered housing scheme in Deptford in London that are an extension of the work carried out in Bath use such a system. Because the Deptford installation is in a care home, any need for backup is initially provided by alerting the warden call system. In addition to the alert, the computer linked to the installation can send text messages via a web server that enables the computers in the warden's office to display messages relating to any need for their assistance.

The external support described could provide details that would enable a care professional to make judgments about the impact of the technology. This is a difficult ethical area that needs much further exploration. On the one hand it might be seen to be useful for an OT to just check on how often one of her clients had used the toilet in case there was evidence of a urinary tract infection, for example. But is such personal intrusion really ethically acceptable? On the other hand it would make sense for the house itself to flag a warning if it detected anomalous behavior that might indicate excessive anxiety, or to let OTs know if the gas cooker had to turn itself off more than 10 times in a week, or if the fridge hadn't been opened for more than a few days. So these links to the outside world seem to make sense if they can be preset to draw attention to some trend in the house, but it becomes much more ethically contentious when it is used as a tool to check and pry.

INFRASTRUCTURE NEEDED FOR INTRODUCTION

A lot of the work carried out so far on the use of smart homes for elderly and disabled people has been on very small-scale installations. They have been more akin to research projects to explore the potential of the technology. As evidence mounts that there are distinct personal benefits to the clients, and as evidence also mounts as to the cost effectiveness of the technology, there is an expectation that the technology can be rolled out to be used throughout the community. However, there are a number of infrastructural requirements that are needed to be satisfied before such a big step.

First of all any such technology can only be used following an extensive assessment of the user's needs by a care professional, probably an OT. The OTs involved need to be knowledgeable about what assistive devices are available and the potential of them to provide support. In this way, they can match the needs of the individual to a prescription of the mix of technology that would best suit the client at that time.

Secondly, there needs to be a knowledgeable set of contractors, either employed by the company manufacturing the assistive technology or able to work for a number of different companies, to carry out the actual installations and configure them according to the results of the assessment process. As with environmental control technology, the commissioning process is complicated because it needs to involve a mix of technical people and OTs.

Thirdly, there needs to be system of operational backup, as described above, in the event of emergencies arising. Such backup may well be provided by call centers, but there is no

reason why this cannot be provided via care professionals directly, or personal carers, particularly through web-based technology.

Fourthly, there needs to be a well thought through system of technical maintenance that can be activated at very short notice. It is clear from the work of projects such as the ENABLE one that users of sophisticated technology can get very anxious when it does not seem to be operating as they expect, and can quite quickly reject the technology if it appears to have gone wrong. Such backup would ideally be provided by manufacturers, but a frontline of quick-reaction local technical support would probably be essential.

All the infrastructures described above would have to be in place before any large scale installation of this technology. Similar facilities are also needed of course for telecare systems and these have been mostly put in place with remarkable efficiency over the last few years in the United Kingdom, mostly through the work of some more visionary manufacturers. The manufacturer involved with the Brunel Millenium homes project has also locally established much of the support needed. So there is every reason to expect such infrastructures can be put in place, particularly once the benefits of using this technology become more widely accepted.

FUTURE TRENDS

There is an important need for much more evaluation of smart home installations to get a better indication of the ways in which it supports users, and indeed the ways in which it does not. Evidence is emerging as to those key features that are of most benefit but much more work needs to be done in this area. In addition, the new support devices developed specifically for the elderly now need to be developed to a more mature state. As has been said, there are a lot of items such as lighting controls that are already available off the shelf. Others such as cooker controllers and reminding devices are less so, and need to achieve the same level of maturity. The one area where there is still a lot of work to do is in terms of the actual physical installations. The logic needed to control even a single home or apartment in a care home can be quite complex, particularly if it has to be able to be configured to suit a range of different users, and deal with power cuts and computer crashes. If installations are to be plug and play, which they need to be, then the logic element that controls the system, and provides the link to the outside world, needs to be plug and play as well. The software needed to configure a system for an individual needs to be developed so that it is very user-friendly and can be used by care professionals.

For installations that are provided in care homes and sheltered housing schemes then, the use of hard-wired communication buses is probably going to be the first choice. Such buses can provide excellent and well-proven reliability, and they can provide the low power needed for many components of an installation. For builders of new housing schemes, it makes sense to install the bus cabling during the build, even if it is not being connected to support installations straight away, because it is very cheap to install at that time. Many housing associations, such as Housing 21, are doing this already. For a retrofit installation, however, especially for those used in people's own homes, the use of hard-wired buses is much less suitable. It is very disruptive and time consuming to install, and therefore expensive. For people who are likely to be anxious anyway, such as those with dementia, such installations can hardly be justified ethically. In these situations, radio-based buses or buses using mains wiring are much more appropriate. A number of radio frequency buses are in use already although an accepted standard does not seem to be agreed yet. Some modern developments such as the Ziggbee radio bus seem to have the right mix of range and bandwidth. It is very likely that an accepted standard will drop out from the various experimental systems currently being explored. Radio-based devices are truly plug and play. They do need battery power and all the backup that that implies for replacements to be provided in a timely manner, but standard replacement times and procedures would probably deal with that. Some of the more modern systems such as the one mentioned above, Ziggbee, have very good power management built-in that provides excellent battery life. There is no doubt that radio-based systems or systems superimposed on normal mains wiring will be the way forward for personal home installations.

There is a need for further work on support devices and sensors, particularly those that can provide support that improves leisure and quality of life more generally. And finally the technology to provide background behavior monitoring, which has been a research topic for some years, is likely to provide added benefits. Such technologies should provide better judgments of complex behaviors that might reflect anxiety levels, or specific issues such as falls. An extra feature incorporated in the Brunel project and one that has been explored by several academic groups (Dewsbury *et al.*, 2004) is to see if the technology can be better tailored to the needs of the individual user by allowing it to learn the typical behavior of the occupant. The house, through its sensors, can acquire a lot of information about the use of various appliances and the patterns of activity within the home. Once this information has been acquired, the house can use this "normal" template to check whether there are major changes that might indicate something is wrong. Such adaptive properties will also enable the installation to adapt to the user's behavior and learn the subtleties of an individual's requirements. All these topics are being researched; some, such as adaptive systems, are being used with clients.

The installations that have been discussed throughout this chapter have been looking at home support technology that can act as a kind of extra care helper. However, the technology also has potential for linking in to other kinds of technological support and may well become integrated with them. For example, the burgeoning developments in telehealth technology could well use some of the same infrastructure as smart homes. If smart homes have appropriate links to the

outside world and can sense user behavior, then there is no reason why they cannot also report health issues resulting from the physiological and other sensors used by telehealth systems. Links between telehealth and telecare have already been made by some companies, so telehealth can certainly be incorporated in smart home installations. There is research also going on looking at telerehabilitation, where home exercises and physiological responses can be remotely monitored in the same way as telehealth systems.

CONCLUSIONS

The application of smart home technology to support elderly and disabled people has developed rapidly over the last few years. Recent work has been much more user-led and aimed at supporting people with a wide variety of abilities, including those with dementia. Evidence is mounting that such systems can provide real benefits to the user, and would also appear to have benefits from a cost point of view. There is still much work to be done, particularly with respect to improving quality of life and leisure activities. However, as long as the relevant infrastructure can be put in place to support the technology, there is no reason why installations in both care homes and people's private homes cannot be a major feature of the support provided to elderly and disabled people in the very near future.

KEY POINTS

- Smart technology has much potential for supporting elderly people, including those with dementia, if it just provides background support and does not rely on user interaction.
- If smart home technology is to be effective, its design must be led by the particular needs of the user.
- Sensors in the home are only going to enable statistical judgments to be made of human behavior, and human backup is needed to deal with mistakes.
- The technology requires an external infrastructure to provide assessment, technical backup, and monitoring.
- Technology can only augment human care, never replace it.

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PART III

Medicine in Old Age

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Preventive Geriatrics

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INTRODUCTION

Preventive geriatrics is not an oxymoron. It is, however, a challenging area of medicine for many reasons. (1) When does prevention actually begin? (2) How can guidelines for prevention take into account the increasing variability seen among older persons? (3) How can preventive geriatrics balance the dichotomy between the treatment of populations and the treatment of the individual? (4) How can clinicians handle the unclear areas or "gray zones" of preventive geriatrics? (5) Does early detection or case finding equate with better outcomes?

This chapter presents two models of preventive geriatrics that deal with these questions. The first model is called the *Health Maintenance Clinical Glidepath*, which is primarily for office-based practices. It addresses screening for geriatric-specific areas (e.g. cognition, gait and balance, etc.) as well as screening for common medical illnesses and diseases (e.g. certain cancers, heart disease, etc.). The second model is the British Health Checks, which is community based. It focuses on comprehensive geriatric assessment (CGA) and is intended for all people over 75 years of age.

BACKGROUND

Prevention in medicine has traditionally been divided into primary, secondary, and tertiary prevention. Primary prevention is the prevention of disease before it actually starts. On the basis of this definition, primary prevention of disease that occurs in old age begins at a very young age. Although gene manipulation was in its infancy at the end of the twentieth century, by the end of the twenty-first century, it could prevent, delay, or modify diseases common in old age, such as Parkinson's disease, cardiac disease, diabetes, and even arthritis. Until then, society's obligation to its future elderly is to advocate health promotion over the life span. Although the health promotion guide in Figure 1 does not include all areas of prevention, it is one example of an educational tool that can be used among all ages.

The traditional definition of secondary prevention is the detection of disease at an early stage. This can be detection of asymptomatic diseases by screening tests or identification of unreported problems by case finding. The following cautions need to be added to the definition. Detection should only be done if it is likely to improve outcomes such as mortality, morbidity, function, or quality of life. The priority and importance of outcomes need to be made on the basis of patient preference (Woolf, 1997).

THE HEALTH MAINTENANCE CLINICAL GLIDEPATH

The Health Maintenance Clinical Glidepath answers questions two and three above but also addresses the limitations of two types of clinical decision-making tools: practice guidelines and evidence-based medicine (EBM). Although practice guidelines and EBM have been important in raising the standards of health care in the past decade, their use in preventive geriatrics is limited. Many guidelines do not include older age-groups, and if they do, they are no more specific than "over 65 years of age". EBM emphasizes outcomes of populations, while clinical practice emphasizes the outcome of the individual. One of the reasons EBM may not be so useful is the discrepancy between patients in the EBM studies and in clinical practice (Kerridge *et al.*, 1998). For example, many randomized controlled trials of medication interventions for common diseases such as congestive heart failure, coronary heart disease, and osteoporosis exclude patients who are frail, demented, or at the end of life (Australia/New Zealand Heart Failure Research Collaborative Group, 1997; Pitt *et al.*, 1999; Liberman *et al.*, 1995).

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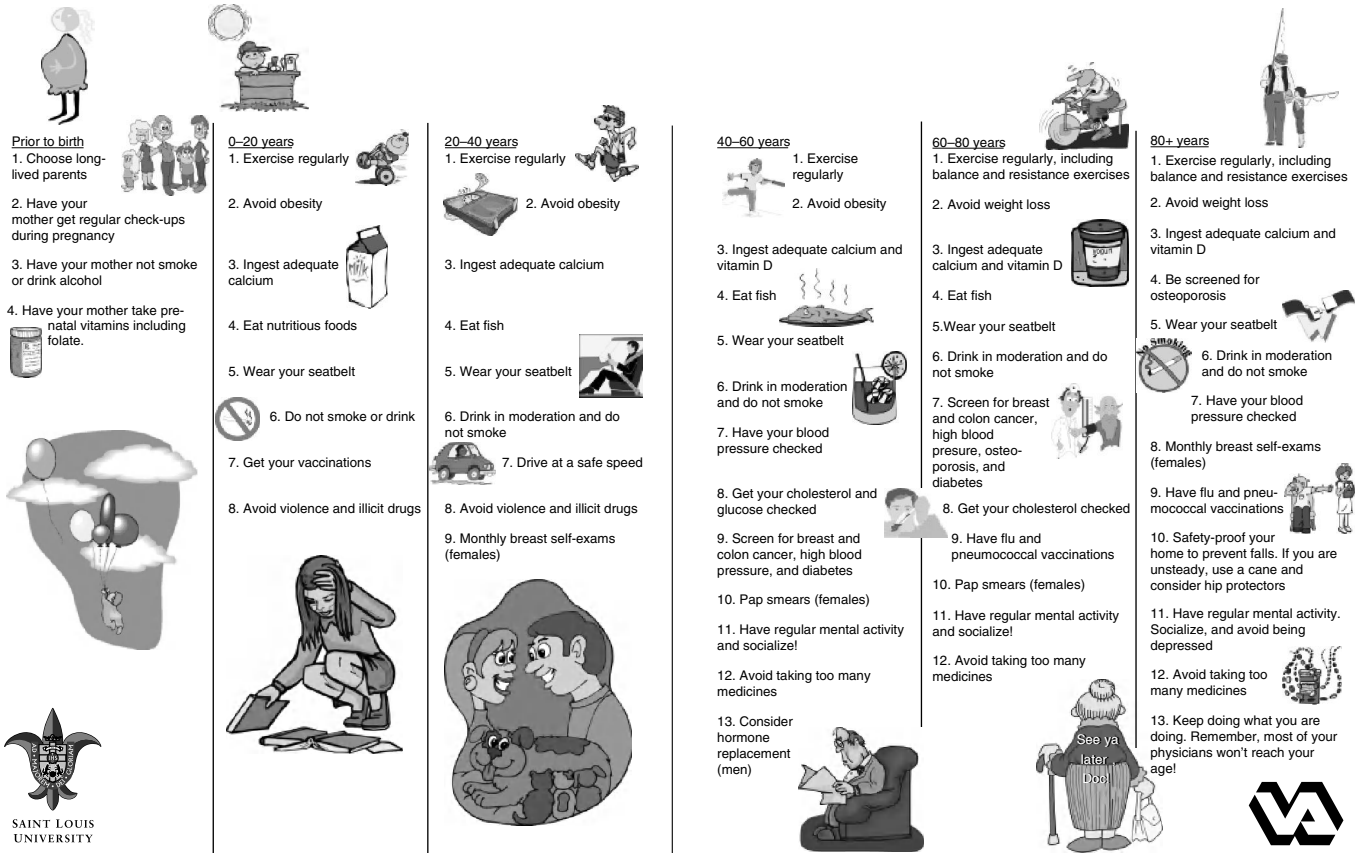

Figure 1 Aging successfully: a guide to health promotion over the lifespan

The older we get, the more unique we become. Chronological age does not equate with physiological or functional age. Guidelines for preventive geriatrics need to take this into account. One approach is to use life expectancy and functional status to help delineate categories of older persons that are more useful than those based on chronological age. Overall health status is a good predictor of life expectancy compared to age alone (Diehr *et al.*, 1998), and functional capacity among older persons has been found to be a predictor of mortality (Corti *et al.*, 1994; Walter *et al.*, 2001). Four categories can be used to help guide decisions about preventive measures. Although overlap exists and functional status may fluctuate, Gillick proposes the following: Robust (life expectancy of greater than 5 years and functionally independent); Frail (life expectancy of less than 5 years and significant functional impairment); and Moderately Demented (life expectancy from 2 to 10 years and may or may not be functionally impaired); End of Life (usually a life expectancy of less than 2 years) (Gillick, 1994).

Preventive geriatrics requires making decisions. Health-care decisions are complex, involving society, health-care workers, and patients. Guidelines for preventive geriatrics need to take into account the following practice principles: (1) patients' expectations and needs, including quality of life, satisfaction, reassurance; (2) physicians' need for diagnostic certainty; (3) physicians' comfort with risk taking and concerns about malpractice; (4) the need for cost-effective medical care; (5) variations in practice patterns, particularly in regard to subspecialty care; and (6) the practical realities of running a practice (Murphy, 1995).

Health-care decisions are not black and white. Thus, four levels of recommendation were developed to allow for decisions to be made on a "graded" rather than an "all or nothing" basis, and to allow for better patient involvement in decision making. The four levels are also based, when available, on the strength or weakness of EBM that exists or does not exist. The four levels are "Do", "Discuss", "Consider", and "∗∗∗∗". "Do" reflects the strongest recommendation. "Discuss" reflects a recommendation that the physician discusses the risk: benefit of the decision with the patient. "Consider" reflects a recommendation that the physician gives consideration, but does not necessarily need to discuss the decision with the patient. "∗∗∗∗" reflects that a particular evaluation or management measure is not recommended, based on these principles.

Table 1 is a shortened version of the original Health Maintenance Clinical Glidepath which details the recommendations for each area of prevention and for each category of Robust, Frail, Moderately Demented, and End of Life. It will be noted in the following paragraphs whether recommendations are based on organizational guidelines, EBM, or expert

Table 1 The Health maintenance clinical glidepath

Recommendations: Highest ↓ Lowest — Do / Discuss / Consider / **** (see text for further explanation)	Robust elderly Life expectancy >5 years and functionally independent	Frail Life expectancy <5 years or significant functional impairment	Moderately demented Life expectancy 2–10 years	Robust elderly Life expectancy >5 years and functionally independent
Office visits	Do yearly	Do 1–4 times/year	Do 1–4 times/year	Do as needed
Blood pressure including orthostatics	Do each visit	Do each visit	Do each visit	Do each visit
Weight	Do each visit. If loss of >5 pounds/year perform MNA[a]	Do each visit. If loss of >5 pounds/year perform MNA[a]	Do each visit. If loss of >5 pounds/year perform MNA[a]	****
Height	Do yearly	Do yearly	****	****
Pain assessment	Do each visit	Do each visit	Do each visit	Do each visit
Medication review including OTCs[a] & herbal medicines	Do each visit	Do each visit	Do each visit	Do each visit
Lifestyle education (exercise, smoking cessation, alcohol, and injury prevention)	Do each visit	Do each visit	Discuss periodically with caregiver	****
Maintain awareness of elder abuse	Do each visit	Do each visit	Do each visit	Do each visit
Assess ADLs[a] and IADLs[a]	Do yearly	Do yearly	Do each visit	Do each visit
Visual acuity testing	Consider yearly	Consider yearly	Consider yearly	****
Auditory testing	Consider yearly	Consider yearly	Consider yearly	****
Ask about urinary incontinence	Do yearly	Do yearly	Do yearly	Do yearly
MALES: Ask about erectile dysfunction and ADAM[a] screen for hypogonadism	Do yearly	Do yearly	Consider yearly	****
Cognitive screening	Do initially; do if symptomatic	Do initially; do if symptomatic	Do initially	Consider if symptomatic
Depression screening	Do initially; do if symptomatic	Do initially; do if symptomatic	Do initially; do if symptomatic	Do initially; do if symptomatic
Screening for gait and balance	Do initially; do if symptomatic	Do initially; do if symptomatic	Do initially; do if symptomatic	Do if symptomatic
Advanced directives	Do yearly and as needed	Do yearly and as needed	Do yearly and as needed	Do yearly and as needed
Influenza vaccine	Do yearly	Do yearly	Do yearly	Do yearly
Pneumococcal vaccine	Do once; consider repeat every 6 years for patients with chronic diseases	Do once	Do once	Consider vaccination once
Tetanus	Do primary series if not vaccinated before and booster every 10 years	Do primary series if not vaccinated before	Do primary series if not vaccinated before	****
Breast exam	Do yearly	Do yearly	Do yearly	****
Mammography	Do every 1–2 years up to 80 years	Consider every 1–2 years up to age 75	Consider every 1–2 years up to age 70	****
Pap smear	Consider 1–3 pap smears if patient has never had pap smears	****	****	****
Fecal occult blood test	Do yearly	Consider yearly	Consider yearly	****
Colonoscopy	Consider every 5 years	****	****	****
PSA[a]	Discuss pros and cons with patient	Discuss pros and cons with patient	Discuss pros and cons with caregiver	****
Osteoporosis	Do at least once; Consider every 2 years	Do at least once	Do at least once	****

(*continued overleaf*)

Table 1 (*continued*)

Recommendations: Highest ↓ Lowest — Do / Discuss / Consider / **** (see text for further explanation)	Robust elderly Life expectancy >5 years and functionally independent	Frail Life expectancy <5 years or significant functional impairment	Moderately demented Life expectancy 2–10 years	Robust elderly Life expectancy >5 years and functionally independent
Cholesterol screening	Consider screening for patients 65–75 years if have additional risk factors (e.g. smoking, diabetes, hypertension)	Consider screening for patients 65–75 years if have additional risk factors (e.g. smoking, diabetes, hypertension)	****	****
TSH[a]	Do every 2 years	Do every 2 years	Do every 3 years	Consider
Fasting blood glucose	Do, if symptomatic or every 3 years if have risk factors	Do, if symptomatic or every 3 years if have risk factors	Do, if symptomatic or every 3 years if have risk factors	Consider if symptomatic
Sleep apnea	Do yearly	Do yearly	****	****

[a]MNA, Mini Nutritional Assessment; OTC, Over the Counter; ADLs, Activities of Daily Living; IADLs, Instrumental Activities of Daily Living; ADAM, Androgen Deficiency in Adult Males; PSA, Prostate-specific Antigen; TSH, Thyroid-stimulating Hormone.

consensus. All areas of the Glidepath underwent a Delphi process (Flaherty *et al.*, 2002).

OFFICE VISITS

Although there is no direct evidence available on how often Robust elderly versus Frail or Moderately Demented elderly need office visits, because other screening procedures need to be done, the minimum frequency should be once a year. "Do as needed" is recommended for elderly at the End of Life because of potential limitations or inability on the part of the patient to get to the office. As will be discussed below, yearly British Health Checks are one model that has been recommended for community-dwelling elderly.

BLOOD PRESSURE (BP) INCLUDING ORTHOSTATIC MEASUREMENTS

Doing BP measurements in all age-groups is recommended at each visit. While this pertains to screening for hypertension in all four categories, it also pertains to hypotension (and associated symptoms) in the Frail, Moderately Demented, and End of Life categories. Recommendations for hypertension screening are based on organizational guidelines. Although most organizations agree on the importance of screening for hypertension, they do not agree on how often. For example, the American College of Physicians (ACP) recommends BP screening in all adults *with office visits* at least every 1–2 years (Littenberg *et al.*, 1990). The United States Preventive Services Task Force (USPSTF) recommends *periodic* BP screening, and reports that the current expert opinion is that adults who are believed to be normotensive should have BP measurement at least once every 2 years if their last BP reading was below 140/85 mmHG; and screening should be annual if the last diastolic BP was 85–89 mmHg (United States Preventive Services Task Force, 1996).

Screening for orthostatic hypotension (OH) is based on evidence that OH is prevalent among older patients (13–30%) and that there is an association between OH and adverse outcomes (Hale and Chambliss, 1999; Luukinen *et al.*, 1999; Davis *et al.*, 1987). Although no studies have been done to show improved outcomes if this screening is done, the cost and risk of the intervention is low enough that postural BP measurements are recommended.

WEIGHT

Weight loss in older patients has significant adverse effects on mortality, morbidity, and other unfavorable outcomes (e.g. loss of muscle mass; decreased muscle strength; altered immune function; decreased wound healing) (Morley, 1996). The data on the benefit and outcome of nutrition management is somewhat controversial, but mostly positive. Oral nutritional supplement was shown to improve weight in nursing home elderly, supplementation was shown to improve weight and reduce falls in frail elderly living in the community, and dietary supplementation led to moderate weight gain and improvements in general well-being in homebound elderly (Johnson *et al.*, 1993; Gray-Donald *et al.*, 1995, 1994). However, another study of frail elderly showed that nutrient-dense foods and exercise were not able to improve appetite or sensory perception, and no functional change was found by nutritional supplementation (De Jong *et al.*, 2000).

Since screening for weight loss is very low in cost and risk and the benefits of interventions are mostly positive, it should be done for patients in all categories except End of

Life. In addition to weighing the patient, the Mini Nutritional Assessment (MNA) is a validated nutritional screening tool that can identify patients who are malnourished or at risk for malnutrition (Garry and Vellas, 1999) (Rubenstein, 1998).

HEIGHT

Since measuring height is a low-cost screening intervention, and as bone loss occurs height may decrease, it may be an effective and economical method to identify early osteoporosis of the spine for the Robust and Frail elderly. However, there is no clear evidence to determine what amount of loss is significant (Ismail *et al.*, 1999); (Hunt, 1996); (Ettinger *et al.*, 1994).

PAIN

Pain should now be considered the fifth vital sign and should be checked at every visit for patients in all categories (Anonymous, 1999c). Use of Likert scales (e.g. 1–10) or pictorial scale (e.g. facial expressions) can be useful to quantify pain. Even patients with dementia can be evaluated for pain (Won *et al.*, 1999; Anonymous, 1998b).

MEDICATION REVIEW INCLUDING OTCs AND HERBAL MEDICINES

The risk of adverse drug events, poor compliance, drug–drug interactions, and even the risk of hospitalization are most associated with number of drugs, while underlying comorbidities and to some extent age contribute to this risk (Hanlon *et al.*, 1997; Nolan and O'Malley, 1998; Col *et al.*, 1990; Flaherty *et al.*, 2000). Thus, medication review including OTCs and herbal medicines should be done for patients in all four categories at every visit.

LIFESTYLE EDUCATION

Recommendations about areas of lifestyle education in general apply mainly to the Robust and Frail elderly, with a lower level of recommendation for the Moderately Demented elderly. Activity level should be queried about because a low level of activity is a significant predictor of mortality among older adults (Fraser and Shavlik, 1997). Walking can be recommended to most older persons; sustained walking for 30 minutes a day can result in health improvement. Even small increases in exercise can be beneficial in inactive older persons, including wheelchair and institutionalized elderly. Exercises can include endurance (walking, climbing stairs), strength, balance, flexibility, and posture (Green and Crouse, 1995; Ettinger *et al.*, 1997).

Physicians should ask patients about smoking and should clearly and directly advise all smokers to quit. Patients who want to quit should be assisted with self-help materials, choosing a quit date, and a possible referral to community programs (Rimer *et al.*, 1994).

In order to screen for alcohol problems, either the CAGE questionnaire or the Michigan Alcohol Screening Test can be used (Ewing, 1984; Pokorny *et al.*, 1972). The CAGE questionnaire for alcoholism screening asks the following questions: (1) Do you feel you ought to **C**ut down on drinking? (2) Are you **A**nnoyed by people criticizing your drinking? (3) Do you feel **G**uilty about drinking? (4) Do you have a drink first thing in the morning (**E**ye-opener)?

Areas of education for injury prevention include the use of seat belts, alcohol-related risks in relation to driving, environmental hazards in the home which may aid the prevention of falls and the dangers of firearms (United States Preventive Services Task Force, 1996).

MAINTAIN AWARENESS OF ELDER ABUSE

Physicians and other health-care professionals should maintain awareness at all times for patients in all categories. This is based on the fact that elder abuse and neglect is prevalent, may often be missed, and may be "asymptomatic". The term "awareness" is used because no particular standardized evaluation tool for elder abuse has been shown to be better than others (Lachs and Pillemer, 1995; Joshi and Flaherty, 2005).

ASSESS ADLs AND IADLs

Prevention of functional decline is one of the hallmarks of geriatric care. Loss of function among older persons is associated with long-term care placement, morbidity, and mortality (Corti *et al.*, 1994). Thus, although there is no direct evidence on how often to screen older patients in each of the four categories for functional change, given the importance of this health parameter, it is recommended for patients in all categories at the intervals as noted in the table.

Two commonly used measurements of function are activities of daily living (ADLs) (bathing, dressing, toileting, transferring, continence, feeding) and instrumental activities of daily living (IADLs) (telephone, shopping, food preparation, housekeeping, transportation in the community, taking medications, handling finances) (Katz *et al.*, 1963; Lawton and Brody, 1969).

VISUAL ACUITY AND AUDITORY TESTING

Although both visual acuity and auditory testing are an accepted part of the CGA, the level of recommendation for testing these areas is "consider" for patients in all categories There is evidence that decreased vision is associated with

negative outcomes. However, according to one systematic review of randomized controlled trials, the inclusion of a visual screening component in the assessment resulted in only a small reduction (11%) in the number of older people with improved self-reported visual problems (Smeeth and Iliffe, 1998). Likewise, although there is evidence that decreased hearing is common and associated with negative outcomes, there is a lack of evidence-based medicine that screening will improve outcomes (Murlow and Lichtenstein, 1991).

ASK ABOUT URINARY INCONTINENCE

The level of recommendation is the highest for all categories because urinary incontinence is common among women and may occur in men, is easy to screen for (usually one to two questions), and multiple effective treatments are available (Nasr and Ouslander, 1998; Schmidbauer *et al.*, 2001; Miller *et al.*, 1995).

MALES: SCREEN FOR ERECTILE DYSFUNCTION AND HYPOGONADISM

It is recommended that this be done for males in Robust and Frail categories, but should only be considered in males with Moderate Dementia. Erectile dysfunction is common and multiple treatments are available (Montague *et al.*, 1996). Male hypogonadism is also common and is associated with muscle weakness and osteoporosis (Morley and Perry, 2000). The ADAM (Androgen Deficiency in Aging Males) screen for hypogonadism has high sensitivity and adequate specificity (Morley *et al.*, 2000; *see* **Chapter 121, Ovarian and Testicular Function**).

COGNITIVE SCREENING

Screening for cognitive impairment is part of a CGA and should be done at initial visits for patients in all categories, except for those at End of Life, where it should be considered. The Mini-mental State examination is a commonly used screening tool (Folstein *et al.*, 1975), but may have limited utility if the cut-off score is set too high (White *et al.*, 2002). For elderly with high education levels, the Saint Louis University Mental Status (SLUMS) examination (see chapter on dementia for details) may be used. The term "symptomatic" refers to any complaint given by the patient or caregiver, or any problem observed/illicited by the clinician.

DEPRESSION SCREENING

Depression screening should be done at initial visits for patients in all categories. There is evidence that detection of depression is higher for older patients compared to younger patients when screening data were made available and effective treatments are available. (German *et al.*, 1987). Screening for depression is part of a CGA. There is no strong evidence for one particular screening instrument for depression (Mulrow *et al.*, 1995; Lyness *et al.*, 1997). The Geriatric Depression Scale (GDS) may be one of the easiest to administer (Yesavage *et al.*, 1982–1983). However, the GDS does not maintain its validity for patients with dementia and the Cornell scale (a 19-item clinician-administered instrument) is recommended (Burke *et al.*, 1989; Alexopoulos *et al.*, 1988). Symptomatic refers to any complaint given by the patient or caregiver or any problem observed/elicited by the clinician.

SCREENING FOR GAIT AND BALANCE

The evidence to screen for gait and balance problems at initial visits in all categories except at End of Life is based on the fact that falls are associated with decreased function, increased nursing home admission, and increased morbidity and mortality in populations similar to patients in these categories (Robbins *et al.*, 1989). One of the best "screeners" for gait and balance problems is to ask patients if they have fallen (Tinetti *et al.*, 1986). The "Get Up and Go Test" may quantify functional mobility as well as testing balance, and may also be useful in following clinical change over time (Mathias *et al.*, 1986; Podsiadlo and Richardson, 1991).

ADVANCED DIRECTIVES

Although the evidence is not strong that advance directives make a difference in outcomes (e.g. one study showed that systematic implementation of a program to increase use of advance directives reduced health-care services utilization without affecting satisfaction or mortality) (Molloy *et al.*, 2000), there are ways to increase discussions and completions of advanced directives (Dexter *et al.*, 1998; Rubin *et al.*, 1994). Advanced directives are especially important for patients in the Frail, Moderately Demented, and End of Life categories.

INFLUENZA VACCINE

This should be done yearly for patients in all categories. More than 90% of the deaths attributed to pneumonia and influenza during epidemics occurred among persons aged 65 and older. Influenza vaccination in the elderly has been shown to reduce hospitalization rates, to be cost-effective, and to reduce influenza-associated mortality (Fedson *et al.*, 1993; Foster *et al.*, 1992; Barker and Mullooly, 1980). In the nursing home, while vaccination is only 40% effective in preventing clinical illness, it is more effective in preventing

pneumonia, hospitalization, and death. Vaccinating more than 80% of nursing home residents has been shown to prevent influenza outbreaks (Saah *et al.*, 1986; Gross *et al.*, 1988).

PNEUMOCOCCAL VACCINE

The recommendations about pneumococcal vaccine are based on some evidence and on the probable life expectancy in various categories. Although pneumococcal vaccination increases antibody levels in older adults to a lesser degree than younger adults, and levels decrease more rapidly in the elderly, vaccination has been shown to be effective in reducing the incidence of pneumococcal bactremia in older, high-risk patients who have good antibody response to the vaccine.

Most organizations recommend that one dose of the 23-valent pneumococcal vaccine be given for all adults over age 65. Older patients who received the earlier 14-valent vaccine should be revaccinated with the 23-valent vaccine if they fall into any of those two groups. If patients have had the 23-valent vaccination before age 65, the recommendations for revaccination are controversial (United States Preventive Services Task Force, 1996; American College of Physicians, 1994). The ACP reports that there is currently insufficient data on repeated revaccination every 6 years in healthy elderly, and most other organizations do not provide specific recommendations for revaccination. However, since older patients with chronic diseases may occasionally be "Robust" for other reasons, clinicians should "*consider* repeating" every 6 years (American College of Physicians, 1994).

TETANUS

Recommendations regarding adult tetanus/diphtheria vaccination do not vary for older persons from recommendations for younger adults. Over half of the cases of tetanus occur in persons 60 years or older. All adults should complete a primary series of tetanus/diphtheria toxoid (Td). If an individual had an incomplete series or an uncertain history, it is recommended that the entire primary series be given. Primary series for adults consists of 0.5 cc of Td intramuscularly as the initial dose and at 2 and 6 months later. Booster doses need to be given every 10 years (United States Preventive Services Task Force, 1996; American College of Physicians, 1994).

BREAST CANCER SCREENING

There is no evidence for or against clinician's recommending self-examination, or the clinician doing the clinical breast exam. Given the low cost and low risk (but not zero risk, e.g. a patient with dementia who may misperceive the exam), this should be done on a yearly basis for patients in all categories except for those in the End of Life category.

Levels of recommendation differ for the different categories. This is because of lack of agreement among organizations regarding screening with mammography. For example, the ACP recommends screening up to age 75 (Eddy, 1989). The American Geriatric Society (AGS) recommends that physicians strongly consider recommending annual or at least biennial mammography until age 75 and biennially or at least every 3 years thereafter with no upper age limit for women with an estimated life expectancy of 4 or more years (American Geriatrics Society Clinical Practice Committee, 2000). The USPSTF recommends screening up to age 69, every 1–2 years, mammography alone, or combination of mammography and clinical breast exam. The USPSTF also notes that evidence is lacking to recommend for or against screening women 70 years or older, but doing this for high-risk patients may be made on other grounds (United States Preventive Services Task Force, 1996).

CERVICAL CANCER SCREENING

The low levels of recommendation for Robust (consider) and "Don't Do" for the other categories are based on lack of evidence and organizational recommendations. The ACP and the USPSTF recommend no further Papanicolaou smears for women over age 65 who have had previous regular screening with consistently normal results (United States Preventive Services Task Force, 1996; Eddy, 1990). The AGS position statement says that regular Pap smear screening at 1- to 3-year intervals until at least the age of 70 seems reasonable. Beyond age 70, there is little evidence for or against screening women who have been regularly screened in previous years. An older woman of any age who has never had a Pap smear may be screened with at least two negative Pap smears 1 year apart (American Geriatrics Society, 2001).

COLON CANCER SCREENING

Since the clinician's choice of screening procedure for colon cancer depends on extrinsic factors (e.g. transportation, availability of a gastroenterologist, patient willingness to do one procedure over the other), clinicians can choose to follow recommendations for either fecal occult blood test or colonoscopy. Recommendations for either of these procedures are the lowest level for patients in most categories because they are based on organizational guidelines.

Both the ACP and the USPSTF recommend annual fecal occult blood testing or periodic flexible sigmoidoscopy, or both. The ACP recommends sigmoidoscopy, colonoscopy, or air-contrast barium enema every 10 years from the ages of 50 to 70 years (Annals of Internal Medicine, 1997). The USPSTF recommends sigmoidoscopy, but does not recommend an interval for screening. There is also no upper age limit (United States Preventive Services Task Force, 1996). The American Cancer Society recommends

either one of the following: total colon examination (air-contrast barium enema or colonoscopy) every 10 years or fecal occult blood tests annually and flexible sigmoidoscopy every 5 years. There is no upper age limit (Anonymous, 1999a; Anonymous, 1999b).

PROSTATE CANCER SCREENING

The level of recommendation for prostate cancer screening is to "Discuss the pros and cons" for patients in the Robust, Frail, and Moderately Demented categories, and "Don't Do" for End of Life. The evidence for screening is not strong enough to recommend this routinely (Ilic *et al.*, 2004). Furthermore, there is no agreement among organizations about this issue. For example, neither the ACP nor the USPSTF recommend prostate-specific antigen (PSA) as a screening test for prostate CA (United States Preventive Services Task Force, 1996). However, many urologic organizations tend to recommend it. Digital rectal examination (DRE) has not been demonstrated to be an effective screening test for prostate cancer. The American Cancer Society believes that health-care providers should offer patients the PSA blood test and the DRE yearly for patients over age 50, if they have at least a 10-year life expectancy (Smith *et al.*, 2000; Eyre, 1997). There is insufficient evidence regarding the use of transrectal ultrasonography to consider this a screening tool.

OSTEOPOROSIS

The recommendations to do screening at least once for patients in all categories except End of Life is based on studies that show inadequate rates of diagnosing and treatment. However, there is lack of evidence to show that mass screening of all elderly women and men will be cost-effective or improve outcomes related to osteoporosis (Kanis, 1994).

Bone densitometry studies are accurate screening tools to diagnose early osteoporosis before bone loss exceeds 3%. The dual-energy X-ray (DEXA) absorptiometry and the single-energy X-ray (SXA) absorptiometry provide safe, low-level radiation. These tools are approximately 94% accurate in diagnosing bone deterioration. Both the DEXA and SXA scans are painless and noninvasive procedures that predict patients who are at high risk for developing bone fractures (Yeap *et al.*, 1998; Kanis and Gluer, 2000).

CHOLESTEROL SCREENING

The reason for a low-level recommendation (i.e. consider) and a targeted approach (only for Robust and Frail with additional risk factors) is because the data for primary prevention in this area for many segments of the elderly population is lacking. Some organizational recommendations exist. For example, the USPSTF recommends screening healthy men and women up to age 65, and reports that there is insufficient evidence to recommend for or against routine screening for asymptomatic persons over age 65. The USPSTF also reports that clinicians should consider screening for persons aged 65 to 75 who have additional risk factors (US Preventive Services Task Force, 2001). The ACP recommends screening up to age 65, reports that there is insufficient evidence for or against screening for persons aged 65–75, and advises against screening after age 75 (Annals of Internal Medicine, 1996; Garber *et al.*, 1996). The most appropriate interval for screening is not known.

THYROID-STIMULATING HORMONE (TSH)

Screening all older adults is not currently recommended by the USPSTF, on the basis of lack of data, but notes that screening may be made on other grounds (United States Preventive Services Task Force, 1996). The ACP recommends thyroid function testing in persons aged 50 or over with symptoms suggestive of thyroid disease. The ACP also notes that screening can detect symptomatic but unsuspected thyroid dysfunction (Helfand and Redfern, 1998; Anonymous, 1998a). The yield is highest for women older than 50 years of age. In this group, 1 in 71 women screened could benefit from relief of symptoms. However, evidence of the efficacy of treatment for subclinical thyroid dysfunction is inconclusive. The American Thyroid Association recommends routine screening every 5 years after age 35, but notes that more frequent screening may be appropriate in individuals at higher risk of developing thyroid dysfunction (Ladenson *et al.*, 2000). Many geriatricians advocate screening high-risk population such as nursing home population, frail elderly, and patients with dementia (Mokshagundam and Barzel, 1993). The sensitive TSH assay is probably the screening test of choice.

FASTING BLOOD GLUCOSE

This recommendation is based on organizational recommendations only. Although the USPSTF recommends against routine screening in asymptomatic individuals, it notes that clinicians may decide to screen selected persons at high risk of diabetes on other grounds (United States Preventive Services Task Force, 1996). The American Diabetes Association has recommended fasting plasma glucose measurement every 3 years in adults with one or more of a long list of risk factors (http://www.diabetes.org/for-health-professionals-and-scientists/cpr.jsp, 2005).

SLEEP APNEA

Because of the low cost of screening (in the form of asking about symptoms of sleep apnea during the routine history and

physical or to use a screening questionnaire tool such as the Epworth Sleepiness Scale) (Johns, 1991) and the potential to miss this diagnosis among older patients, it is recommended for robust and frail elderly (Baumel *et al.*, 1997). However, there is no evidence to date that screening for sleep apnea is cost effective or will change outcomes related to this problem.

BRITISH HEALTH CHECKS

The British Health Check model has its origins in the many studies over the past 50 years that have consistently identified high levels of unreported and unrecognized physical, mental, social, and environmental problems among older people living in the community (Williamson *et al.*, 1964; Williams and Wallace, 1993). Thus, repeated annual assessments will detect on average about two new medical problems and one psychosocial problem per person per year (Stuck *et al.*, 2004). The findings have led to numerous randomized controlled trials of general practice-based case finding and intervention, with an emphasis on identifying people with functional loss and dependency, rather than detection of disease. Most of these trials have reported some positive results, for example, with benefits in reduced mortality, fewer nursing home admissions, fewer and briefer hospitalizations, improved functional health status and quality of life outcomes. However, the results have not all been consistent and recent systematic reviews have come to contradictory conclusions (van Haastregt *et al.*, 2000; Elkan *et al.*, 2001; Stuck *et al.*, 2002b). The most effective programs seem to involve an enthusiastic professional (general practitioner or nurse), repeated comprehensive assessment, with the same person responsible for identification of problems and arranging intervention and long-term follow-up.

In 1990, the new contract for general practitioners working in the UK National Health Service established an annual health check to be offered to all patients aged 75 years and over (Freer, 1990). Furthermore, this specified the broad areas that were to be addressed:

- A home visit, at least annually, to see the home environment and to find out whether carers and relatives are available;
- social assessment (lifestyle, relationships);
- mobility assessment (walking, sitting, use of aids);
- mental assessment;
- assessment of the senses (hearing and vision);
- assessment of continence;
- general functional assessment;
- review of medication.

Unfortunately, the policy did not give guidance on appropriate methods or levels of assessment and it was implemented haphazardly, though nearly half the patients who were screened had problems for which some action was taken (Brown *et al.*, 1997).

Table 2 The single assessment process: standardized domains of need (NSF)

User's perspective
- Problems and issues in the user's own words
- User's expectations and motivation

Clinical background
- History of medical problems
- History of falls
- Medication use

Disease prevention
- History of blood pressure monitoring
- Nutrition
- Vaccination history
- Drinking and smoking history
- Exercise pattern
- History of cervical and breast screening

Personal care and physical well-being
- Personal hygiene, including washing, bathing, toileting, and grooming
- Dressing
- Pain
- Oral health
- Foot care
- Tissue viability
- Mobility
- Continence
- Sleeping patterns

Senses
- Sight
- Hearing
- Communication

Mental health
- Cognition including dementia
- Mental health including depression

Relationships
- Social contacts, relationships, and involvement
- Caring arrangements

Safety
- Abuse or neglect
- Other aspects of personal safety
- Public safety

Immediate environment and resources
- Care of the home
- Accommodation
- Finances
- Access to local facilities and services

Those general practitioners who were enthusiastic about the potential benefits of the over-75s checks provided comprehensive screening to all of their patients by invitation, often establishing special clinics and appointing specialist health visitors to help with detailed assessment and follow-up at home. Most general practitioners, however, delegated responsibility to practice nurses. Many adopted a 2-stage targeted approach, using a brief initial screening schedule administered to all the population, to identify the minority thought to justify more detailed assessment. The first stage often used a postal questionnaire, sometimes accompanying a birthday card, while other schemes used volunteers to collect information, or integrated the process into routine care. The latter approach was based on the fact that over 90% of over 75-year olds have contact with their general

practitioner during the year and the nonattenders are generally fit and well (Ebrahim *et al.*, 1984). At worst, this opportunistic method means that only 10% require to be specially contacted. A recent trial involving over 40 000 general practice patients compared the universal versus the targeted approach and subsequent management by a hospital-based geriatric team versus the general practitioner and showed few important differences after 3 years of follow-up (Fletcher *et al.*, 2004). However, the study once again confirmed the high frequency of unreported need amongst the elderly study participants.

The latest General Medical Services General Practice Contract does not include over 75 checks, but the National Service Framework (NSF) for Older People (Department of Health, 2001) envisages that the new Single Assessment Process will incorporate case finding. This aims to provide a more standardized assessment across health- and social-care services so that older people's needs are "assessed in the round" at first contact, using the two-stage targeted approach to explore a wide range of specified domains of need (Table 2). The NSF also aims to ensure that older people have fair access to programs of disease prevention and health promotion, including cancer screening, BP management, smoking cessation, influenza immunization, advice about lifestyle including nutrition and physical activity, and falls prevention.

While the targeting of the older over-75s population will maximize the yield of significant problems, some of these people will be identified too late for effective intervention. Certainly, benefit in terms of reduced mortality associated with preventive home visits in clinical trials appears to be restricted to the younger old. Health risk appraisal combined with reinforcement of recommendations has been suggested to be best suited to those aged 60–75 years, using a self-administered questionnaire to identify potentially modifiable risk factors for functional status decline (Stuck *et al.*, 2002a).

KEY POINTS

- This chapter presents two models of preventive geriatrics that deal with the challenge of heterogeneity seen among older persons, the dichotomy between the treatment of populations and the wishes of the individual, and the unclear areas or "gray zones" of preventive geriatrics?
- The first model is called the Health Maintenance Clinical Glidepath which is primarily for office-based practices, and addresses screening for geriatric-specific areas (e.g. cognition, gait and balance, etc.) as well as screening for common medical illnesses and diseases (e.g. certain cancers, heart disease, etc.).
- Instead of using strict chronological age to tell clinicians when to do certain preventive measures, the Clinical Glidepath helps guide clinicians in their decision making by utilizing four categories of health status based on life expectancy and functional status: Robust, Frail, Moderately Demented and End of Life. The Glidepath also allows for decisions to be made on a "graded" rather than an "all or nothing" basis by using four levels of recommendations: Do, Discuss, Consider, Don't Do.
- The second model discusses the background of the British Health Checks, which is community based, and focuses on comprehensive geriatric assessment for all people over 75 years of age.
- Although the original British Health Checks have historically been effective in identifying unreported and unrecognized physical, mental, social, and environmental problems among older people living in the community, the latest General Medical Services General Practice Contract does not include over 75 checks. The new Single Assessment Process under the National Service Framework for Older People (Department of Health, 2001) aims to provide a more standardized assessment across health and social-care services and access to programmes of disease prevention and health promotion.

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20

Polypharmacy, is this Another Disease?

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INTRODUCTION

Geriatric patients are frequently prescribed multiple drugs in complex dosage schedules. In some instances, this is justified because of the presence of multiple chronic medical conditions, the proven efficacy of an increasing number of drugs for these conditions, and practice guidelines that recommend their use. In many instances, however, complex drug regimens are unnecessary; they are costly and predispose to noncompliance and adverse drug reactions. Many older patients are prescribed multiple medications, take over-the-counter drugs, and are then prescribed additional drugs to treat the side effects of medications they are already taking.

Although persons aged 65 and older comprise only about 12% of the US population, they consume one-third of all prescribed drugs and more than a half of over-the-counter medicines. Overall, more than 80% of all community-dwelling elders use prescription drugs, with the average older person using between 3 and 8 drugs (Morley, 2003).

The devastating consequences of medical errors have been clearly detailed in the book *To Err is Human* by the Institute of Medicine. Medical errors are not uncommon, leading to a number of deaths ranging between 44 000 to 98 000 at a cost to the United States of $17–29 billion a year. A Harvard study done in 51 New York hospitals involving 30 000 patients reported that 3.7% had a treatment adverse event and there was a doubling in the number of undesirable treatment effects in persons over 65 years of age. Most errors are preventable; errors of omission are as important as errors of commission (Morley, 2003).

In addition to concerns about the risks of excessive and inappropriate drug prescribing, there are also concerns about the consequences of underprescribing potentially beneficial drugs. With the increasing numbers of patients surviving to older ages and comprising such a large proportion of drug use, a clear understanding of the risks, benefits, and consequences of drug therapy in older patients is needed.

PHARMACOKINETICS

Pharmacokinetics (the study of the action of a drug in the body over time) changes with age. The physiologic changes that accompany aging alter the pharmacologic processes of absorption, distribution, metabolism, and elimination. The effects of these age-related changes are variable and difficult to predict. Some of these physiologic changes are related solely to aging, whereas others are most likely caused by the combined effect of age, disease, and the environment. Even though increasing age is often accompanied by reductions in the physiologic reserve of many organ systems, independent of the effects of disease, these changes are not uniform; substantial variability exists from individual to individual, which makes some older patients more vulnerable than others (Schmucker, 1985).

Of the four traditional components of pharmacokinetics – absorption, distribution, metabolism, and excretion – only the last three are meaningfully affected by age. In the absence of malabsorptive syndromes, traditional oral formulation of drugs are absorbed as well in old age as in youth, indeed the well-reported changes in gastric motility and blood flow to the gut with aging do not appear to alter the efficiency with which medications move (mainly by passive diffusion) from the gastrointestinal tract into the systemic circulation. More important changes occur from the concurrent administration of several medications at the same time. However, some drugs commonly used for older persons require food for optimum absorption, for example, megestrol acetate which is used to stimulate appetite and weight gain has minimal absorption without food (Table 1).

Unlike absorption, drug distribution is affected by age in clinically meaningful ways. Serum albumin, the major drug binding protein, declines in sick patients due to cytokine excess. Even in healthy patients where there is a small decline, this can substantially increase the amount of free drugs available for action. This effect is of particular relevance for highly protein-bound drugs, especially when they are used simultaneously and compete for

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Table 1 Relevant changes in aging and pharmacology

Pharmacological parameter	Age-related changes	Clinical effect
Tissue sensitivity	Alterations in: Receptor number and affinity Nuclear responses Second messenger function	Patients are more sensitive or less sensitive to a given medication
Absorption	Decrease in: Splachnic blood flow Absorptive surface GI motility Increased gastric Ph	Minimal changes associated with aging
Distribution	Decrease in: Total body water Serum albumin Lean body mass Increased fat	Higher concentration of drugs Longer elimination half-life of lipid soluble drugs
Metabolism	Decreased liver blood flow and enzyme activity	Decreased biotransformation and first-pass metabolism
Excretion	Decreased renal perfusion, glomerular filtration rate and tubular secretion	Decreased renal elimination of drugs

GI, gastrointestinal.

protein-binding sites (Schmucker, 1985). In long-term-care residents, diphenylhydantoin toxicity with low serum levels can occur because the decrease in albumin. Thus, measuring a free dilantin level can be essential in these situations.

The relative increase in body fat and decrease in lean body mass alters drug distribution, such that fat-soluble drugs distribute more widely and water-soluble drugs less widely; this fact can potentially lead the health-care professional to the wrong decision due to misinterpretation of serum drug levels. Many assays measure the total amount of drug that is present in serum, both protein-bound and unbound (free). The unbound concentration is more clinically relevant than the total concentration because only unbound drug is pharmacologically active (Grandison and Boudinot, 2000). For a patient with hypoalbuminemia or another deficiency in binding protein, any given serum drug level reflects a greater concentration of unbound drug than the same level would signify in a patient with normal protein-binding capacity. A hypoalbuminemic patient with a normal total serum drug concentration may actually have an unbound drug concentration that is unacceptably high. By contrast, the same patient with a slightly lower than normal total serum concentration may have an unbound drug concentration that is in reasonable range (Grandison and Boudinot, 2000; Table 2).

In evaluating serum drug levels in the older patient, it is also important to recall that the therapeutic range routinely reported on such assays may not be an accurate guide to either efficacy or toxicity in the geriatric patient. Such ranges have typically been defined in nonelderly subjects and cannot take into account pharmacodynamic differences or idiosyncratic aspects of specific agents (Beyth and Shorr, 2002).

Table 2 Volume of distribution for commonly used medications

Decreased volume	Increased volume
Ethanol	Diazepam
Gentamicin	Oxazepam
Digoxin	Prazocin
Cimetidine	Acetaminophen
Phenytoin	Salicylates
Quinine	Tolbutamide
Theophyline	Chlordiazepoxide
Meperidine	Thiopental

Note: If the volume of distribution is higher, drug levels are higher.

The other important aspect is the drug distribution, which varies importantly with age; volume distribution is a virtual space in a given patient which a particular drug occupies. Age-related changes in body composition can prominently affect pharmacology by altering the volume of distribution (Vd); the elimination half-life of a drug varies with the ratio Vd:drug clearance. Thus, even if the same rate of clearance of a drug is unchanged with age, changes in Vd can affect a drug's half-life and duration of action.

Because the total body water and lean body mass decline with increasing age, drugs that distribute in this compartments, such as antibiotics, digoxin, lithium, and alcohol, may have a lower Vd and can, therefore, achieve higher concentrations from given amounts of drugs. On the other hand, drugs that distribute in body fat, such as many of the psychotropic agents, have a large Vd in the geriatric patients. The larger Vd will thus cause a prolongation of the half-life unless the clearance increases proportionately, which is unlikely to happen with age (Beyth and Shorr, 2002).

As a good example of the necessary precautions that needs to be implemented in elderly patients, warfarin is an excellent candidate because it has been used more often in older persons. Warfarin inhibits the 4 vitamin K–dependent coagulant proteins, factors II, VII, IX, X, and it is highly protein-bound (97–99%) which could be a problem in malnourished patients, metabolized in the liver and with a half-life of 42 hours, its onset of action is approximately 36–72 hours, with a peak effect within 5–7 days.

Warfarin has been proven to be effective in prophylactic or therapeutic anticoagulation, but the risk of major bleeding with increasing levels of (prothrombin time/International Normalized Ratio) PT/INR is a major concern; they are increased by the presence of comorbid conditions such as heart failure, liver or kidney failure, or cancer. Warfarin dose should be highly individualized and may have to be adjusted several times, based on laboratory test results depending on the target INR for the patient's condition; strict adherence to the prescribed dosage schedule is necessary and patients should be informed not to take or discontinue any other medications, except on the advice of a physician or pharmacist.

In elderly patients, initial doses of warfarin typically are lower, and INR monitoring should be performed more frequently, and because warfarin possesses numerous drug interactions, some of which increase the effects of warfarin

Table 3 Metabolism of some drugs by the hepatic cytochrome P450 system is altered by aging

	Cytochrome P450				
	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Substrates	Olanzapine Theophyline	Phenytoin Warfarin	Diazepam Omeprazole Phenytoin	Codeine Desipramine Haloperidol Metoprolol Paroxetine Risperidone	Alprazolam Nifedipine Terfenadine Triazolam Verapamil
Inducers	Omeprazole Smoking		Rifampin		Phenytoin St. John's Wort
Inhibitors	Cimetidine Ciprofloxacin		Amiodarone Fluconazole		Erythromycin

and others that decrease its effects, caution must be observed when any drug, herbal, nutritional supplement or dietary changes are made to existing regimen of a patient receiving warfarin.

METABOLISM AND DRUG CLEARANCE

The liver represents the major site of metabolism for many medications. Hepatic transformations of drugs are categorized into phase I (preparative) and phase II (synthetic) reactions. Phase I reactions include oxidations (hydroxylation, N-dealkylation, and sulfoxidation), reduction and hydrolyses. Phase II reactions involve conjugation of the drug molecule to glucoronides, sulfates, or acetates. There is evidence of decline in phase I reactions with increasing age, and that the decline is more prominent in men than in women. In contrast, the second phase of drug metabolism appears to be less affected by age. There is also evidence that the ability of environmental factors (most importantly smoking) to induce drug-metabolizing enzymes declines with age (Routledge and O'Mahony, 2003).

Significant age-related declines in liver size and in liver blood flow have been described; in terms of absolute hepatic blood flow, reductions of 25 to 47% reported in persons between the ages of 25 and 90. This decrease is clinically important because hepatic metabolism is the rate-limiting step that determines the clearance of most metabolized drugs. This effect is especially relevant for drugs that undergo rapid hepatic metabolism (e.g. propranolol). Also, drugs that undergo extensive first-pass metabolism are likely to reach higher blood levels if hepatic blood flow is decreased.

The cytochrome P450 (CYP) system located in the smooth endoplasmic reticulum of hepatocytes, is the main catalyzer of phase I reactions. Many isoforms of CYP exist; the most important being CYP 3A4, approximately 60% of CYP enzymes are found in the liver and the remainder are found in the intestine, kidney, and brain. Many commonly prescribed medications serve as substrates for these enzyme systems. Phase I metabolism often undergoes a substantial decrease in activity in elderly patients as a result of illness or drug interactions; drugs that are metabolized through phase I enzymatic activity will have prolonged half-lives, but there is no easy way to predict the effects of changes in phase I metabolism in an individual patient or to adjust maintenance doses of drugs that undergo this form of metabolism (Routledge and O'Mahony, 2003; Table 3).

In contrast, phase II hepatic metabolism involves the conjugation of drugs or their metabolites to organic substrates. The elimination of drugs that undergo phase II metabolism by conjugation is generally less altered with age. Thus, drugs that require only phase II metabolism for excretion do not have a prolonged half-life in older people (Beyth and Shorr, 2002).

ELIMINATION AND RENAL EXCRETION

Unlike those of metabolism, the effects of aging on renal functions are somewhat more predictable. The tendency for renal function to decline with increasing age can affect the pharmacokinetics of several drugs (and their active metabolites) that are eliminated predominantly by the kidney. Clearance of drugs from the body occurs more slowly, their half-lives are prolonged, and there is a tendency to accumulate to higher drug concentrations in the steady state (Table 4).

Although blood urea nitrogen (BUN) and serum levels may be useful (albeit crude) markers of renal function, it must be remembered that each is susceptible in its own way to perturbations that can occur with aging but have nothing to

Table 4 Medications with decreased renal excretion

Triamterene	Atenolol
Sotalol	Amantadine
Procainamide	Ampicillin
Ranitidine	Cimetidine
Pancuronium	Cephradine
Phenobarbital	Ceftriaxone
Penicillin	Digoxin
Lithium	Furosemide
Kanamycin	Doxycicline
Hydrchlorothiazide	Gentamicin

do with renal function itself. For example, the BUN reflects the concentration of urea in the blood. However, the origin of much of this urea is ingested protein, so that a malnourished older patient may not consume enough nitrogen to produce an appropriate rise in BUN, even in the face of renal impairment. Similarly, creatinine is produced by muscle, and if a patient has a markedly diminished muscle mass, whether because of chronic illness or any other cause, he or she may not produce enough creatinine to reflect a change in the ability of the kidney to excrete this substance. This, overreliance on normal appearing BUN and creatinine in older patients can severely underestimate the degree of renal impairment. Further decrement in renal function is common in the elderly because they frequently have chronic illnesses that affect the kidney such hypertension, diabetes mellitus, and atherosclerosis.

Early cross-sectional studies of renal function in aging suggested that there is a linear decrease in renal function between young adulthood and old age, amounting on average to a reduction in glomerular filtration rate by nearly a third. The average clearance declines by 50% from age 25 to 85, despite the serum concentration that in healthy adults remains unchanged. Because the serum levels tend to overestimate the actual clearance in older persons, the commonly cited formula devised by Cockcroft and Gault may be used to estimate clearance in older adults (Muhlberg and Platt, 1999). However, it should be recognized that this equation represents a poor approximation of renal function in the old-old.

$$\mathrm{CrCl} = \frac{(140\text{-age}) \times \text{weight (kg)}}{70 \times \text{serum Cr}}$$

(for women, multiply $\times 0.85$)

Altered renal clearance leads to two clinically relevant consequences: (1) the half-lives of renally excreted drugs are prolonged and (2) the serum levels are increased. For drugs with large therapeutic indexes (e.g. penicillin), this is of little clinical importance; however, for drugs with narrower therapeutic index (e.g. digoxin, cimetidine, aminoglycosides), side effects may occur in older patients if a dose reduction is not made. Thus, digoxin is the drug that most often causes side effects in the elderly, especially when doses exceed $0.125\,\mathrm{mg\,day^{-1}}$. To further define dose requirements, therapeutic drug monitoring is useful for doses of drugs with a low therapeutic index (Muhlberg and Platt, 1999).

A common goal of pharmacotherapy in older persons is to achieve and maintain a therapeutic steady-state serum concentration. The steady-state drug concentration is proportional to the medication dosing rate and is inversely proportional to drug clearance. This equality has a number of important ramifications for the prescriber. Although drug clearance is a biologically determined characteristic of each patient over which the prescriber has no control, dose and dosing interval are variables that can be modified. To prevent the excessive accumulation of a drug when its clearance is reduced, one can reduce the dose, increase the interval between doses or both, depending on the situation.

PHARMACODYNAMICS

A proportion of the drug or its active metabolite will eventually reach its site of action. Age-related changes at this point, that is, responsiveness to given drug concentrations (without regard to pharmacokinetic changes) are termed *pharmacodynamic changes*.

Pharmacodynamics has been less extensively studied in older patients than pharmacokinetics. Generalizability is not straightforward; the effect of age on drug sensitivity or the binding of drug to receptor sites varies with the drug studied and the response measured. These differences in sensitivity occur in the absence of marked reductions in the metabolism of the drug and its related compounds (Beyth and Shorr, 2002).

Older persons are often said to be more sensitive to the effects of drugs. For some drugs, this appears to be true; however, sensitivity to drug effects may decrease rather than increase with age. For example, older persons may be more sensitive to the sedative effects of given blood levels of benzodiazepines but less sensitive to the effect of drugs mediated by β-adrenergic receptors; thus, the sensitivity to drug effects may either increase or decrease with increasing age. Other possible explanations offered for these differences are alterations in second messenger function and cellular and nuclear responses.

In general, and because the response of older patients to any given medication is variable, medications should be used with caution to achieve the goal of minimizing risks. This problem could be minimized by knowing the pharmacology of the drugs prescribed, limiting the number of medications used, determining the dosage and preparation on the basis of the characteristics of each individual patient, with downward adjustment for known hepatic or renal illness, and by surveying for side effects (Table 5).

PHARMACOGENETICS

This novel area of research and development in the medical sciences has been defined as the identification of differences in drug effects that have a genetic basis, but also development of simple methods by which susceptible individuals can be recognized before the drug is administered.

Table 5 Examples of adverse drug reactions

Type of drug	Common adverse reaction
Aminoglycosides	Renal failure, hearing loss
Anticholinergics	Dry mouth, delirium, constipation
Narcotics	Constipation, sedation
Diuretics	Dehydration, hyponatremia, hypokalemia, Incontinence
Sedative-hypnotics	Excessive sedation, delirium, increased risk for falls
Antiarrhytmics	Diarrhea, urinary retention
Antipsychotics	Delirium, sedation, extrapyramidal movements

It has been said that the major concern of pharmacogenetics is related to using information about how the effect of variations in the genetic makeup could affect the clinical efficacy of drugs, the required dose of drugs, the choice of the correct agent and the risk for side effects to drugs (David, 2004).

The fundamental theory of pharmacogenetics states that genotype effects expression of genes resulting in a phenotype, and the expression of genes is modified by agents in the environment as well. Conversely, the expression of the gene may influence the efficacy of a drug by effecting its metabolism, availability at its site of action, and by how the drug binds to its target receptors and achieves a desired pharmacologic action. The rapid growth of pharmacogenetics has been helpful in terms of rapid identification and gene sequencing for drug targets, including receptors, transport proteins, ion channels, and enzymes that metabolize drugs (David, 2004).

Current available data on pharmacogenetic research has shown that it will be useful in the near future since the therapeutic-pharmacological approach in many chronic diseases is promising. For example, in chronic conditions or environmental exposures like nicotine addiction, the response of smokers to drugs for smoking cessation differ according to variations in genes encoding several receptors and enzymes. Genetic variation that affects the function and availability of proteins (dopaminergic DRD2-C32806T receptors, and the enzymes dopamine β-hydroxylase DBH-G1368A) could increase the efficacy of drugs for smoking cessation (David, 2004).

In the specific case of Alzheimer's disease, several mutations and polymorphisms, including apolipoprotein E4, have been associated with increased risk for Alzheimer's disease. Furthermore, clinical trials demonstrate that carriers of the APOE E3 allele respond better to cholinesterase inhibitors than those who lack the allele. There is also evidence that treatment response to noncholinergic drugs is affected by the APOE gene and that response to cholinesterase inhibitors is influenced by interactions with other genes involved in drug metabolism.

Another example of how pharmacogenetics is helpful is in the treatment of hyperlipidemia, where genetic variations at the APOE locus has been associated with fasting and postprandial plasma lipoprotein concentrations and with cardiovascular disease. The APOE E2 polymorphism is associated with an increased lipid-lowering response to statin therapy, whereas E4 polymorphism is associated with a decreased response to therapy. However, testing for this genetic variation is not yet part of routine clinical care.

In the near future, pharmacogenetics will give the chance to provide to our patients information about their probability of responding to treatment with a particular medication, given their genotype. Although the discipline is beginning to come of age, only some of pharmacogenetic applications are available currently in clinical settings, whereas many promise to enter the realm of clinical practice in the next few decades (David, 2004).

PRESCRIBING FOR GERIATRIC PATIENTS

The Beers Criteria, a Useful Consensus for Inappropriate Medication Use in the Elderly

The purpose of this initiative was to revise and update criteria for potentially inappropriate medication use in adults aged 65 and older in the United States. The reviewed criteria covered two types of statements: (1) medications that should be avoided in persons older than 65 years and (2) medications that should NOT be used in persons known to have specific medical conditions (Fick and Cooper, 2003).

The Beers criteria identifies 48 individual medications or classes of medications to avoid in older adults and their potential concerns and 20 diseases and conditions and medications to be avoided in older adults with these conditions. Adverse drug events have been linked to preventable problems in the elderly patients, such as depression, constipation, falls, immobility, confusion, and hip fractures.

The 1997 study on adverse drug reactions found that 35% of ambulatory older adults experienced an adverse drug event and 29% required health-care services; some nursing facility residents have one of these events over a 4-year period. In summary, these criteria have been extensively used for evaluating and intervening in medication use in older adults over the past decade. However, owing to the continuous arrival of new medications in the market, increased knowledge about older drugs and side effects from the new ones needs to be updated periodically in order to keep physicians updated on how to avoid undesirable medication side effects in the elderly population (Table 6; Fick and Cooper, 2003).

Clinical Strategies

The quality of life for the older patient can be greatly enhanced with the intelligent use of medications and keeping certain key points in mind. A major problem when facing elderly populations is the fact of prescribing multiple and occasionally unnecessary medications with increased risk of significant drug interactions; establishing a diagnosis is critical to avoid treating a symptom with *hit* or *miss* drugs versus treating a specific condition. Discussions about geriatric pharmacology are frequently centered around age-related changes in drug pharmacokinetics and pharmacodynamics; nonetheless, nonpharmacological factors can play an even greater role in the safety and effectiveness of drug therapy in the geriatric population.

Frequently, neither the patients nor the health-care provider have a clear picture of the total drug regimen. New patients undergoing initial geriatric assessment should be asked to empty their medicine cabinets and to bring all bottles to their first appointment. When asking the patient about their medication, it is important to be specific about prescription medications, over-the-counter products, as needed medications, vitamins, minerals herbal products and home remedies (Cassel and Leipzig, 2003).

Table 6 Inappropriate medication use in older adults: considering conditions and diagnoses

Disease	Drug	Comment
Heart failure	Disopyramide and high sodium content drugs (alginate, bicarbonate, phosphate)	Negative inotropic effect. Potential to promote fluid retention and exacerbation of heart failure
Hypertension	Phenylpropanolamine hydrochloride (removed on 2001), pseudoefedrine, diet pills, and amphetamines	May produce elevation of blood pressure secondary to sympathomimetic activity
Gastric or duodenal ulcers	NSAIDS and aspirin >325 mg per day	May exacerbate existing ulcers or produce new ones. (cox-2 excluded)
Seizures or epilepsy	Clozapine, chlorpromazine, thioridazine	May lower seizure thresholds
Blood clotting disorders, or on anticoagulant therapy	Aspirin, NSAIDS, dipiridamol, ticlopidine, clopidogrel	May prolong clotting time and elevate INR values or inhibit platelet aggregation resulting in increased potential for bleeding
Bladder outflow obstruction	Anticholinergics and antihistamines, GI antispasmodics, muscle relaxants, anticholinergics, antidepressants	May decrease urinary flow, leading to urinary retention
Stress incontinence	α-blockers, anticholinergics, tricyclic antidepressants, and long acting benzodiazepines	May produce polyuria and worsening of incontinence
Arrhythmias	Tricyclic antidepressants	Proarrhythmic effect and ability to produce QT interval syndrome
Insomnia	Decongestants, theophylline, methylphenidate, and amphetamines	Concern to CNS stimulant effects
Parkinson disease	Metoclopramide, conventional antipsychotics	Concern about anticholinergic/dopaminergic effect
Cognitive impairment	Barbiturates, anticholinergics, antispasmodic, muscle relaxants	Concern due to CNS altering-effects
Depression	Long-term benzodiazepine use, sympatholitic agents (methyldopa, reserpine)	May exacerbate depression
Anorexia and malnutrition	CNS stimulants, fluoxetine, methylphenidate	Concern due to appetite suppressing effects
Syncope/falls	Short to intermediate acting benzodiazepines, tricyclic antidepressants	May induce ataxia, impaired psychomotor activity
SIADH/hyponatremia	Fluoxetine, citalopram, fluvoxamine, paroxetine, sertraline	May cause SIADH
Obesity	Olanzapine	May stimulate appetite
COPD	Long acting benzodiazepines, propranolol	May induce respiratory depression
Chronic constipation	Tricyclic antidepressants, anticholinergics, calcium channel blockers	May exacerbate constipation

Source: From Archives of Internal Medicine **163**(22); Dec 2003, pg 2716–24.
NSAIDS, nonsteroidal anti-inflammatory drugs; CNS, central nervous system; SIADH, syndrome of inappropriate ADH secretion; COPD, chronic obstructive pulmonary disease.

Compliance

Compliance is a major problem in all persons, and particularly so in many older persons. Cognitive impairment, depression, decreased hearing, and poor vision can all lead to failure to take a drug or for the drug to be taken inappropriately. Instructions on how to take drugs need to be written in large letters with legible handwriting. The healthcare professional needs to check that the patient understands the instructions. Pill boxes need to be set up for older persons having problems remembering to take their medicines.

When choosing the dose of a medication for an older patient, always remember to *start slow, go slow, and do not stop too soon.* Initially, doses should be modified on the basis of pharmacokinetic predictions, but actual pharmacodynamic responses to the medication should be used to adjust the dose. If the pharmacokinetic information is not available, doses can be initiated at one half the usual dose of adult dose; this can be achieved by splitting tablets or by extending the dosing interval. Minimizing the number of doses per day is easier for the patient and can improve compliance. The use of sustained release dosage forms or taking advantage of prolonged elimination half-lives in older persons can decrease the number of doses per day (Table 7).

Cost is key factor in compliance. Drug costs need to be noted at the time of prescribing. Patients need to be asked if they can afford the drug. It is useful to remember that cheap drugs (e.g. thiazides, β-blockers and reserpine) often perform approximately as well as more expensive drugs. Most pharmaceutical companies have programs to help persons obtain drugs they cannot afford.

There is an increasing recognition that failure to appropriately treat an older person may be as bad as over treating. For example, failure to use β-blockers following myocardial infarction would be a clear error of omission. Most older persons in nursing homes have osteopenia or

Table 7 General recommendations for geriatric prescribing

Source: Reproduced from Fick D *et al.*, 2003. Copyright American Medical Association.

osteoporosis, yet they do not receive calcium with vitamin D, and neither biphosphonates. Many older persons have anemia and chronic renal failure; despite evidence that treatment with erythropoietin or darbopoeitin α improves outcomes including quality of life, they are rarely prescribed. But, the other side of the coin is overtreatment of conditions, for example, there is no evidence for treating blood pressure below 160/90 mmHg in older persons and even less for primary prevention of heart disease by lowering cholesterol in octogenarians (Morley, 2003).

There are many factors that contribute to the underuse of beneficial therapies in the geriatric patient population. Physicians may fail to prescribe potentially beneficial medications to elderly patients owing to the scarcity of data on which to base pharmacotherapeutic decisions or for fear of causing adverse drug events in patients who are already using multiple medications. While some may consider this practice to represent therapeutic nihilism, others may consider this to be prudent prescribing. A fair and balanced assessment of the issue of undertreatment of elderly patients must give consideration to three important areas: (1) the lack of high-quality evidence derived from clinical studies with relevance to treating the older patient with multiple chronic medical conditions; (2) the need for systems of care that improve drug safety and enhance adherence in elderly persons on complex medication regimens; and (3) the persistence of financial barriers to access to medications (Morley, 2003; Cassel and Leipzig, 2003).

The Division of Geriatrics at Saint Louis University has developed many different resources to teach physicians and patients as well in the field of geriatric medicine. The developing of mnemonics, that is the mnemonic developed toward avoiding polypharmacy, has been very successful.

GUIDELINES FOR PROPER MEDICATION PRESCRIBING AND MEDICATION REDUCTION

Alternatives
Vague history or symptoms
OTC (over-the-counter) medications have side effects too
Interactions (drug–drug, drug–disease)
Duration
Therapeutic vs Preventive
Once a day versus twice or four times a day
Other doctors
Money
Adverse effects of other drugs
Need
Yes/No (Is the person actually taking the medication?)

The use of large numbers of medications will always be a key factor of the medical–scientific care of the growing older population around the world. However, there is always a gray area where there is concern about avoiding the excessive use of drugs and providing access to therapeutic guidelines that might have beneficial effects on morbidity and mortality, function and quality of life. The health system should address this issue focusing on including more elderly people in clinical trials, especially patients with multiple comorbidities. The implementation of efforts toward the development of interdisciplinary teams to care for elderly patients and the use of information technology to improve medication adherence and safety should be encouraged.

KEY POINTS

- Older persons take more medications than their younger counterparts.
- The older body does not accommodate drugs in the same manner as the younger body does.
- There is no such thing as an absolutely safe drug.
- Elderly patients are more likely to experience undesirable side effects from drugs than are younger persons.
- Always “start slow, and go up slow”.

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21

The Problem-Orientated Approach to Geriatric Medicine

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INTRODUCTION

The transitional decades leading into the twenty-first century have seen a period of major organizational change in health-care systems, with a major focus on economic concerns. The health-care needs of aging populations have been economically, if not scientifically, prominent within this process. The compulsion to justify patterns of clinical practice with hard evidence has grown, while this in turn has led to the more widespread development and application of sets of clinical management guidelines and the need for more consistent documentation in clinical practice.

To some extent, the professions concerned with the care of older people have welcomed the impetus to record and quantify their activity in this way, thus to achieve greater consistency, to promote greater recognition of the skilled processes involved (and of the corresponding standards), and to make the case for more appropriate resource provision in the field for services, training, and research. On the other hand, much organizational change (including the growth of documentation) has to some extent generated bureaucracy and impaired flexibility of interaction among the professions and agencies involved. The need, therefore, not only to sustain the best qualities of clinical practice enshrined within geriatric medicine but also to grasp the opportunities presented by a changing organizational climate to categorize and promote those standards is clear.

There has, as a result, been some progress in the development of methodologies to measure activity, but with a distinct slant toward what is required either for cost prediction or cost containment, for the management of defined diagnostic categories, or for modeling the activity of single professions. Examples have included the system concepts of diagnosis-related groups (Goldfarb *et al.*, 1983; Wood and Estes, 1990; Price, 1994), managed care (Wan, 1989; Curtiss 1989) and critical care pathways (Falconer *et al.*, 1993; Bowen and Yaste, 1994; Tallis and Balla, 1995; Anders *et al.*, 1997) – most commonly for application to defined disorders or clinical situations. There is still a need for better methods of scrutinizing the quality and effectiveness of overall service provision for older people–the largest and most rapidly expanding segment of population health-care need.

Categorization is not, however, synonymous with the achievement of standards, although it is a useful instrument in the right hands for service delivery, training, and research. This chapter, therefore, discusses some key principles of problem-orientated decision making in the care of older people (which have not themselves fundamentally altered over this period) rather than pursuing a primary emphasis on measurement methodology, although some measurement tools will be referred to. This somewhat didactic emphasis reflects not only a concern to focus on consensus standards but also the relative paucity of focused evaluative work in this area specific to the health needs of older people. There is a pressing need for comparative trials of delivery models using such standards as end-points, not least because every available indicator suggests that the cost-effectiveness of health services for older people is directly proportional to the expertize and quality of specialist practice achieved.

RATIONALE: PROBLEM ORIENTATION – WHY AND WHAT?

The concept of problem orientation as a practical approach to clinical decision making was elaborated by Lawrence Weed in his system of problem-orientated medical records (POMR) (Weed, 1969). Targeted particularly at clinicians, it was in some respects a precursor of the current fashion

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for "protocols". The motivating principle was a recognition that the traditional "ideal medical model" (syndrome → pathological basis → etiology → treatment → resolution) is in the real world a gross oversimplification of the decision-making process, based as it is on a single train of thought arising from a single encounter with the patient. In real life clinical practice, the clinician is often faced with several related and/or unrelated problems simultaneously, while the patient is faced with several encounters over a period of time with several clinicians (across a range of professions) before some or all of these problems are properly resolved. There is, therefore, a need for accurate and cohesive documentation. This is to provide a reliable and consistent framework of information on which to base decisions and also to achieve a measure of continuity across periods of time, as well as among different clinicians and departments.

The key components of the original Weed system are:

1. an accurate list of presenting problems;
2. a "defined database" (full coverage of agreed categories, e.g. in case history taking or examination);
3. statements of plans of investigation and/or management related to each presenting problem;
4. progress notes comprising a systematic assessment of progress and a statement of further plans in relation to each problem (McIntyre, 1979).

Historically, the fully developed system of POMR did not find its way into the routine practice of most clinicians, nor into all teaching programs. Opponents claimed that the database was too diffuse, that the "catalog" of problems inhibited diagnostic reasoning, or that the day-to-day implementation of POMR was too unwieldy and heavily structured to be routinely workable (Feinstein, 1973). The advocates maintained that comprehensive patient care, interdisciplinary professional working, and clinical audit were fundamentally advanced by POMR (McIntyre, 1979). It is certainly the case that the system properly implemented is more than a style of medical record keeping and is, in fact, a structured approach to clinical decision making, based on a standardized system of documentation. Information technology advances present enhanced opportunities for using such methods more effectively, both in clinical practice and medical education (Weed, 1996).

The concept of problem orientation still strikes a chord, therefore, with experienced geriatricians, many of whom consider it to be a cornerstone of effective modern clinical practice in the field. The main reasons for this are:

1. *The historical failure of the "Ideal Medical Model" to meet the needs of older people*

The key to resolving any problem lies in its correct initial identification. The agenda presented to the earliest geriatricians was characterized as a *process problem* affecting the health-care system, namely overcrowding in poor law institutions, "blockage" of beds in "acute" hospitals, and waiting lists and delays affecting dependent elderly people in the community. The "geriatric problem" was seen as that of health-care providers facing a seemingly inexorable tide of chronically infirm elderly people, and, as a result, that of angry and frustrated clinical colleagues hampered (as they saw it) in practising "proper" medicine in hospitals and in teaching it to their junior staff and medical students. Thus, the issue was perceived as one of accommodation, not at all as one of diagnosis and intervention.

What in fact took place was a shift in focus and orientation, recognizing the agenda in terms of the *health-care problems of older people themselves*, an emphasis that the clinicians of the day had omitted to address. Skill in diagnosis was combined with systematic identification of the functional and social consequences of ill health and a plan of management agreed in conjunction with an organized team of allied professionals. The success of this changed emphasis is now legendary (Brocklehurst, 1992) and has been replicated and refined many times over, particularly when brought into the arena of early acute intervention.

2. *The complex nature of health-care needs in late life*

- Exacerbation, relapse, recovery: The proportion of medical conditions alleviated rather than eradicated increases with advancing age. Successive clinical encounters thus tend to become the rule.
- Cumulative pathology: Case record folders, best measured in kilograms rather than pages, commonly testify to the numerous departments previously involved in the care of a majority of older patients.
- Masked and/or late presentation of disorders.
- Multidimensional impact: The management of pathology alone is insufficient to achieve a satisfactory outcome in most circumstances. Hence, the scope of the "database" has to encompass the problem of functional autonomy and social relationships arising not only from disease, but from aging itself.
- Multiagency/multiprofessional involvement: Access to reliable information is required by all.
- Orchestration/coordination of multiple assessments and therapeutic objectives.

Problem orientation is thus, to some extent, built into the heart of geriatric medicine. Weed (1969) emphasized the importance of dividing problems into medical and social. For the geriatrician, the overriding objectives of autonomy and self-determination for older people add an additional dimension, that of "function". The definition of a problem thus includes any observation or finding that poses a threat to the health or autonomy of an older individual. The approach does not, of course, supplant the search for unitary diagnosis. It does, however, recognize parallel priorities that may sometimes take precedence.

APPLICATION: PROBLEM IDENTIFICATION AND MEASUREMENT

Assessment as Problem Orientation

The approach to comprehensive patient care adopted within geriatric medicine is commonly given the label "assessment."

(The particular area of functional assessment is elaborated in greater detail in **Chapter 131, Multidimensional Geriatric Assessment**; **Chapter 132, Function Assessment Scales**). Assessment is in essence the preparation of a problem list in the following categories:

1. Problems of medical, surgical, and psychiatric diagnosis.
2. Problems of autonomous function or competence.
3. Problems of relationships.
4. Problems of living conditions and environment.

Successful assessment should be factual, prompt, efficient, and dynamic (i.e. subject to regular review as a health problem pursues its clinical course, or as new information becomes available). Its components should take place simultaneously, and from the moment of presentation. Assessment as an afterthought to acute medicine is far too late. In the context of emergency hospital admission, the process may well be initiated by ambulance personnel.

Preparation of the "database" will incorporate a thorough scrutiny of previous case records and a highly systematic review of a patient's functional and social background. The latter may entail the acquisition of information from many sources, more closely resembling a piece of journalistic research than a consultation. Weed (1969) advocated the inclusion of a "personal patient profile" in the database. This is desirable in all branches of medicine, but is mandatory in geriatric medicine. The whole process is likely to take considerable professional time and effort; thus, any sense of day-to-day inertia in a unit caring for older people indicates that the work is not being covered.

All clinical professionals, especially physicians, need to adopt this comprehensive, multidimensional approach in a systematic way. In order to achieve this, it is highly probable that an acceptable structured form of documentation will be required.

Problem Identification and the Multidisciplinary Team

The composition of a more or less typical multidisciplinary team is indicated in Figure 1. This core team composition has so far stood the test of time as reflecting the blend of competence required to provide information, expertize, and advice in the four problem domains itemized earlier. It is sufficiently small to achieve consensus and make efficient decisions, but depends on *ad hoc* contributions from many other professionals, including dietitians, clinical pharmacists, home-help organizers, prosthetists, transport and portering staff, housing and environmental officers, residential home and sheltered housing supervisors, as well as from various informal supporters and voluntary organizations. Within the team, each professional retains his or her traditional competence, but there is sometimes modification of that function, and invariably heightened awareness of the competence of others arising from cross-fertilization and the team context. The multidisciplinary team is the mandatory core unit central to both problem identification and to decision making and to efficient therapeutic management. (The respective roles of some of its constituent members are considered briefly in the following).

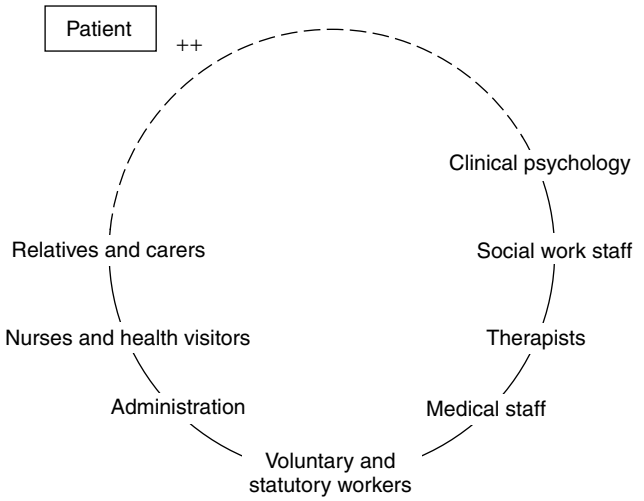

Figure 1 The multidisciplinary network

Objectives and Pitfalls

Problem identification with no prospect of constructive intervention is an academic and largely pointless exercise. Conversely, efficient "management by objective" distinguishes a *problem* from a mere *observation* by the existence of at least some possibility of resolution. Successful problem orientation recognizes and avoids the following well recognized pitfalls, which are more or less common themes across the professions:

Diagnostic overindulgence: Consultant physicians rely heavily on their junior staff to sharpen both their knowledge base and their diagnostic acumen: they have, however, a time-honored duty to protect patients (particularly older ones) from the overzealous pursuit of diagnosis with no prospect of therapeutic benefit. Similarly, for therapists, preoccupation with the use of a "perfect" functional assessment tool to quantify an impairment, the clinical or potential therapeutic relevance of which is dubious, should be avoided.

Therapeutic overindulgence: This is the targeting of some isolated "ideal" therapeutic objective for an individual at the expense of the broad aim of that individual's overall recovery of autonomy. Examples might include total abolition of extrasystoles on a 24-hour ECG, or the relentless pursuit of impeccable gait symmetry before hospital discharge after stroke.

Collective introspection: There is considerable scope in an interdisciplinary context for lengthy in-depth case analyses of individual patients, consisting of a sequential series of explanations from every conceivable discipline as to why

no help can be offered with the particular problem. "Case conferences" in this mold have more to do with professional self-interest than patient well-being and should not be held.

Bureaucracy and delay: The notion that ill older people are less "acute" and that waiting lists for services are "acceptable" has compromised the effectiveness of clinical and social services for decades. A night sitter in 3 months' time is of no use to a caring spouse facing a crisis of sleep deprivation. A waiting list of 8 weeks for the installation of stair rails may do untold damage to the resettlement program of a stroke sufferer. Thus, the 2001 England National Service Framework for Older People correctly set standards for prompt and integrated community equipment supply (Department of Health, 2001a). Successful problem-orientated assessment promotes anticipation, planning, interaction, and flexibility of response among professionals and agencies. Timing may be critical, both to the individual and to the service, and its mastery is a hallmark of effectiveness in the care of older people. A central agenda item for multidisciplinary teams is therefore the agreement of a finite and preferably rapid timetable for the individual care plan.

Inappropriate expectations: Consumer choice in medical care is a topical political issue. It is also a proper objective for physicians, but there is a compelling obligation to identify the choices correctly. A clinician may, for example, have a hard battle to persuade an older person or her relatives that recovery of autonomous function and a return to community living are among the options! Conversely, it may be necessary to dispel unrealistic expectations of miracle recovery, wonder drugs, or costly biotechnology. The clinician's advisory role may be the less popular one of offering limited (but important) improvement through persistence with clear, if modest, objectives. A frequent further element is an appropriate culture of risk taking, without which no rehabilitative program can proceed.

CONTENT: PROBLEM CATEGORIES

The modifying effect of age on the presentation of many specific disorders is covered elsewhere in this volume. In addition, the medical, functional, and social aspects of the health of older people are in a continuous state of dynamic balance and interaction. A problem in any one category seldom exists in isolation without impact on one or both of the other two. Presentation may be functional when the root cause is medical; for example, reduced mobility or falls may result from infection or adverse drug reactions. Conversely, stasis leg ulceration or venous thromboembolism may be caused by impaired function (loss of mobility). Poor housing may be responsible for osteomalacia or hypothermia, while problems of continence or pressure sores may be the culmination of intolerable stress on a caring relative. Exclusion of any one dimension of concern from the assessment is therefore to invite failure.

Medical Problems

Geriatric medicine is rightly concerned with a whole range of clinical situations, including acute life-threatening illness, acute exacerbations of chronic disease, subacute, or chronic health problems, disabling disorders of high prevalence among older people, the assessment and management of special clinical problems (e.g. the "geriatric giants" of cognitive impairment, immobility, and incontinence) and the preventative medicine of old age. Both the importance and the difficulty of careful and accurate diagnosis are well recognized.

Principles of diagnosis: The opposing extremes of academic interest and diagnostic apathy, therapeutic overoptimism and therapeutic nihilism, are unacceptable pitfalls in clinical practice from which older people have suffered extensively. Thorough investigation may be justified on the grounds of (1) therapeutic potential, (2) practical management, and (3) (under certain circumstances) prognosis. In considering any investigation, particularly if at all invasive, the question "how will the results influence management"? is always legitimate, but interpreting the answer for an older patient increasingly requires careful review of recent advances and should invariably be a flexible and sensitive exercise.

Therapeutic potential: It is now clear for many interventions, both medical and surgical, that conservatism based on chronological age alone has no foundation in scientific evidence. Large-scale clinical trials have shown for a whole range that results and cost-effectiveness are at least as satisfactory in older as in younger patients. Examples include:

- effective control of hypertension (SHEP Cooperative Research Group, 1991; Amery *et al.*, 1986; Lever and Brennan, 1993; Dahlof *et al.*, 1993; Julius *et al.*, 2004),
- antithrombotic agents in atrial fibrillation (Ezekowitz *et al.*, 1993; Stroke Prevention in Atrial Fibrillation Study, 1991; Connolly *et al.*, 1991),
- thrombolytic agents and aspirin in myocardial infarction (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico, 1990; ISIS-2 (Second International Study of Infarct Survival) Collaborative Group, 1988; ISIS-3 (Third International Study of Infarct Survival) Collaborative Group, 1992; The GUSTO Angiographic Investigators, 1993),
- angiotensin converting enzyme inhibitors and angiotensin-2 antagonists in left ventricular dysfunction and after myocardial infarction (ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group, 1995; Granger *et al.*, 2003; Pfeffer *et al.*, 2003),
- lipid lowering agents in cardiovascular risk (Shepherd *et al.*, 2002),
- bone antiresorptive agents and calcium and Vitamin D in fracture prevention (Chapuy *et al.*, 1994; Larson *et al.*, 2004).

Persuading surgical colleagues of therapeutic potential from surgery in older people is now far less often a problem

than formerly, as a result of advances in anesthetic and surgical techniques and of rapidly expanding experience of surgery in the age-group. An excellent example is carotid endarterectomy after stroke (Alamowitch *et al.*, 2001; Aune *et al.*, 2003).

Logistics: In view of the above, there can be no justification for the organization of services in such a way as to exclude older people from sophisticated diagnostic and treatment facilities, or to undertake their care in less technically well supported environments (Working Party of the Royal College of Physicians, 1994). Equally, the role in interdisciplinary practice of physicians trained in the care of older people is clear. The difficulties of prompt diagnosis are well recognized. Symptomatology is notoriously unreliable. The "presenting complaint" frequently bears no relation to the real problem. Occult disease and presentation as stereotypes of aging pose a constant challenge. Physical signs may be modified, unreliable, or absent. As suggested earlier, any unexplained change in function in an older person should prompt the search for a medical diagnosis.

The place of structured models of clinical decision making in medicine is yet to be established and would require specific evaluation for older patients. The relative merits of different processes of diagnostic logic have been considered (McCartney, 1987). Problem orientation has been criticized as having some affinity with the "blunderbuss" approach (uncritical listing of clinical observations and ordering of every conceivable test). This criticism arises mainly from a perception of the database as a cataloguing process to prevent missing any abnormalities. This is unfair to the original concept. It also assumes that the database is totally prescribed rather than flexibly determined for different categories of patient. There is no evidence that problem orientation has a negative effect on diagnosis in the elderly. Other approaches (e.g. the hypothetico-deductive model, algorithmic diagnosis, and league-table diagnosis or its mathematical equivalent, Bayesian probability analysis) (McCartney, 1987) are all potentially compatible with a problem-orientated approach.

The traditional systematic enquiry taught to medical students may be a sterile exercise in real life diagnosis (Hoffbrand, 1989), especially with older patients, for whom its verbal content requires considerable adaptation. Conversely, with the comparative rarity of single problems, the clinician will probably always need to explore a fairly large problem space both in history taking and physical examination to be sure of picking up the important points (Harrington, 1989). Common omissions from the medical assessment include failure to elicit abnormalities of mental status and their timescale, impairment of the special senses, scrutiny of drug therapy, dietary intake and alcohol consumption, examination of the locomotor system (especially the hip joints) and gait, problems of continence and their timescale, and detailed examination of the feet and hands. Important components of functional and social status (see following text) are also commonly overlooked.

Practical approaches to the application of these principles within geriatric medicine are discussed in other chapters in this text and elsewhere. The justification for a structured medical record as an absolute minimum seems incontestable.

Functional Problems

A detailed interest in levels and components of function is a strong distinguishing feature of modern geriatric medicine. It is unusual for health problems to have no short- or longer-term impact on an older person's range of activity. Measurement tools for the assessment of function are discussed in **Chapter 132, Function Assessment Scales** and the more difficult issues of their relative merits will not be considered here. There are considerable differences of opinion as to how broad functional status should be measured and documented and how change should be quantified. Largely because of this difficulty, the tendency both in service delivery and in health services research has been to opt for an increasingly widely accepted core set of "lowest common denominator" scales for the measurement of change, such as the Barthel Index, the Instrumental Activities of Daily Living scale or (in psychiatry) the Clifton Assessment Procedure for the Elderly (Pattie and Gilleard, 1975). Such tools are clearly not intended for more specialized measurement of impairments, or very specific disabilities, for which they lack sensitivity. Instead, they cover a key range of abilities, including, for example, the special senses and continence and/or their consequences for an individual's range of activities.

In principle, there are analogies in this field with the medical model; overemphasis on "diagnostic" categorization should not stand in the way of pragmatic problem-orientated assessment, but those measures that are required should be applied alongside it. The technical skills within the multidisciplinary team for specialized functional assessments reside predominantly with physiotherapists, occupational therapists, speech and language therapists, and clinical psychologists, but other team members, including medical and nursing staff, require a level of competence in the assessment and recognition of functional problems, for which the capacity to use a minimum set of more globally applicable instruments is necessary.

An example of a shorthand form of operational documentation for multidisciplinary decision making is shown in Figure 2, the essence of which is its problem-orientated emphasis. The domains covered are in common with a most general functional assessment scales, but each category of function is graded on a five point scale, the components of which attempt to quantify problems in terms of requirement for assistance or supervision from a third party, that is, "to what extent is the dysfunction an active problem requiring outside intervention?" Thus, if an individual is able independently to travel from point A to point B using a wheelchair, then "ambulatory function" is classed as unimpaired. Similarly, if he or she has an indwelling catheter, which is independently managed without difficulty and with

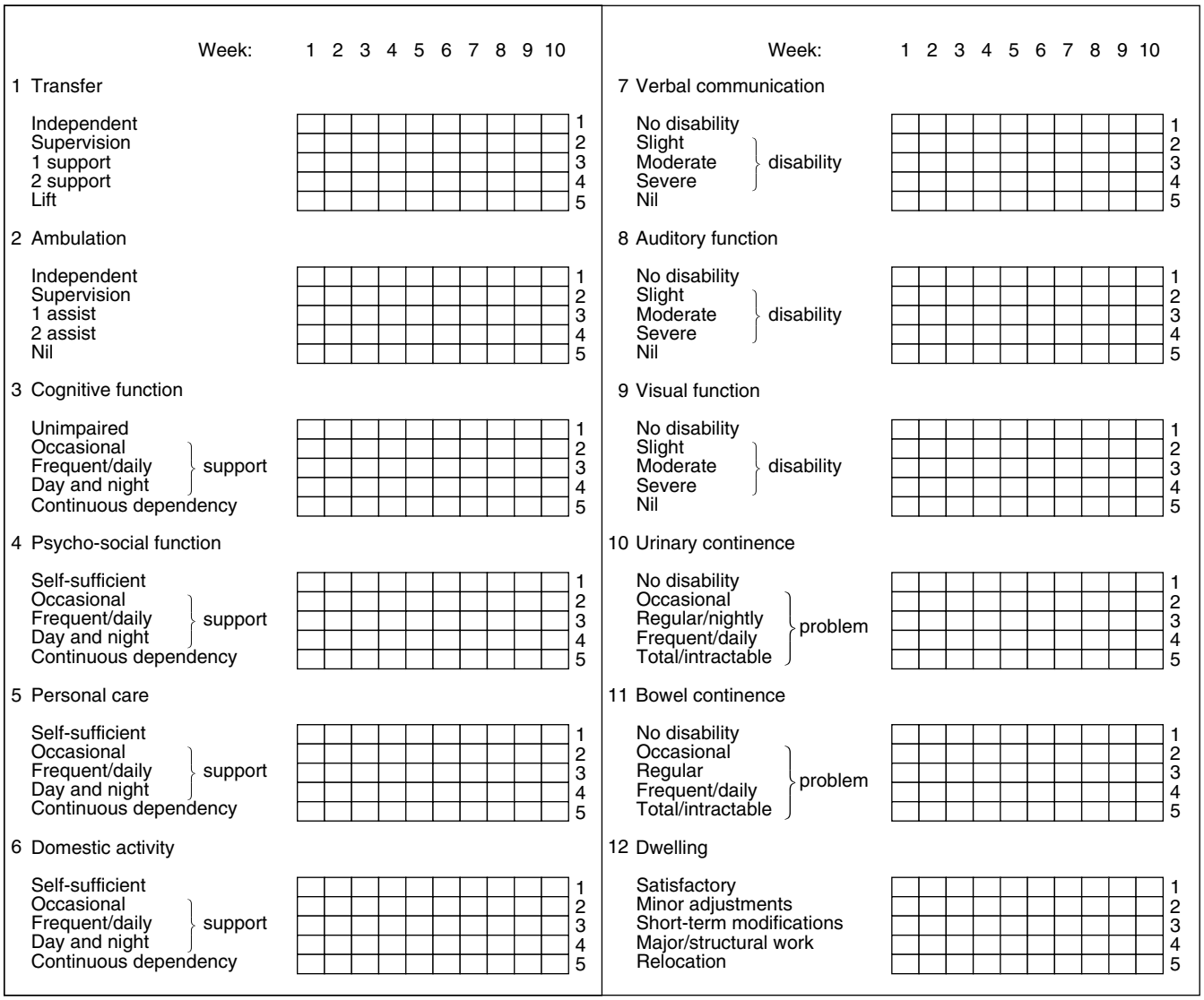

Figure 2 A shorthand operational chart for interdisciplinary decision making

no problems of bypassing or spillage, then urinary continence is classed as unimpaired. Where the criterion of extrinsic assistance is less clear-cut (e.g. in the case of auditory dysfunction), but the category of function is considered to be of major importance, then it is also included. The display and content are designed to be visual and operational rather than quantitative and specific, allowing any member of the team a rapid impression of a patient's functional status, as well as an indication of change over time.

Similar pragmatic and operational approaches to multidimensional assessment, decision making and documentation have been elaborated elsewhere, for example, in the context of community care (Donald, 1997) and rehabilitation (Turner-Stokes and Nyein, 1999; Nyein and Turner-Stokes, 1999).

As with medical diagnosis and treatment, functional assessment and the resulting rehabilitative strategies should be clearly linked to finite and time-limited objectives.

Relationship Problems

Although in this context the skills of social workers and clinical psychologists are vital, the cumulative information to be obtained from all professionals who interact with patients and/or their relatives is indispensable. It is salutary to observe how often the "social prognosis" is good. This reflects the phenomenal contribution to patient care (including "continuing care") made by the army of spouses, relatives, friends, neighbors, and other informal carers who provide governments with major annual savings. Contrary to popular perception, most families in the majority of countries in both the developed and the developing world still consider it the norm to be involved in the care of their older people and as a result, constitute the best possible target for the investment of money, manpower, and time by governments. The health-care services should be their enablers.

Presenting problems in these categories can often be traced to changed circumstances or failure of adequate provision. For older people on their own, the difficulties are often those of isolation or bereavement. Where others are involved, the problems include loss or withdrawal of support, carer stress, rejection (root causes of which may be simple, e.g. remediable disability, incontinence or sleep disturbance, or more complex, such as a long-standing failure of marital relationship) or relocation. Health-related events in older people commonly precipitate an acute imbalance in a fragile structure of family and social relationships. Failure to recognize and address these problems successfully contributes substantially to poor clinical and functional outcome and to health-care costs.

Environmental and Housing Problems

Poor quality: Responding successfully to problems of environment and housing remains a major difficulty in the health care of older people. Some of the more common problems are itemized in an earlier chapter. Housing design for late life has been inadequately addressed in the past and is still at a comparatively rudimentary stage (Frain and Carr, 1996). In addition, the capacity to carry out significant adaptations to existing homes is typically fraught with delay, lack of financial commitment, and bureaucracy. Although, in the United Kingdom, older people are more likely than their younger counterparts to occupy housing that lacks basic amenities, is unfit, old, and in poor repair (Department of the Environment, 1988) (especially private sector housing), adaptations can make a profound difference to the prospects for even the very disabled to remain in their own homes or return there after illness (Statham *et al.*, 1988). Unfortunately, the scale and nature of an individual's need for reorganization or adaptation of their home often cannot be determined until some time after the acute phase of illness, when a "plateau" of functional recovery has been reached.

Assessment: A common and important practice for older people undergoing hospital treatment is the home assessment visit prior to discharge. The work of the occupational therapist is paramount in this, both in assessing the individual's performance and advising on what changes, if any, are required. Not infrequently, the needs for rearrangement are minor inexpensive additions, such as grab rails or stair rails, but where there are problems of access, structural alterations may be necessary.

Relocation: Relocation to another area takes place among very elderly people more often than is commonly realized (Graham and Livesley, 1986). This may or may not be for good reasons (such as proximity to family, particularly where the latter have moved out of inner-city areas to the suburbs). Relocation at any time of life is known to be a stressful event and brings its own range of problems, such as loss of previous social contacts and difficulty in establishing new circles. The same may well be true of rehousing within the district or relocation into an institutional setting, although there is evidence that relocation between institutional settings well managed need not be deleterious (Harwood and Ebrahim, 1992).

Individual choice: Some older people are extremely reluctant to consider moving to new housing, even though the "ancestral" home may be falling around their ears. They may also be reluctant to consider structural alteration or even minor adaptations. The writer recalls an octogenarian double amputee, staked out in an ancient caravan heated by a paraffin stove in the middle of a farmer's field in the South West of England; he developed substantial cortical blindness as the result of occipital lobe infarctions. In spite of everyone's best efforts, he could not be persuaded to relocate and accepted the installation of a new electric mains cable and a safer form of heating, only with the greatest reluctance. In functional terms, however, his abilities within the caravan, the layout of which he knew well, proved to be superior to those within the hospital department, and the decision to support him in his endeavors was subsequently shown to be the correct one. The patient's wishes and preferences are commonly pivotal in housing and environmental matters and should be respected. Having identified the problems, a general rule of thumb is to err on the side of supporting an individual in his or her wish to take certain risks, provided everything possible has been done to minimize their scale.

The option of institutional care may appear at first sight highly preferable when environmental problems are identified, and there is commonly a range of pressures to pursue a "custodial" course under the pretext of greater safety. If other options are open, however, even to those with severe disability, there is a responsibility to identify these and to ensure that the choice which an individual makes is fully informed (Wanklyn, 1996). Too often, older people feel under constraint to "go into a home" because they have no apparent choice. The decision may subsequently be regretted for many years – life with no problems may not be life at all!

The institutional environment: Although there are improvements, institutional design has far to go before optimal standards are universally available. Many old converted premises are totally unsuitable for disabled people and carry their own hazards. There is a very high incidence of falls among elderly people living in institutional settings (Askham *et al.*, 1990) and it is simplistic to equate the institutional environment with "safety". Thankfully, very large numbers settle comfortably and happily into residential and nursing homes, but such a radical decision for an older person should never be made without careful consideration of the alternatives in the framework of a comprehensive problem-orientated assessment. Housing and environmental problems should be addressed in detail and resolved wherever possible, rather than compounded by ill-founded decisions in the direction of institutional care.

Social and environmental issues often require skilled counseling of older individuals, their relatives, and their supporters. This, like all other aspects of successful care,

should be an informed and coordinated team effort. All professionals involved in the medical care of older people should acquire counseling skills. It is well known that many complaints addressed to hospital administrators and managers can be traced back to inept communication.

IMPLEMENTATION: PROBLEM MANAGEMENT – ORGANIZATIONAL IMPLICATIONS

Information and Communication

Records: A central function of POMR is to make available to the clinician the necessary information for decision making more or less at a glance. Such information will be factual, reliable, and relevant, and presented in a format that can be quickly digested. Because of the complexities of a program of investigation and treatment for an older person with multiple problems, this facility is indispensable to the practice of geriatric medicine. The records departments of many large district general and teaching hospitals have so far been unsuccessful or incompletely successful in achieving this objective.

A major problem has been to achieve a synthesized account of functional assessments. The generation of a centralized, multidisciplinary problem-orientated patient record in a variety of formats is a practice that is becoming more widespread. The ideal objective is to have information sited with the individual and available for scrutiny by all professionals, whether in an inpatient setting (i.e. at the end of the bed) or in the community (i.e. with the individual in his or her home). This is one of the aims of the "Single Assessment Process" recommended in the England National Service Framework for Older People. (Department of Health, 2001b) The capacity to make such information available in electronic format (e.g. as "smart cards") presents significant opportunities for improved continuity of care of older people and warrants further evaluation in a service context.

Communications base: It is a common practice of many departments of geriatric medicine to run their own liaison offices. These serve as a central communication point for all enquiries and decisions requiring access to recent patient information. They commonly contain hard copy of recent discharge summaries and outpatient letters, together with other information such as day hospital discharge information or domiciliary assessment correspondence. Contact between professionals (such as a general practitioner-to-hospital telephoned referral) can thus be supported by instant access to a large body of recent summarized patient data on diagnosis, treatment and progress, medication, support services, social and environmental data – in fact, the components of a good problem-orientated record. This arrangement permits rapid decisions on assessment and practical management (including decisions on hospital admission) to be fully informed, thus, reducing the scale of misplacement, duplication of investigations, and delay in diagnosis.

Liaison office staff (normally trained administrative and clerical officers) progressively acquires the skills of handling enquiries and of interprofessional contact, and find a combination of such activity with record keeping both challenging and rewarding. Computerization of patient records has brought further advances allowing access (including out-of-hours access) for designated staff from remote terminals on wards and elsewhere. This contrasts sharply with the situation in some emergency departments and receiving wards, where older people, whose complex background is unknown and who are too ill or incapacitated to provide the necessary information themselves, undergo numerous (often duplicated) investigations and sometimes inappropriate treatment strategies, before the true nature of their underlying problems comes to light some days later.

Whatever organizational structure is adopted, the advantages of a coordinated single entry point to geriatric services are clear, particularly where such services are diverse.

Written interagency exchange: Such access to information is a cardinal requirement of problem-orientated clinical practice. Equally important is the quality and content of information exchanged between different treatment settings. An adequate medical discharge summary, for example, should incorporate a clear problem list, a short narrative section on presentation, progress, and management, a list of ongoing drug therapy with dosages, a clear statement of functional ability, relationships, environmental setting and any aids, adaptations or appliances, a list of domiciliary support services, and a clear statement of the future program of monitoring and follow-up. It should be brief, readable, and accurate.

Multidisciplinary Work Patterns

The multidisciplinary team is the nucleus not only of problem identification but also of management and implementation. Precise work patterns vary between departments, but every mainstream setting for the medical care of older people (e.g. the acute general hospital ward or day hospital) requires the support of a multidisciplinary team to be successful. It is common practice for the team to convene in association with every ward round or day hospital review. The meeting should be no more than a focus for ongoing and continual communication between team members.

A program of mobilization for a patient will, for example, go badly wrong if nursing staff and physiotherapists fail to maintain an effective dialogue and to agree identical approaches around the clock. If medical and social work staff are at cross-purposes in discussing options with patients and their relatives, then irreparable damage may be done to any strategies for return to the community. In the best departments, strong team identity develops with the recognition of mutual interdependence, flexibility over "demarcation" between disciplines, clear lines of accountability and not

uncommonly a little healthy interprofessional rivalry. Direct dialogue is one of the major strengths, for which written referrals or communications are no substitute.

Medicine: The physician within the team, who will require both training, experience, and specific skills in interdisciplinary practice, exercises the traditional functions of diagnostician, therapeutician, and prognostician, but recognizes that none of these can be satisfactorily achieved without substantial input from team colleagues. Their trained observations are crucial in diagnosis. The physician's knowledge and experience of the natural history of disease processes in late life are essential, particularly in assessing prognosis. In most settings, the physician carries the ultimate clinical and medicolegal responsibility for the admission and discharge of patients and has therefore a critical role in holding an overview, in realistic goal setting, and in timing the various stages of assessment and management.

Nursing: The nurse is in the best possible position to acquire a comprehensive day-to-day understanding of the problems confronting individual patients, because of the continuity of contact entailed (McGovern, 2002). He or she is best able to make the close and detailed observations on which correct diagnosis may depend and to obtain an understanding of psychological and emotional problems. The nurse will acquire first-hand awareness of a patient's personal care capacity and motivation and will have an enabling role in communication with the individual, with visitors and with all other professional staff involved. The "key worker" concept is often most readily applicable to the nurse and underlies modern approaches to primary nursing (McGovern, 2002).

The therapies: The expertize of therapists is paramount in defining and assessing problems of functional disability. They have the skills, necessary equipment, and measurement techniques to quantify the challenges involved in regaining autonomy, to present an accurate picture of performance capacity and to determine the strategies, facilitated relearning programs and therapeutic procedures required.

Social work: The role of the social worker in defining the contribution of problems of relationships (or lack of relationships), economic, and environmental problems, is critical. The wealth, variety, and fascination of casework in the field of geriatric medicine make it one of the social work's most exciting challenges. Recent organizational changes leading to a preoccupation with the division of costs between health and social services have in some cases placed this key interdisciplinary function in jeopardy to the extent that social work staff have become caught up in a cost-driven bidding process for "packages of care" and perceive themselves to have little or no time for "family work". Any suggestion that social work for older people requires fewer professional skills or presents fewer intellectual and clinical challenges than other areas of practice, but rather entails the dispensing of aids and support services is supremely outdated and uninformed. A skilled operator in the field regularly transforms the perception of a patient by the multidisciplinary team and radically alters its decisions.

Liaison: Specialist liaison health visitors or nurses have historically played a valuable part in bridging the hospital-community interface. Feedback from follow-up visits of older people resettled in their homes after illness is invaluable self-audit for the hospital-based team. It maintains an indispensable community perspective and frequently enables early troubleshooting where errors or omissions may have occurred, or where aspects of the assessment may have been miscalculated. This function has latterly been undertaken by a variety of personnel, including case managers or discharge coordinators, but the basic concept is the same – a coordinating role among other professionals and agencies, based in the community rather than the hospital. Many holders of the newer posts have a professional background in nursing.

In summary, effective teamwork is fundamental to problem-orientated practice in the medicine of old age. Even the most successful teams get it wrong some of the time, but in clinical settings where team work is underdeveloped or present only in token form the error rate is substantially greater.

Clinical Care Settings

In the United Kingdom the most efficient structural unit containing all the necessary facilities for investigation, treatment, access to other specialties, exchange of information and the presence of on-site multidisciplinary staff is the general hospital. There is ample evidence that the effectiveness of district geriatric medical services depends on the degree of access to acute general hospitals available to competent clinicians in the field (Evans, 1983). Many new technologies, for example, in noninvasive organ imaging and surgery, have particular applicability and effectiveness in the management of older people. Access to these techniques (always assuming careful stewardship) and to other specialties such as vascular surgery, is accepted as necessary and appropriate for the practice of geriatric medicine (Evans, 1983). This degree of "centralization" is an economic necessity, since many of the facilities cannot be cost-effectively dispersed across the community. Provided the service is clearly targeted at the local population, the advantages generally outweigh the disadvantages (e.g. those of transport). Ready access for older people to technically sophisticated and comprehensive medical care is a strong imperative, for which quality "care in the community" should never be perceived as a substitute (as distinct from a parallel partnership).

The need to generate cohesive specialist teams immediately available to ill older people constitutes a strong argument for the positioning of acute assessment units within the acute hospital. Where the acute medical care of older people is wholly integrated (i.e. older patients receiving care in a common pool of general acute beds alongside their younger counterparts) then specific arrangements are necessary to

ensure their prompt access to a fully accountable multidisciplinary process (for example, a team attached to a medical "firm" and incorporating that firm's physician with specialist responsibility for the medicine of old age) (Evans, 1983). The need to position specialized acute assessment and/or rehabilitation facilities in acute hospitals lies in the development of a "tailored" inpatient environment for older people and the maintenance of a clear focus for standards, for training, and for the dissemination of clinical and interdisciplinary skills.

The potential for these disciplines to extend into an increasingly wider range of settings is now being evaluated, with a strong impetus from the desire to reduce costly hospital bed-days. In addition to established practice within geriatric medical rehabilitation units and day-hospitals, the application of different models of the team (problem-orientated) approach, for example, to early or supported hospital discharge and "hospital-at-home" schemes (Hyde *et al.*, 2000) continuing care in the community and strategies for stroke rehabilitation (Kalra *et al.*, 2000) have been investigated. Such applications have potential in so far as they build on established standards and expertize, can be shown to make a measurable, equivalent contribution to the total service (or core need), do nothing to delay or prevent ready access to mainstream medical care and are not primarily "cheaper," unsustainable, short-term alternatives. In terms of cost-benefit and cost-effectiveness, such questions are so far unresolved.

Risk Taking

As already implied, the restoration of autonomy to an older person invariably implies the taking of at least some risk. The concept of restrictive custodialism has now thankfully become unacceptable in most developed and developing societies, but in the past has been the cause of much fear and apprehension among older people. Specific initiatives have been undertaken to minimize or abolish the use of the various forms of restraint, both physical and pharmacological (Dunbar *et al.*, 1996; Brooks, 1993). There is in any case ample evidence that such practices are not only ineffective, but generate their own risks (Frank *et al.*, 1996).

Positive approaches to rehabilitation have instead come of age. Within these, the aim of the problem-orientated approach is to identify and quantify the risks correctly, to take all reasonable treatment and preventative measures to minimize them, and to set a high premium on an individual's successful return to autonomy – in her or his own home wherever possible. Where some risk is entailed, an individual's choice should weigh substantially against the anxieties of others and (perhaps even on occasions the attentions of the legal profession).

The success rate of this approach is high. Modern departments of the medicine of old age have become increasingly interventionist, with a substantial relative decline in their custodial role. Those aspects of the organization of facilities and of clinical practice discussed earlier are a direct consequence of this orientation.

EVALUATION: PROBLEM RESOLUTION – SUCCESS OR FAILURE?

The capacity for activities associated with health care to become self-perpetuating means that this interventional approach, like any other, should have its effectiveness tested. Given that the problem-orientated approach finds its expression predominantly in interdisciplinary practice, the following questions are pertinent:

1. What are the short-, medium-, and long-term benefits for patients?
2. What is the wider impact on older populations at an epidemiological level?
3. How can the standard of practice be assessed?
4. What are the effects on the service in terms of efficiency and cost?

These areas of enquiry broadly reflect the Donabedian categorization of audit criteria – structure, process, and outcome (Donabedian, 1980). Although "health care–technology assessment" is an expanding discipline, the earlier questions remain to be comprehensively answered with respect to Geriatric Medicine. "Outcome measures", in particular, are the subject of much ongoing debate and the health economic aspects are extremely complex. Such answers as exist so far have emerged sporadically in the context of service development rather than as a result of any clear research strategy.

A number of UK departments of Geriatric Medicine providing comprehensive services (and adopting problem-orientated interdisciplinary service patterns) published reports (mainly in the 70s and 80s) showing substantial changes in hospital-based activity consequent on their development (Hodkinson and Jeffreys, 1972; Bagnall *et al.*, 1977; Rai *et al.*, 1985; Mitchell *et al.*, 1987). The changes included substantial increases in patient throughput per year, with concurrent reductions in total bed numbers, duration of patient stay and hospital bed occupancy. It was also possible to demonstrate a facilitating effect of this pattern of service on other areas of clinical activity, most notably acute general medicine, in which the numbers of patients treated also grew as a result of the resolution of "bed blockage". The descriptive content of these models included elements of structure (notably provision of inpatient and day patient places, of places in homes in the community and also the levels and skill-mix of available multidisciplinary staff) and process (notably clear definition of operational policy, patterns of interdisciplinary practice, community and social-services links and specific geriatric service components, e.g. respite care, dementia caseload). Their reports demonstrated the capacity to translate the principles of problem-orientated practice and interdisciplinary activity into viable services, with a measurable positive impact on adjacent clinical services (Swift and Severs, 1997). Detailed conclusions concerning clinical outcome, with the exception of mortality statistics, were by inference, although it is unlikely that service viability would have been sustainable had the clinical

consequences been broadly unacceptable to patients and to the local communities concerned.

Such process data are a fundamental component of evaluation, even though the need for more information on clinical outcome is accepted. The published models have to some extent set standards for resource use efficiency and bear careful scrutiny with respect to this. The delivery of a service will invariably require some balancing of benchmark criteria of practice with the availability of finite resources. There is little point in setting up the "perfect" model if it can only be available to a small proportion of those who need it. The concept of a service entails its ready accessibility to the total population served in relation to need.

More recent health care–technology research has allowed prospective experimental evaluation of the problem-orientated/interdisciplinary approach in randomized controlled clinical studies.

A good example is a study of the efficacy of stroke units (as a model of focused interdisciplinary practice) (Figure 3) (Kalra *et al.*, 1993). This work, using a stratified design based on a validated prognostic scale of severity, showed that assessment and rehabilitation in stroke units versus dispersed wards resulted in more rapid discharge from hospital to community, a reduced requirement for long-term institutional care and an improved and more rapid functional outcome (for those with intermediate stroke severity) as well as a reduction in late mortality (for those with more severe stroke). These operational and clinical outcomes were achieved without the requirement for increased therapy staff or total therapy time. It is important to stress that the findings were set in the context of a comprehensive district geriatric service with corresponding specialist leadership. They do not constitute a carte blanche for the universal deployment of stroke units, but rather provide evidence of the effectiveness of focused problem-orientation and interdisciplinary practice. This leaves the way open for a range of alternative strategies based on these principles, ranging from well-run generic geriatric medical units to peripatetic teams bridging the hospital–community interface (Kalra *et al.*, 2000) and strengthens the case for investment in this general approach to the care of all patients with complex need.

A further example is the application of interdisciplinary assessment strategies in the prevention of falls among older people. In a controlled study, consecutive older people presenting to a London accident and emergency department were randomized to existing discharge and communication procedures or to a subsequent single bi-disciplinary, problem-orientated risk identification and referral protocol comprising a full medical examination and an occupational therapy assessment at home (Close *et al.*, 1999). In only 16% of the assessments was no further action considered necessary. Analysis showed that the odds of a fall in the 12 month follow-up period were reduced in the intervention group by a factor of 2.5 (95% CI; 1.5–4.3) relative to the control group after adjusting for differences in Barthel and AMT scores at baseline and number of falls in the 12 months prior to the index fall (Figure 4). The odds of recurrent falling (3 or more falls) were reduced in the intervention group by a factor of 3.0 (95% CI; 1.5–6.1). There is now a substantial literature indicating the capacity for falls prevention at population level using multidimensional, multidisciplinary approaches (Chang *et al.*, 2004).

There is much discussion about measuring the broader epidemiological impact of the problem-orientated approach. One of the difficulties is getting consensus on the most appropriate measure of achieved autonomy or health over a given time span. One proposal is to develop the concept of measuring Healthy Active Life Expectancy (HALE) within served populations (Evans, 1993).

The proliferation of guidelines may prove to be of limited or little value in the scrutiny of services if no account is taken of the degree of expertize and competence applied. The mere presence of an operating theater, a team of individuals, and a textbook of operative surgery gives no guarantee of the outcome of a series of surgical procedures. The same principal holds in the health care of older people for the existence of a defined service structure, organized "teams" and agreed guidelines. Effectiveness requires the work to be underpinned by good training, professional commitment, research and development, and well-developed career structures. There have been a number of instances where schemes put in place

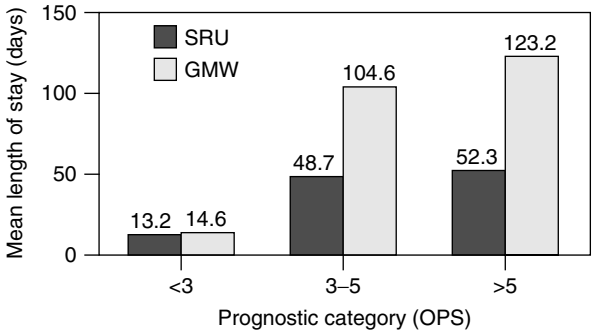

Figure 3 A randomized prospective study showing the effect of stroke-unit based interdisciplinary practice (SRU) compared with care on dispersed general wards (GMW) on duration of hospital stay after stroke (From data of Kalra *et al.*, 1993)

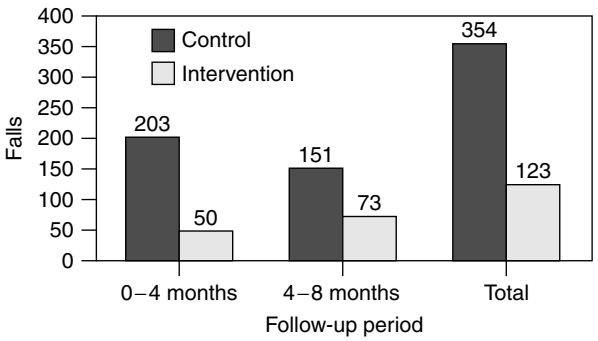

Figure 4 Reduction in the incidence of falls in older people in a randomized prospective study of an interdisciplinary assessment protocol (Reproduced from Close *et al.*, 1999). Copyright Elseveir

(e.g. for community care) have achieved short-term results, but have proved unsustainable in the medium term because of difficulties of professional recruitment and gradual de-skilling. In this context it is gratifying that Geriatric Medicine (where well developed) is no longer a shortage specialty. It is probably correct that success or failure of continued professional recruitment is an invaluable, if indirect, service audit criterion.

In conclusion, the skilled application of a system of problem orientation substantially defines decision-making expertize in the practice of Geriatric Medicine, perhaps more than in any other speciality. The evidence underpinning its effectiveness continues to grow, but on the whole too slowly in relation to the explosion of population need. There is still insufficient consensus among geriatricians on the best measures of effectiveness, minimum datasets and comparative standards of service performance to enable the necessary comparison of "like with like". This remains an urgent and major challenge for clinical age research. In the meantime, it is incumbent on clinicians concerned with the care of older people to ensure that they have well defined and well-used systems in place to optimize and monitor their own practice.

KEY POINTS

- The accurate identification and documentation of "problems" and the resulting application to multidisciplinary decision making constitutes the core method of clinical practice in geriatric medicine. It may be well or badly implemented and the potential pitfalls should be recognized and avoided.
- The four interdependent problem domains fundamental to effective practice are those of diagnosis and treatment, functional autonomy, human relationships, and living environment. The level of skilled practice and experience within each domain and the capacity of multidisciplinary teams to collaborate successfully are the principal determinants of outcome for patients.
- Pragmatic problem-orientated decision support tools (as distinct from solely measurement and assessment instruments) may enable best practice.
- The success, efficiency, and cost-effectiveness of health-care systems for older people are directly proportional to the extent to which they are organized to promote, support, and facilitate such activity rather than constrain and inhibit it. A major presence in the acute general hospital and dedicated communication/liaison systems have both been found to be pivotal.
- The effectiveness for patients and for health systems of implementing the approach within organized service models is now well proven both by audit of routine data and in randomized controlled prospective studies.

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PART III

Medicine in Old Age

Section 1

Eating Disorders and Nutritional Health

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Oral Health

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INTRODUCTION

Healthy teeth and oral tissues and the need for oral health care are as important for older people as any other section of society. Tooth loss can have a profound impact on quality of life (Davis *et al.*, 2000), whereas good oral health has real health gains in that it can improve self-image and social interaction, and contribute to general health and quality of life (Fiske *et al.*, 2000). Older people perceive oral health as being important to quality of life in a variety of ways (McGrath and Bedi, 2002). However, priority must be given to the elimination of disease, and abnormality; comfort, mastication, and aesthetics are paramount in helping the individual to maintain an overall perception of self-esteem and dignity, and generate confidence in making regular use of the services that are available.

DEMOGRAPHIC POPULATION CHANGES AND ORAL HEALTH CARE

Improvements in life expectancy in developed countries have led to an increase in an aging population (*see also* **Chapter 9, The Demography of Aging**). In the 2001 United Kingdom (UK) census, over 12 million people were aged 60 and over, approximately 20.8% of the population (ONS, 2002). The proportion of people aged 65 and above in 2001 is predicted to rise from 16.9% to 19.3% in 2020 (GAD, 2002). Population projections based on declining fertility may need to be revised in the light of migration, and medical advances in the treatment of conditions such as dementia may reduce the burden of care (Tinker, 2003). Nevertheless, there will be an overall increase in the numbers and percentages of older people, of very old people, and of older people from black and ethnic minority groups, and a continued preponderance of older women. Similar increases are noted in other industrialized societies. This will have an impact on most forms of health care provision and will place increasing demands to develop systems that cater for all aspects of health care, including dental services. Future development of oral health care services will need to consider the diversity of demand and need within this aging population (BDA, 2003).

IMPAIRMENT AND DISABILITY

In discussing the oral health needs of older people and their use of services, the self-evident increase in impairment and disability with age must be considered. The 2001 UK census estimates that almost 9.5 million people in England and Wales have some form of disability (ONS, 2002), significantly higher than previous estimates. Of these, 18.2% reported a long-term illness, a health problem or disability that limits their daily activities. Over a third of respondents aged 65 to 74 and approximately a half aged over 75 reported long-term illness that limited their lifestyle (ONS, 1999).

Physical and mental health influence access to services, including oral health care. Loss of mobility increases with age, with the greatest decline in people aged 75 and above (ONS, 1999). Immobility is a frequent pathway by which many diseases lead to further disability (Walsh *et al.*, 1999) (*see also* **Chapter 112, Gait, Balance, and Falls**). Sensory impairments are more common with advancing years (*see also* **Chapter 101, The Older Patient with Down's Syndrome**; **Chapter 104, The Epidemiology of Hearing in Aging Population**; **Chapter 105, Auditory System**; **Chapter 106, Disorders of the Vestibular System**). Approximately 80% of the population over 60 have some form of visual impairment, 75% have a hearing impairment, and 27% experience both visual and hearing impairment (Living in Britain, 1994). Cognitive impairment increases sharply with age affecting 1 person in 20 over the age of 65 and 1 in 5 over the age of 80, and this is predicted to increase Alzheimer's Disease Association (ADS, 2004) (*see also* **Chapter 94, Mild Cognitive Impairment**;

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Chapter 95, Vascular Dementia; **Chapter 96, Other Dementias**).

Older people are distinguished by functionality in the National Service Framework (NSF) for Older People, which refers to the functionally independent and the frail or functionally dependent regardless of age (DoH, 2001a). This classification is used by the British Dental Association (BDA) in addressing the diverse oral health needs and demands of older people for the next two decades (BDA, 2003). This chapter primarily addresses the needs of the frail and functionally dependent older population.

ORAL AND DENTAL STATUS

Tooth loss is irreversible although stem cell research still in its infancy offers future potential for implantation of the patient's own cells to grow and replace missing teeth. Prevalence of edentulousness (total tooth loss) in the general population over time and dental status, together with patterns of dental attendance, can be used to predict dental service needs. Comparison of the UK national surveys confirm a steady decline in tooth loss in adults (Table 1). In 1988, the dental status of older people in the United Kingdom was primarily one of edentulousness. However, the number of older people who are edentulous is declining. In 1968, 79% aged 65 to 74 were edentulous as compared to 36% in 1998, and in people aged over 75, edentulousness fell from 88% to 58% over the same period (Todd and Lader, 1991; Kelly *et al.*, 2000). Retention of some natural teeth is sufficiently common amongst the "younger–old" population; nearly two-thirds (64%) in the 65 to 74 age group and almost half of all the people of "pensionable" age in the United Kingdom (54%) have some natural teeth (Steele *et al.*, 2000).

Age is highly correlated with dental status. Other factors include sex, social class, region of residency, ethnicity, and dental attendance. Social class differences in total tooth loss were much greater among men than women, and particularly noticeable amongst older men compared with older women; it is suggested that differences arise from social values attributed to appearance (Steele *et al.*, 2000). Women from unskilled working backgrounds were most likely to have the lowest proportion of natural teeth. Regional differences in social class structure may account for regional differences in total tooth loss but the highest proportion of retained natural teeth is still in the South of England. Despite a trend toward retaining some natural teeth into later life, a small but varied group of people will continue to become edentulous and these are more likely to be in the older age groups. Similar trends of tooth retention are recorded in other developed societies. Variability is strongly influenced by place of residence, geographic region, and cultural factors; however, edentulousness is more frequently associated with lower socioeconomic status.

Table 1 People aged 45 and over with no natural teeth (1968–1998)

Age group	England & Wales	England & Wales	United Kingdom	United Kingdom	United Kingdom
Year	1968	1978	1978	1988	1998
45–54	41%	29%	32%	17%	6%
55–64	64%	48%	56%	37%	20%
65–74	79%	74%	[a] 79%	57%	36%
75+	88%	87%	[a]	80%	58%

(Based on data from Todd and Lader, 1991; Kelly *et al.*, 2000)
[a]No separate data for age groups in 1978.
In 1978, 79% over the age of 65 had no natural teeth.

Not only has the number of dentate adults in older age groups increased, the number of undiseased and filled teeth have increased (Nunn *et al.*, 2000). It is suggested that increased experience of dental treatment among older people is largely reflected by a lower experience of dental extractions. In older people, a significant proportion of the caries burden falls on exposed root surfaces although there is also an increase in coronal caries often recurring around existing fillings. Prevalence of toothwear increases with age, affecting 89% of the dentate population aged over 65. In 1998, older people had more restored teeth, often large and complex restorations requiring time and advanced professional skill to maintain them. Fifty percent of the teeth of dentate adults aged 45 years and over are filled and crowned, and many will retain their teeth for life (Pine *et al.*, 2001). It appears that regular dental attenders benefit in real terms over a lifetime in terms of tooth retention (Kelly *et al.*, 2000).

Periodontal disease is a major concern in the older dentate population. Seventy-eight percent of dentate adults over 65 had visible plaque and 83% had visible calculus, which can only be removed by professional dental treatment (Morris *et al.*, 2001). Depth of pocketing around teeth is also an indicator of periodontal disease but gingival recession is likely to be a common feature in older age groups, reflecting a lifetime's disease history. The high prevalence of periodontal disease needs to be viewed in the context of larger numbers of dentate older people who are now potentially at risk. Control of periodontal diseases, whether mild or moderate, will be a central issue if large numbers of teeth are to be retained into old age.

It seems that older people are now more concerned with preserving their natural dentition (Kelly *et al.*, 2000). In 1998, dentate adults over 55 were the most likely to say that they attend regular checkups; the proportion reporting this has more than doubled over the last 20 years (Bradnock *et al.*, 2001). A greater proportion aged over 55 have expectations of retaining some or all of their natural teeth for life, and older age groups would consider having more extensive restorative treatment such as crowns and bridges in order to achieve this expectation. Dental attendance does appear to be of substantial benefit in retaining teeth (Steele *et al.*, 2000). Greater awareness of oral and dental health measures together with a greater desire to remain dentate will create an increasing demand for dental services.

In the older UK population, three broad cohorts in relation to oral health are described:

- *People who are old and very old, of whom a large proportion are edentulous,*
- *Those now entering old age, who have retained much or most of their natural dentition, but in a condition that requires a lot of maintenance,*
- *Those in middle age and younger, who are retaining a sound dentition, and assuming the status quo, are unlikely to need complex oral health care, but who may opt for cosmetic dentistry* (BDA, 2003).

Whereas the "new older" health consumer will be more informed and more demanding, for a significant proportion of older people, the maintenance of an aging dentition will pose significant challenges to the dental profession. It is the frail and functionally dependent that have a significant normative treatment need and that pose even greater challenges to their identification and service delivery.

It is generally agreed that poor standards of oral hygiene and lack of access to professional dental care contribute to poor oral health amongst the frail and functionally dependent population (Fiske *et al.*, 2000). Surveys within nursing and hospital care report high levels of oral disease, heavy deposits of plaque and debris, oral mucosal pathology related to inadequate denture hygiene and inadequate support to maintain oral health or access services (Frenkel *et al.*, 2000; McNally *et al.*, 1999; Simons *et al.*, 1999). Poor oral health is also identified in the frail and housebound living in the community (Chalmers *et al.*, 2002).

The dental profession is concerned about the oral health of this client group, and in particular, those who rely on professionals for personal care and activities of daily living (BDA, 2003; Frenkel *et al.*, 2001; Fiske *et al.*, 2000; Simons *et al.*, 1999). Oral health does not have a high profile in the context of personal care. Lack of training for health professionals in oral health care is reported (Longhurst, 1998; Travers *et al.*, 1997). Gaps between theory and practice are noted in pre and postregistration nursing practice and education (White, 2000; Frenkel, 1999; Longhurst, 1998). This has led to a range of initiatives to address the issues and raise standards of oral health care for this client group (BDA, 2003; WAG, 2003; DoH, 2001b; Fiske *et al.*, 2000).

BARRIERS TO ORAL HEALTH CARE

Many older citizens face barriers to oral health care. These include attitudes developed in early life that place oral health as a low priority in the context of other factors such as past dental experiences, dental attendance patterns, lack of information, in addition to practical and financial barriers. Lack of perceived need is an important barrier.

Social problems that influence perceived need are related to age, socioeconomic factors, and residence. The presence of natural teeth, residential status, and age were statistically significant independent variables for the time since the previous reported dental visit (Lester *et al.*, 1998). There is a trend toward decreased perceived need in older populations; this was found to be a barrier to care for 86% of frail and dependent older adults (Lester *et al.*, 1998) although the new elderly have significantly more favorable attitudes to dental care. Uptake of dental care is greater among patients of higher socioeconomic status. Cost, lack of perceived need, and transport were the most frequently quoted barriers by housebound subjects although the true implications of cost were poorly appreciated (Lester *et al.*, 1998). Removal of the examination charge as a financial barrier to screening and, if possible, care is recommended (Walls and Steele, 2001; BDA, 2003). Legislation in Wales has removed the fee for a dental examination for the population aged 60 and over; it remains to be seen whether this alone will increase the uptake of care.

Lack of perceived need and inability to express need are identified within residential care facilities and housebound persons in the community (Lester *et al.*, 1998; Fiske *et al.*, 2000). Fewer dental attendances in this population are in part attributed to the inadequacy of carers' perception of their clients' oral health needs and lack of knowledge of the benefits of oral health and access to dental services. The prevailing management culture that gives oral health a low priority reported in residential care may be a contributory factor. A dental emergency rather than a routine dental check was the usual reason for requesting a dentist's services for a resident (Frenkel *et al.*, 2000).

Fear and anxiety are commonly cited as reasons for irregular dental attendance. Over 12% of older people in the United Kingdom express dental anxiety associated with their use of services and self-reported oral health status (Bedi and McGrath, 2000). This must be viewed in the context of past dental experiences prior to the foundation of the National Health Service (NHS) when the practice of extracting teeth and replacement with dentures was considered to be the most effective form of treatment as opposed to the current philosophy of maintaining and restoring the dentition.

Impaired mobility, access to transport, and ability to reach services have implications for access to dental care for housebound and disabled persons. Inequalities in the distribution of general dental services pose problems for availability of care. This is particularly true of rural areas where transport difficulties and costs create disincentives. Difficulties registering for NHS dental treatment are being widely encountered by the general population. Older people with mobility problems may experience even greater difficulty in accessing NHS care owing to poor physical access to premises that do not comply with the requirements of the Disability Discrimination Act (1995) (Griffiths, 2002). Domiciliary dental care services are not widely known about and yet frail and functionally dependent older adults expressed a preference for treatment in their own home (Lester *et al.*, 1998). Illness and impairment only become disabling if dental services fail to take them into consideration. The provision of adequate domiciliary dental services will be essential to provide professional advice and treatment to residents in care facilities and increasing numbers of frail people living at home or in sheltered accommodation (BDA, 2003).

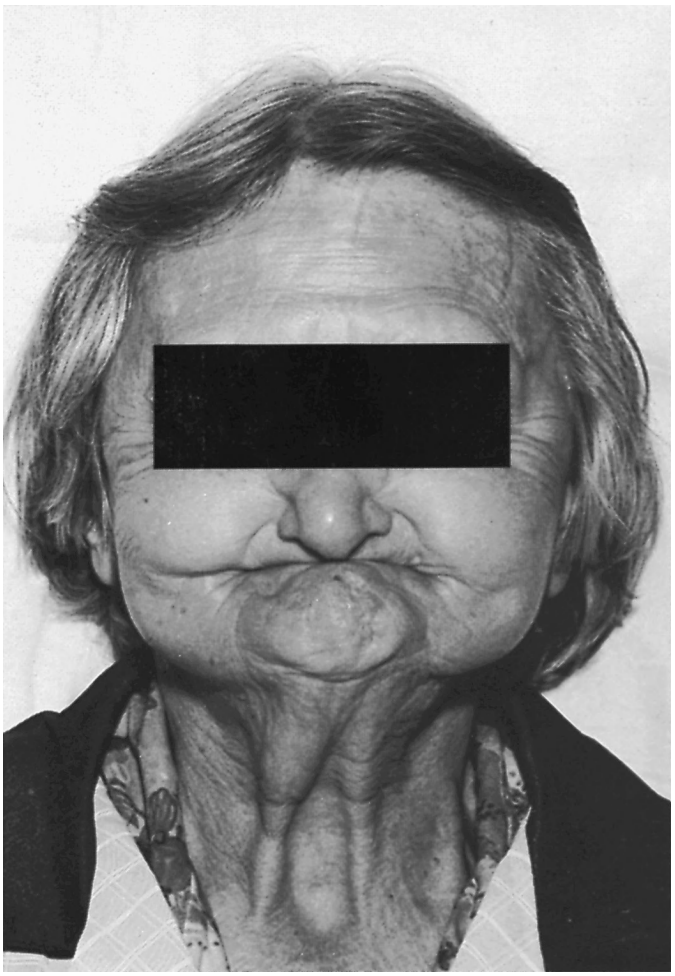

Figure 1 Loss of vertical dimensions in a 68-year-old female who had been edentulous for more than 20 years

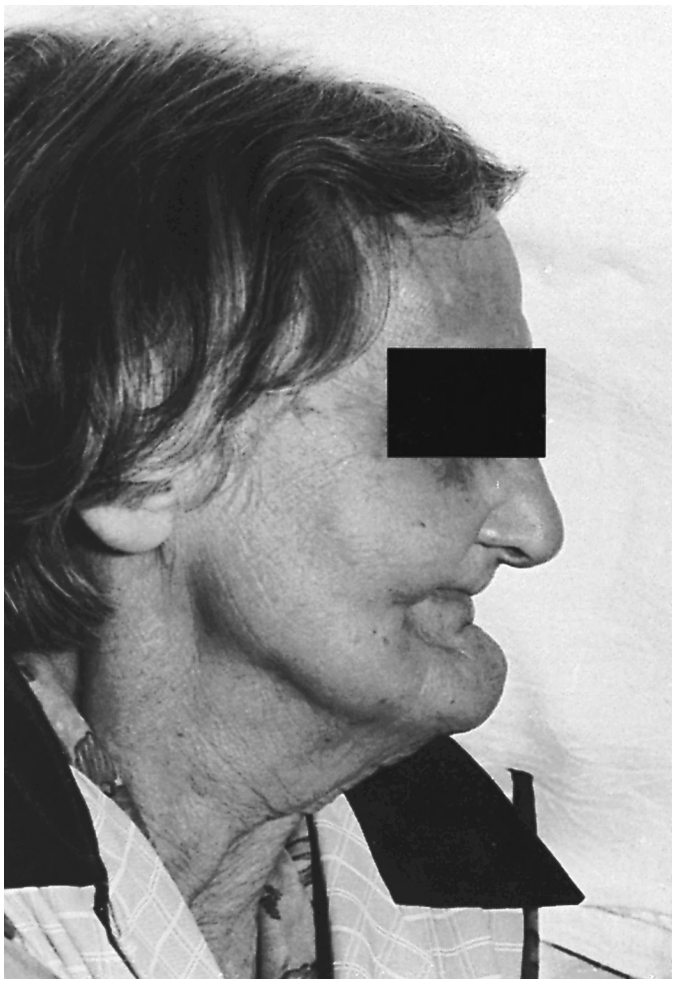

Figure 2 Loss of vertical dimensions in a 68-year-old female who had been edentulous for more than 20 years

Beliefs about lifespan and expectations of dentures may contribute to reasons for low levels of dental attendance among the edentulous. Inadequate advice following the provision of dentures may contribute to this. Misconceptions exist about the management and lifespan of dentures, even though denture-induced stomatitis and mucosal lesions are known to be associated with old, worn, and ill-fitting dentures. Lifespan of dentures is variable and depends upon individual changes in hard and soft tissues. Resorption of alveolar bone and occlusal wear can occur gradually with resultant reduction in vertical dimensions which may be associated with unsatisfactory aesthetics, an overclosed facial appearance, problems with mastication, cheek-biting and possibly tempero-mandibular joint dysfunction (Figures 1 and 2). Gradual adaptation and muscular control allow many people to compensate for loss of dentition. With gradual oral changes and habituation to changing oral status, it comes as no surprise that worn and ill-fitting dentures are perceived as functional and cosmetically acceptable. This, combined with an exaggerated expectation of the lifespan, may contribute to a fall in dental attendance with advancing age, particularly among the edentulous.

Carer-related barriers include deficiencies in knowledge of basic oral hygiene among health care professionals and carers, chronic inadequate oral hygiene practices, and limitations of workloads on long-term care staff (Fiske *et al.*, 2000; Frenkel *et al.*, 2000; Longhurst, 1998). Lack of information on how to access dental services and difficulties in arranging dental care are reported (Lester *et al.*, 1998).

Professional barriers are also identified (BDA, 2003; Fiske *et al.*, 2000). Older patients are less likely to receive restorative treatment than younger patients. Lower socioeconomic groups are less likely to receive advanced dental care, and previous dental attendance patterns influence treatment patterns. Negative stereotypes of older people and lack of confidence in treating older patients with more complex medical histories may contribute to limitations in treatment planning and reluctance to provide dental care. Reasons given for not providing dental services for people with impairments are that it is too time consuming in relation to remuneration, and lack of experience and training (Oliver and Nunn, 1995). The level of dental remuneration for NHS dental care is increasingly being regarded as financially

nonviable and many dentists are opting out of providing NHS coverage (Walls and Steele, 2001). Therefore, vulnerable groups who are frail and functionally dependent are likely to be the most disadvantaged by reduced access to NHS dental care.

Barriers to oral health and dental behavior are complex. The mechanisms by which these barriers may be lowered should be investigated in order to address the unmet oral health care needs and demands of older people (Lester *et al.*, 1998). Good oral health and access to dental care should be available to all older people on the basis of clinical need regardless of age, geography or home circumstances (BDA, 2003).

CLINICAL ORAL HEALTH CARE

The principle underlying oral health care for older people is to provide a service and standard of care that is qualitatively and quantitatively equal to that available to the population at large. This is acknowledged by the BDA in its policy document for the next two decades (BDA, 2003). Provision of oral health care requires a sound knowledge of clinical and preventive dentistry in the adult. Understanding of the aging processes associated with normality and disease, cognitive and attitudinal changes that may accompany aging, and socioeconomic influences in later life are fundamental in providing appropriate care. Knowledge of the effects of organic disease, treatments, and tissue changes on physical and mental well-being is essential. Functional changes that accompany the aging process and an increasing tendency toward organic disease are well documented (Walsh *et al.*, 1999). Deteriorating oral health should not be accepted as an inevitable consequence of aging, and the benefits of good oral health as a contribution to holistic health are recognized.

Oral changes that occur with age are frequently the consequences of earlier disease, wear, and habits. Muscle activity may decline and is hastened by early tooth loss. Speech may be affected by tooth loss and taste perception may be reduced. Xerostomia and a subjective feeling of dry mouth are receiving increasing attention. Age and medication are significant risk factors for xerostomia but medication is a better predictor of risk than age (Field *et al.*, 2001). Xerostomia is more prevalent among institutionalized populations and those on multiple prescribed medications (Locker, 2003). Onset of xerostomia is usually associated with other oral symptoms, problems with eating, communication, and social interaction.

Saliva has an important role in preserving oral health. Its functions include

- lubrication of soft tissues in speech and mastication;
- mechanical flushing of food and debris;
- neutralization of acids created by breakdown of sugars by bacterial plaque;
- remineralization of enamel surface;
- bacteriostatic and bactericidal effect;
- denture adhesion and retention.

A reduction in salivary secretion therefore increases the potential for dental caries, periodontal disease, oral infections, and problems with the retention and comfort of dentures. Composition of saliva with age appears to have fewer protective properties and combined with xerostomic side-effects of medication can have a significant negative impact on oral health status and quality of life (Locker *et al.*, 2002a; Locker, 2003).

Masticatory ability may be reduced by opposing tooth loss, lack of posterior teeth, poor or ill-fitting dentures, or even the absence of dentures (Figures 1 and 2) (*see also* **Chapter 24, Epidemiology of Nutrition and Aging**). While the loss of teeth does not conclusively lead to malnutrition, lack of masticatory efficiency does lead people to modify or adapt their diet to avoid material which is tough and fibrous. Poor diet and impaired food choice is associated with declining number of teeth and increasing age (Daly *et al.*, 2003). Edentulous subjects and those with poor oral health are more likely to report limitations in chewing ability (Locker *et al.*, 2002b).

Surveys of frail and functionally dependent older people report high levels of oral pathology, high levels of plaque, and moderately severe gingivitis in dentate subjects unable to perform their own oral hygiene (Frenkel *et al.*, 2000; Simons *et al.*, 1999; McNally *et al.*, 1999). Much oral pathology in edentulous subjects is associated with inadequate denture hygiene (Figure 3), denture misuse, and loose or ill-fitting dentures and is significantly related to clinically diagnosed denture stomatitis (Simons *et al.*, 1999) (*see also* **Chapter 23, Oral Disease**).

The incidence of oral cancer is increasing in Europe and throughout the developed world. It is primarily a disease of older age groups with a mean age of diagnosis of approximately 60 years (*see also* **Chapter 23, Oral Disease**; **Chapter 128, Cancer and Aging**). Incidence in males is around twice that in females although rates in women are rising. Smoking is a major risk factor (*see also* **Chapter 14, Smoking in the Elderly**). Pipe smoking has been linked to lip cancer, and chewing tobacco to intra-oral cancers. Alcohol also features as a risk factor and acts synergistically with tobacco (*see also* **Chapter 15, Alcohol Use and Abuse**). Chewing betel nut products and quat, practices that occur in certain ethnic minority groups, are implicated in oral malignancy. Long exposure to sunlight is also linked with lip cancer.

Cancerous and precancerous oral lesions are frequently painless until the more advanced stages of disease. Signs and symptoms include persistent oral ulceration, warty lumps and nodules, and red, white, speckled or pigmented lesions (*see also* **Chapter 23, Oral Disease**). Onset of symptoms may be associated with difficulty with speech or swallow and enlarged cervical lymph nodes. Early diagnosis and treatment improve prognosis and therefore regular oral examination is recommended as a screening strategy, which should target people who are not in regular contact with dental services. The dental team is in a unique position to screen for oral cancer and premalignant conditions. However, other health professionals should be trained to distinguish between

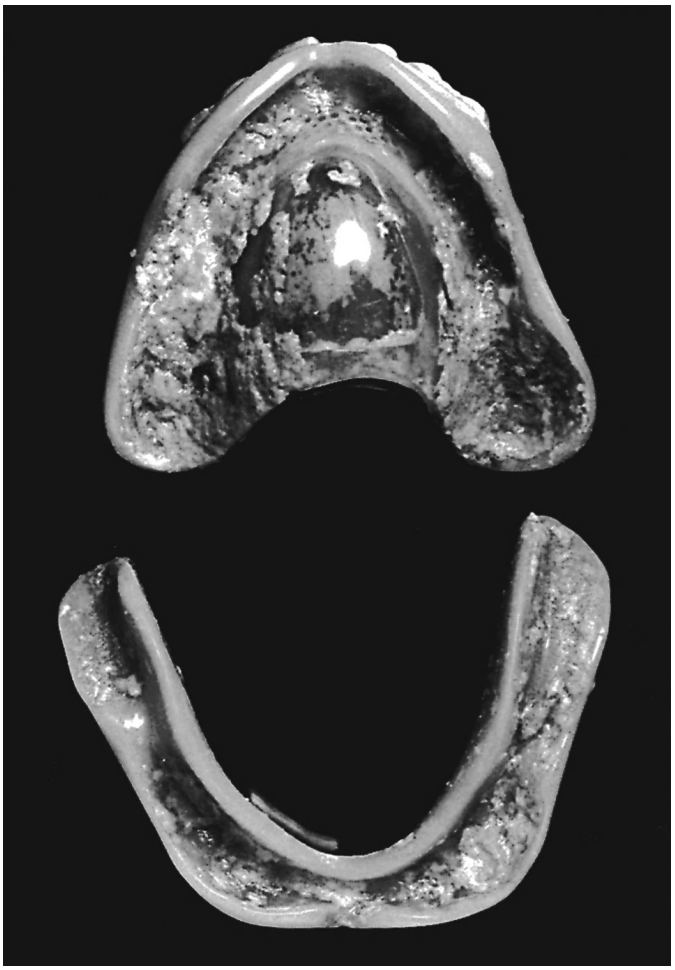

Figure 3 Fresh and old food deposits and bacterial plaque present on the fit surface of dentures being worn by a frail and dependent older patient in continuing hospital care

healthy and diseased tissue and screen for abnormalities as part of routine oral assessment, with a care pathway for referral when abnormalities are noted.

CLINICAL DENTAL CARE

Older people are not a homogenous group and treatment planning must take account of subjective need and demand and the individual's mental and physical health in order to achieve a successful outcome that is acceptable to the patient.

A detailed medical and social history is essential, and when appropriate, information on care and support services is desirable. Advice and support from family, carers, and the multidisciplinary team should be sought for patients with cognitive impairment in order to clarify the individual's capacity for informed consent to the proposed treatment plan. It is the clinician's responsibility to assess the patient's capacity for informed consent, to consult widely, and to act in the best interests of the patient (BSDH, 2004). Detailed referrals help reduce unnecessary ambiguity or inconvenience at initial assessment, and reduce the stress to patient or carer associated with dental care.

It may be difficult to assess the benefits of treatment to improved quality of life; however, relief of pain and discomfort is a priority and treatment plans may be modified as a result of physical and mental illness, and pharmacology. The individual's ability to maintain oral hygiene and cooperate in the provision of clinical dental care are factors that influence treatment planning. Lengthy clinical techniques may be contraindicated and the retention of decayed teeth advised. Dentists unfamiliar with the socio-medical factors associated with aging may find difficulty in adjusting their normative assessment to the needs and abilities of the individual. However, the overall physical and psychological well-being of the patient must be a constant consideration.

Restorative Care

The principal features associated with the aging dentition are attrition, erosion, and abrasion. Increased length of clinical crowns as a consequence of long-standing periodontal disease and gingival recession, over-eruption of unopposed teeth, tooth mobility, and exposed root surfaces make oral hygiene measures more complicated and increase susceptibility to caries and periodontal disease.

Restoration of the dentition can pose problems due to structural changes in dentine, which becomes harder and more brittle with age. Sclerosis may cause narrowing of the root canals with consequences for the success of endodontic treatment. Provided that roots and periodontal tissues are relatively sound, preservation of the dentition is recommended. Partial dentures should be designed before restoring teeth so that features for retention can be incorporated into tooth restoration. Complex partial dentures are generally contraindicated for patients with impaired comprehension or manual disability. The decision to render someone edentulous is not taken lightly. Older people exhibit a reduced learning ability, which influences adaptation to dentures. If complete dentures are proposed, gradual transition via partial dentures assists the process of adaptation and learning. The advantages of tooth and root retention lie in preserving the periodontal membrane, which provides proprioceptive feedback in chewing and helps to maintain alveolar support for dentures or over-dentures.

Age-related oral changes require extra clinical care in extracting teeth. Soft tissues are more fragile and exhibit slower healing. Teeth are more brittle and more prone to fracture if heavily restored. Extraction of maxillary roots close to the maxillary antrum may lead to the development of an oro-antral fistula. Chronic periodontal disease leads to hypercementosis, which increases risk of fracture during extraction, and osteoporosis poses risks of pathological fracture. Surgical extraction may therefore be necessary except when teeth are mobile through periodontal disease. The extraction of asymptomatic retained roots may be contraindicated in the presence of other risk factors; however, pain relief remains a priority.

Extractions must be considered in the light of medical complications and pharmacology, and are best carried out under local anesthesia with a sympathetic and reassuring approach. Mild sedation may be necessary to relieve anxiety and increase cooperation. If multiple surgical extractions are indicated in anxious or uncooperative patients, treatment should be provided under sedation or general anesthesia, with due assessment of the medical history and associated risks.

Generally, simple rather than complex restorations are more successful; the final assessment must be based on the individual's choice, their ability to receive treatment, and standard of oral hygiene. New materials and atraumatic restorative techniques (ART) require minimal tooth preparation. More complex restorative techniques need to be considered in relation to the number of visits, the duration of clinical time, and the potential for deterioration in self-care with impairment or disability.

If minimal intervention and clinical time is indicated, partial dentures may be the choice to restore occlusion. They should be designed for ease of insertion and removal, and incorporate design features for cleanliness and plaque reduction. Keeping gingival margins free from food residues reduces the risk of plaque accumulation (Figure 4). Clasps should be designed or modified to ensure atraumatic insertion and removal. Reduced dexterity or manual disability may require further design modifications so that the denture can be inserted and removed by wearer or carer.

Recurrent coronal caries and carious activity at the margins of existing restorations are prominent features in the neglected dentition. Large intracoronal restorations are avoided due to brittleness of dentine. Rather than replacing and extending existing restorations, it is better to add to them, repairing marginal deficiencies as necessary. For more advanced restorative treatment, the patient must be capable of maintaining good oral hygiene.

Cervical and root caries are significant problems in the presence of gingival recession and poor oral hygiene. Restoration may be complicated by erosion or toothbrush abrasion (Figure 5). Amalgam is not the material of choice for aesthetic restoration of anterior teeth. Restorative techniques for cervical caries have improved with new materials that bond directly to enamel and dentine, and require less invasive tooth preparation. However, they do have limitations in their bonding capacity.

Attrition due to excessive wear may be the result of earlier tooth loss placing abnormal loads upon the remaining teeth (Figure 5). Sensitivity may develop as a result of loss of occlusal or incisal enamel surfaces. Reduction in vertical facial dimensions gives an overclosed appearance. Preventing further tooth wear is a priority, although the level of attrition must be considered in relation to the person's age and ability to accept treatment (Figures 5 and 6). Slight wear does not necessarily merit treatment; moderate wear is usually treated conservatively. In extreme cases, attrition is repaired by crowning or with adhesive filling materials. If bruxism is a

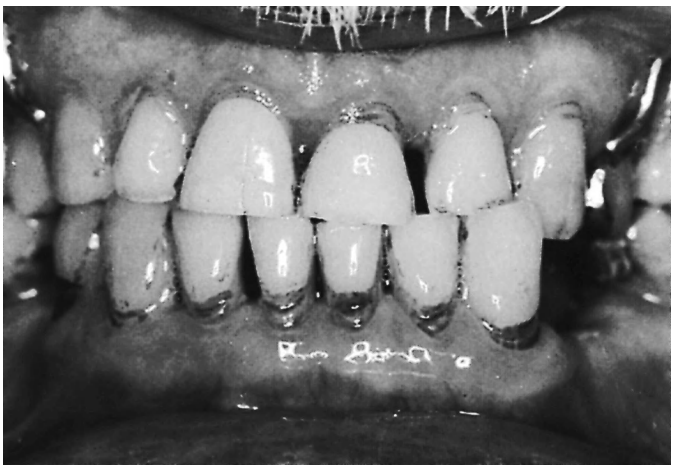

Figure 5 Self-caring 85-year-old male with attrition and abrasion. Attrition (wear of the incisal and occlusal surfaces) caused by loss of posterior teeth. Abrasion at the cervical margins caused by horizontal toothbrushing

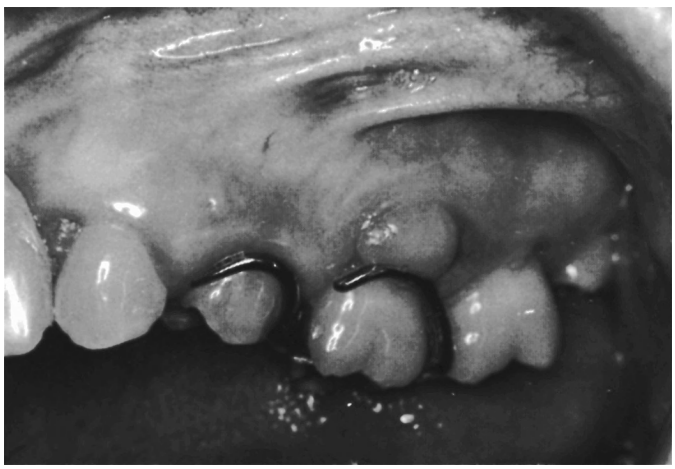

Figure 4 Gingival hyperplasia associated with nifedipine therapy, and complicated by a poorly designed denture with the clasp lying too close to the gingival margin and encouraging plaque accumulation

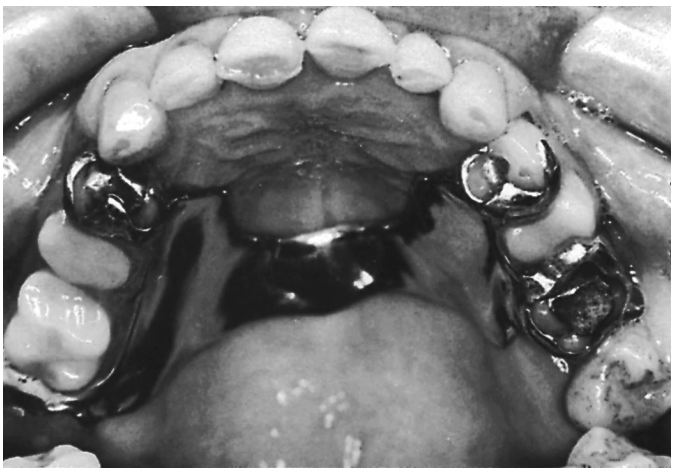

Figure 6 The same 85-year-old male with no denture experience, successfully wearing a partial upper cobalt chrome denture to restore the loss of posterior teeth. Denture design keeps gingival margins as free as possible

feature, a soft vinyl occlusal guard worn at night may prevent further wear and interrupt the habit.

With excessive loss of vertical dimension, it is advisable to acclimatize the patient gradually to the increased vertical height by providing a removable bite-raising appliance to cover occlusal surfaces. An over-denture retained on existing teeth or a cast cobalt chrome splint covering occlusal surfaces may be an alternative to multiple crowns (Figure 7). Major restorative measures are contraindicated if the patient cannot accommodate to increased vertical dimensions.

Erosion caused by excessive intake of acidic food, recurrent vomiting or reflux may cause sensitivity. Medical history and dietary analysis should establish the cause, although it may more rarely be related to previous occupational exposure to acid aerosols. Topical fluoride preparations to remineralize enamel surfaces and relieve sensitivity, and dietary advice, and protective splints may be required.

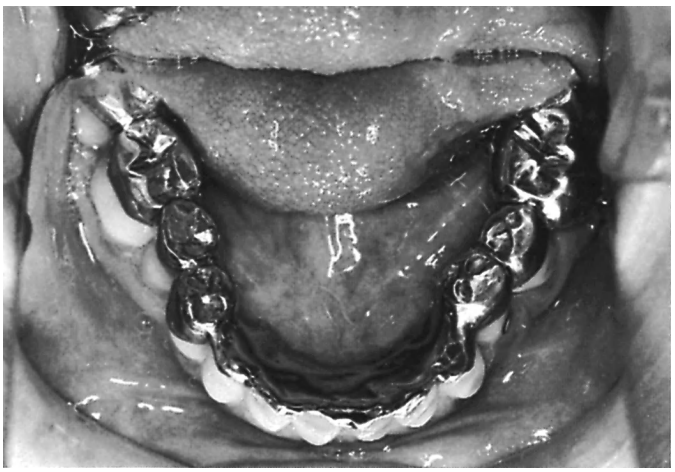

Figure 7 A cobalt chrome bite-raising appliance which fits over the lower teeth to prevent further occlusal attrition

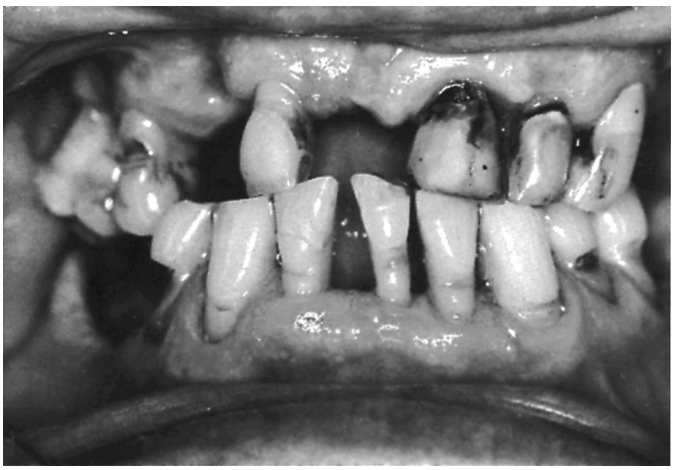

Figure 8 Before treatment: a neglected mouth with gross gingival recession, toothbrush abrasion in the lower arch, and erosion and tooth loss in the upper arch (By courtesy of A. Ali)

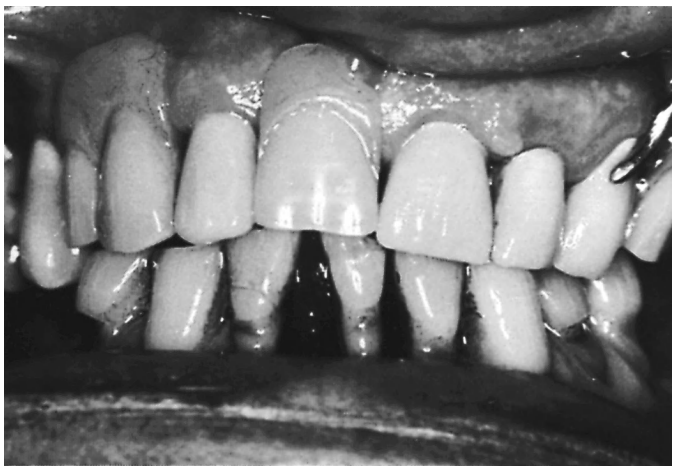

Figure 9 After treatment: upper anterior teeth restored with porcelain veneers and a partial acrylic denture (By courtesy of A. Ali)

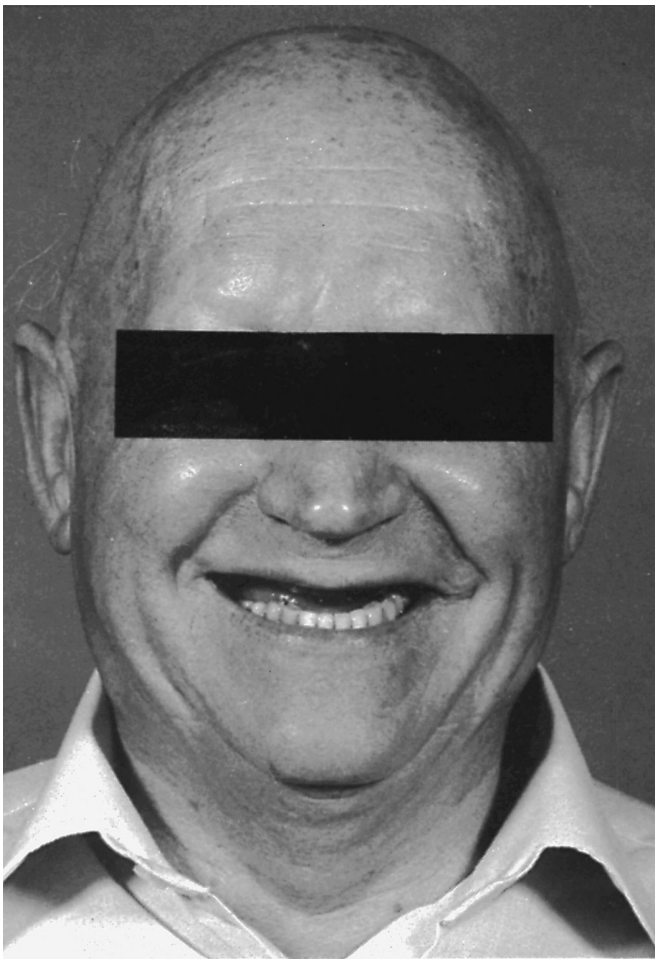

Figure 10 Male aged 68 with fractures and worn maxillary incisors (By courtesy of A. Gilmour)

Abrasion caused by vigorous or incorrect toothbrushing action creates distinctive cavities in the cervical area (Figure 5). Abrasion superimposed on cervical caries may

complicate restoration, and tooth-brushing techniques need to be modified to prevent further damage. Porcelain veneers are effective in cosmetically restoring labial enamel surfaces (Figures 8 and 9). The technique is less destructive of coronal tissue than conventional crowning and the veneer is bonded or cemented to the labial surface. The technique does not produce very aesthetic results with excessive gingival recession.

Teeth and roots may be restored or crowned and retained beneath an over-denture (Figures 10 to 15; the figures provide a case study to illustrate an over-denture in a 68-year-old male). Endodontic treatment may not be necessary and unsuccessful if root canals are sclerosed. Modification of coronal tissue to support a partial denture or the construction of crowns to receive precision attachments retaining a partial denture are accepted and useful methods of improving denture stability and distributing occlusal forces (Figure 16).

Complex bridge work is more rarely indicated. Tooth preparation involves lengthy clinical procedures and supporting teeth will need to withstand the extra occlusal load. Oral hygiene requirements are more stringent and may be difficult for the individual with limited dexterity or diminished self-care. Adhesive bridges require minimal tooth preparation and less destruction of abutment teeth; they provide an acceptable method of replacing one or two missing teeth (Figures 17 and 18) although problems of adhesion to enamel occur in older agegroups. Bonding the crown of an extracted tooth to adjacent teeth acts as a temporary solution (Figure 19); however, the bond must be secure to reduce the risk of displacement and accidental inhalation.

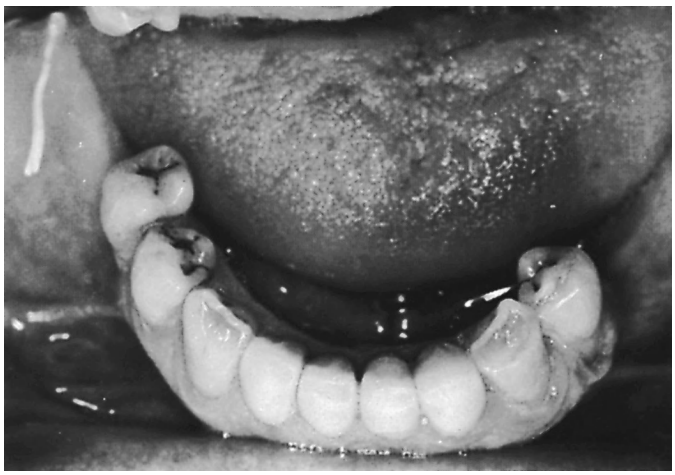

Figure 11 Porcelain crowns in the lower jaw and loss of posterior teeth have contributed to the excessive wear of the upper anterior teeth (By courtesy of A. Gilmour)

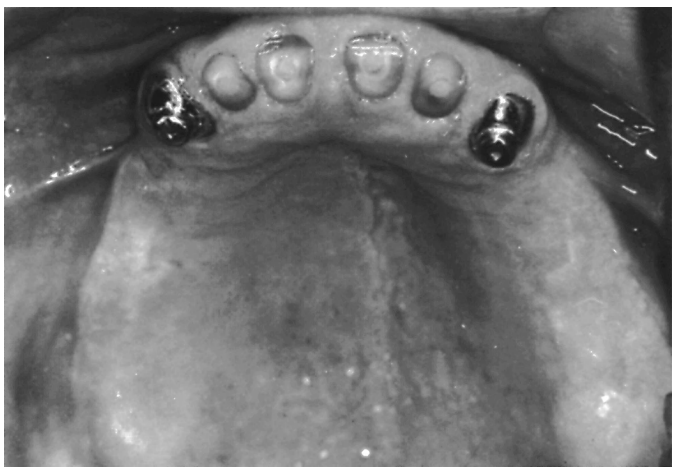

Figure 12 Rotherman eccentric clips on gold posts *in situ* (palatal view) (By courtesy of A. Gilmour)

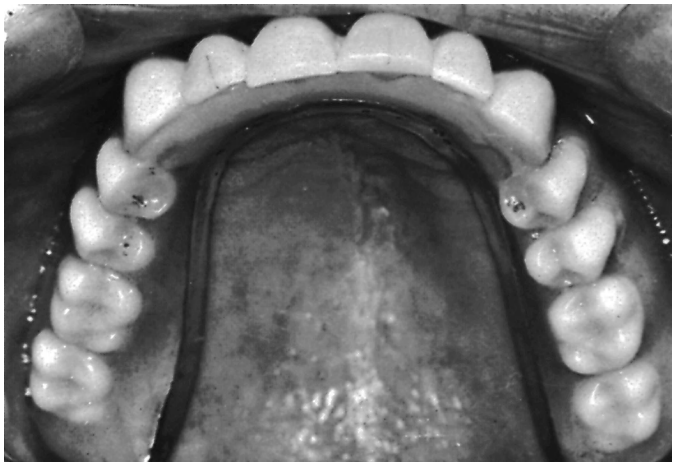

Figure 13 Complete upper over-denture retained by clips. The extra retention permits a palatal free design (palatal view) (By courtesy of A. Gilmour)

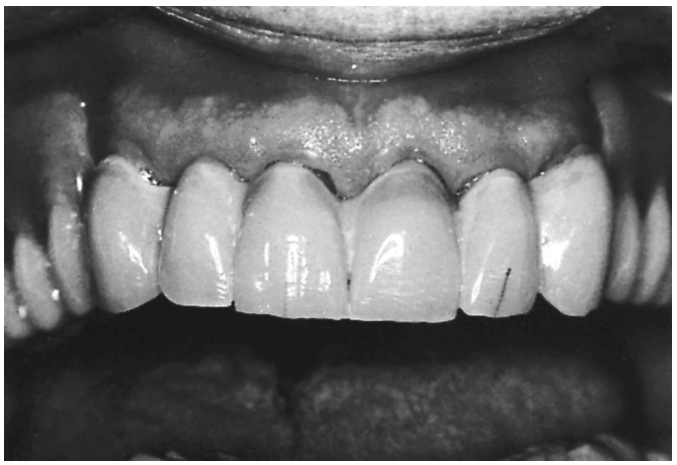

Figure 14 Close-up of over-denture *in situ* (By courtesy of A. Gilmour)

Periodontal Treatment

Periodontal health is maintained by effective tooth brushing to control bacterial plaque. With diminished ability for self-care, oral hygiene tends to deteriorate, and coupled with a

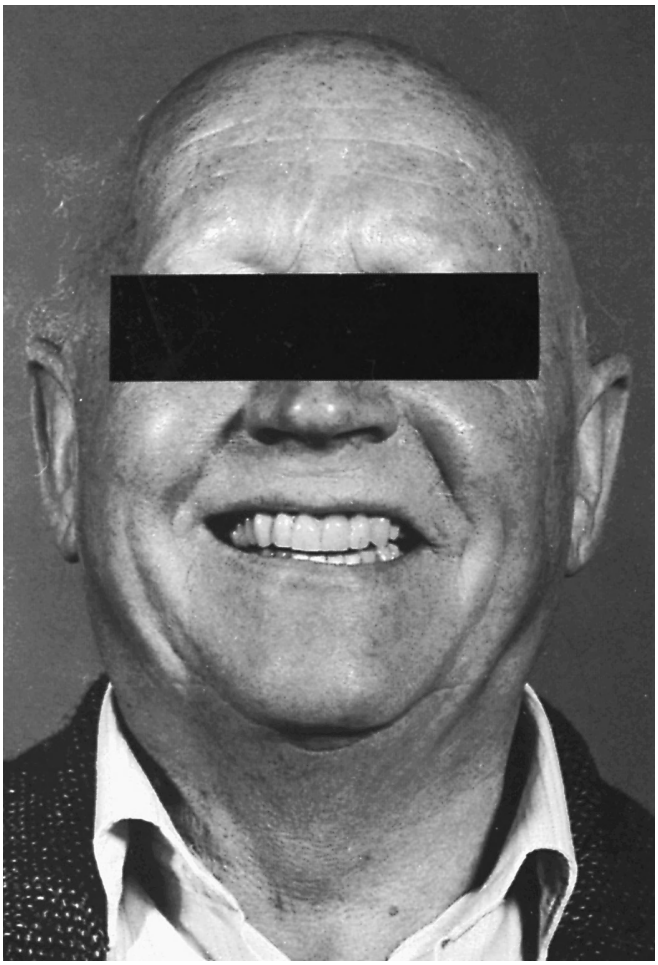

Figure 15 Completed treatment with upper over-denture and lower partial denture to replace missing posterior teeth (By courtesy of A. Gilmour)

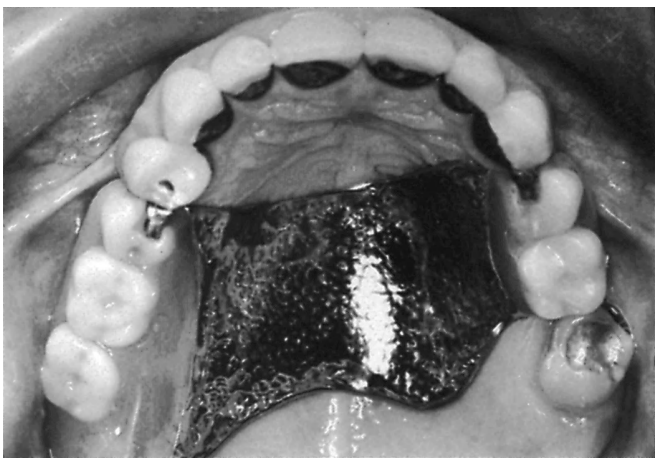

Figure 16 Partial upper cobalt chrome denture retained by precision attachments to canine and premolar crowns (By courtesy of A. Ali)

lack of dental health education and a belief in the inevitability of tooth loss, can lead to a significant deterioration in periodontal health. Pain or sensitivity due to recession, periodontal disease or gross sepsis may result (*see also* **Chapter 23, Oral Disease**). The prevalence and severity of periodontal disease increases with age; however, there are problems of differentiating between the aging process and the effects of disease. Since periodontal health can be maintained by good plaque control, it is a matter of concern that older people who are dependent for personal care do not receive appropriate assistance with oral hygiene (Frenkel *et al.*, 2000).

Resorption and gingival recession lead to an increase in the interdental space and a tendency to greater plaque accumulation, pocketing, and ultimately tooth mobility unless plaque is controlled effectively. Ill-fitting or poorly designed partial dentures increase the tendency for plaque accumulation (Figure 4). These areas are more difficult to clean by conventional brushing methods. Individual oral hygiene advice and instruction is essential.

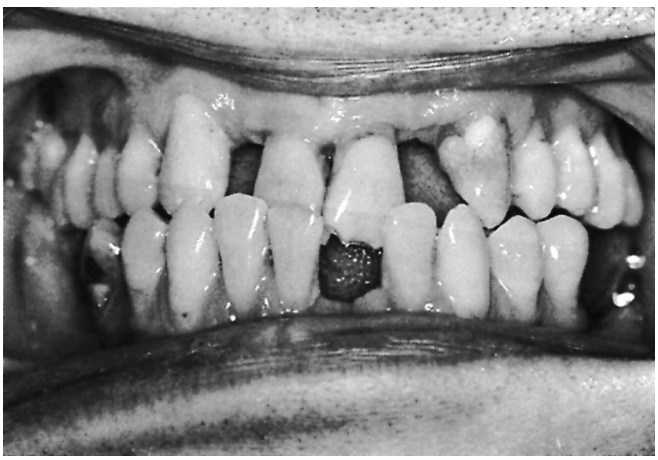

Figure 17 Before: malocclusion and tooth loss causing problems for construction of an aesthetic partial denture

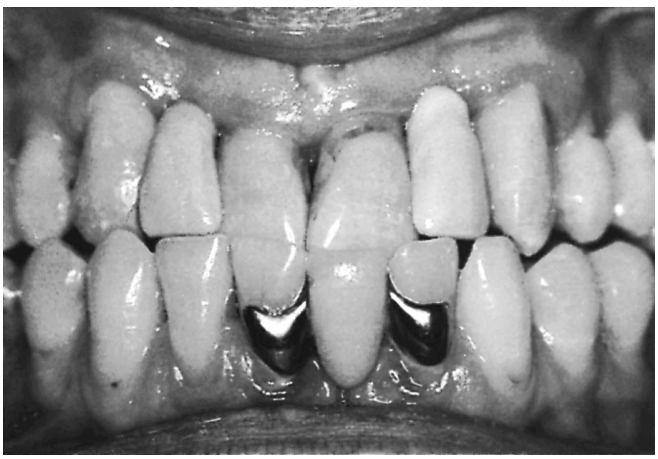

Figure 18 After: Maryland adhesive bridges which are bonded to the palatal surfaces of maxillary incisors and canines, and to the labial surfaces of mandibular incisors. The patient's high lip line concealed the visible metal attachments of the bridge in the lower jaw and produced an acceptable aesthetic result

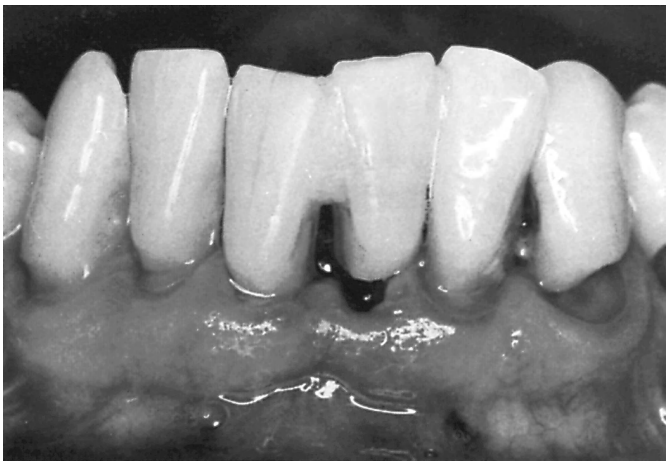

Figure 19 The crown of an extracted tooth used as a temporary bridge, cemented to adjacent crowns with composite resin (By courtesy of A. Ali)

Thorough and regular prophylaxis may be preferable to extensive periodontal surgery. Professional removal of plaque and calculus, and oral hygiene instruction is best delivered by a dental hygienist with good communication skills, and carried out under the written prescription of a dentist. It is essential that hygienists receive appropriate training to provide care for older people.

Toothbrush modification may be necessary for people with impaired dexterity; simple adaptations and commercial aids are described (Griffiths and Boyle, 2005a). Interdental brushes may be more effective for cleaning isolated areas. Electric toothbrushes with a wide grip may be more acceptable. Flossing is a technique requiring manual dexterity, and gauze or tape may be easier to handle and more effective for cleaning around isolated teeth.

Chlorhexidine gluconate has a specific effect in inhibiting the formation of dental plaque and is an effective adjunct to plaque control, particularly if oral hygiene deteriorates and mechanical cleansing is inadequate. Commercial brands are available as mouthwash (0.2%), mint flavored mouthwash (0.12% and 0.2%), gel (1%), and spray (0.2%); spray delivery is useful when access is limited, and gel for dysphagic patients. Long-term use of Chlorhexidine stains teeth and in rare cases produces idiosyncratic mucosal irritation but the benefits in reducing plaque far outweigh the side-effects.

Effective mechanical plaque control and dietary control of sugar intake are the most effective methods for prevention of periodontal disease and dental caries. COMA (1992) recommends that "*elderly people should restrict the amount and frequency of consumption of non-milk extrinsic sugars because their teeth are more likely to decay due to exposure of tooth roots and reduced salivary flow*". It is important that dietary advice for oral health does not jeopardize the health and well being of the individual. A significant energy intake is derived from sucrose and fats, foods with little or no nutrient density. Guidelines for putting oral health into the context of healthy eating for older people can be adapted for particular client groups and care settings (Fiske and Lewis, 1995).

Prescription of sugar-based medicines for dentate persons is also a matter of concern, and of even greater concern if taken with xerostomic medication (Field *et al.*, 2001). Sugar-free alternatives should be considered. Food supplements taken orally to ensure adequate nutritional intake are a risk factor for dental caries in dentate persons of all ages as many of the these products contain cariogenic sugars and carbohydrates. In order to encourage intake, cartons may be sipped at frequent intervals throughout the day, thus increasing the tooth–food contact time. Aggressive preventive measures are therefore essential for dentate persons on xerostomic medication, long-term sugar-based medication or cariogenic food supplements.

Toothpaste containing fluoride or monofluorophosphate is advocated routinely to remineralize and strengthen surface enamel, increasing its resistance to decay. Sensitivity due to recession can be relieved by toothpastes containing strontium chloride hexahydrate or formalin. However, oral hygiene products may appear expensive and have a low priority for people managing on reduced domestic budgets.

Topical fluorides confer significant resistance to decay and reduce dentine sensitivity but should not be prescribed without prior reference to the fluoride content of the local water supply; fluoridation is currently confined to approximately 10% of water supplies in the United Kingdom (West Cumbria, West Midlands, and the North East). Fluoride varnish is applied professionally. Fluoride mouthwashes (sodium fluoride 0.05% daily and 0.2% weekly) are available as pharmacy medicines. Concentrated fluoride mouthwash (sodium fluoride 2%) is not recommended for people who have difficulty preparing the correct dilution. Brush on fluoride gel (0.4% stannous fluoride) may be more suitable for self-administered prevention. The older dentate person who is medically compromised or at risk of caries or periodontal disease due to diminished self-care or reduction in salivary flow, will benefit from preventive measures which include topical fluorides, chemical plaque control and saliva substitutes. Oral care procedures and a guide to assessment for the dependent patient are summarized (Tables 2 and 3) (Griffiths and Boyle, 2005b; Griffiths and Lewis, 2002). It is important to ensure that toothpaste residue is removed after brushing because of the drying effect.

Prosthetic Treatment

Normative prosthetic need is high; however, demand is considerably lower. Denture replacement will be concentrated more and more in the elderly population, and adults needing a full clearance will be increasingly elderly. Treatment should aim to eliminate pathology and provide comfort, improve aesthetics and masticatory ability, but with due consideration of the individual's needs, previous denture experience and ability for self-care.

Table 2 Summary of oral care for the dependent patient (Griffiths and Boyle, 2005b)

NB: Gloves should be worn for all oral hygiene procedures
Prepare appropriate oral hygiene materials
Place the patient in a sitting or semi-fowler's position to protect the airway
Protect the patient's clothing
Remove dentures or other removable appliances

- *Dentate patient*
  If necessary insert a mouth prop to gain access
  Floss interproximal surfaces of teeth, taking care not to traumatize gingivae
  Brush all surfaces using Fluoride toothpaste or Chlorhexidine gel. (Remember that traditional foaming agents in toothpaste inactivate chlorhexidine so use one or other or alternate their use, at different times of the day).
  Rinse or aspirate to remove saliva and toothpaste
- *Dentate and edentulous patients*
  Gently retract cheeks and brush inside surfaces with soft, gentle strokes
  Using gauze to hold the tongue, gently pull the tongue forward and brush surface gently from rear to front
  Gently brush palate
  Towel or swab mouth if toothbrushing is not possible
  Aspirate throughout procedures if airway is at risk
- *Dentures and removable appliances*
  Brush vigorously with unperfumed household soap
  Pay particular attention to clasps
  Rinse well in cold water
  Saliva substitute may be required before replacing denture in the mouth
- *Intubated patients*
  Reposition tube frequently to prevent lip soreness
  Ensure tube is secure before proceeding with oral care
  Proceed with oral care as appropriate

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Successful restoration of occlusion with partial or complete dentures will depend upon patient motivation and the ability to learn the skills necessary to control and use them. Aesthetics may be of more importance to some patients than function. Improved aesthetics and masticatory ability should be stressed and may be effective in improving motivation. Previous successful denture experience is a useful indicator of likely success with new dentures; the main difficulty is in making an accurate assessment of the patient's motivation and adaptability. It may be necessary to approach this through the multidisciplinary team and enlist the advice and support of relatives and carers, particularly if the patient is confused or cognitively impaired.

Learning to wear dentures is more difficult for the older person as muscular patterns are established and learning ability is decreased. Gradual rather than sudden changes in the dentition make adaptation easier. Failure of partial dentures is frequently due to overloading abutment teeth and plaque accumulation leading to periodontal disease, but patient motivation and regular recall are as important as design in determining success rates. With poor motivation, extraction and the provision of dentures may be contraindicated.

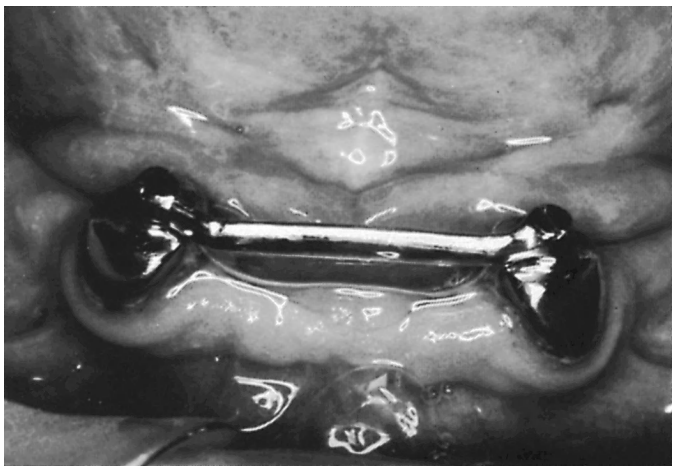


Figure 20 Dolder bar anchoring the crowns of mandibular canines (By courtesy of A. Ali)

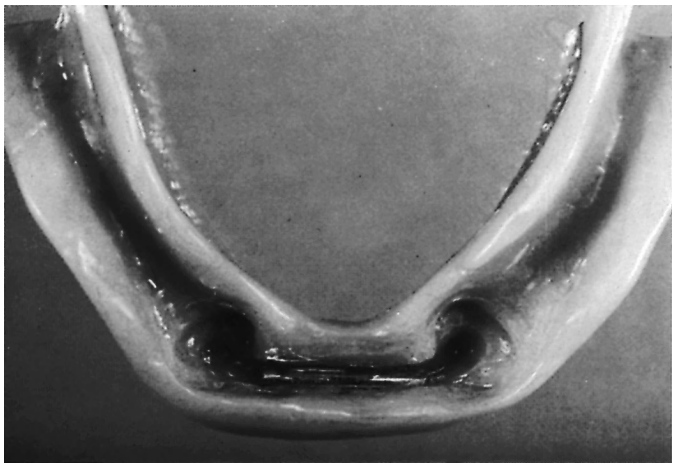
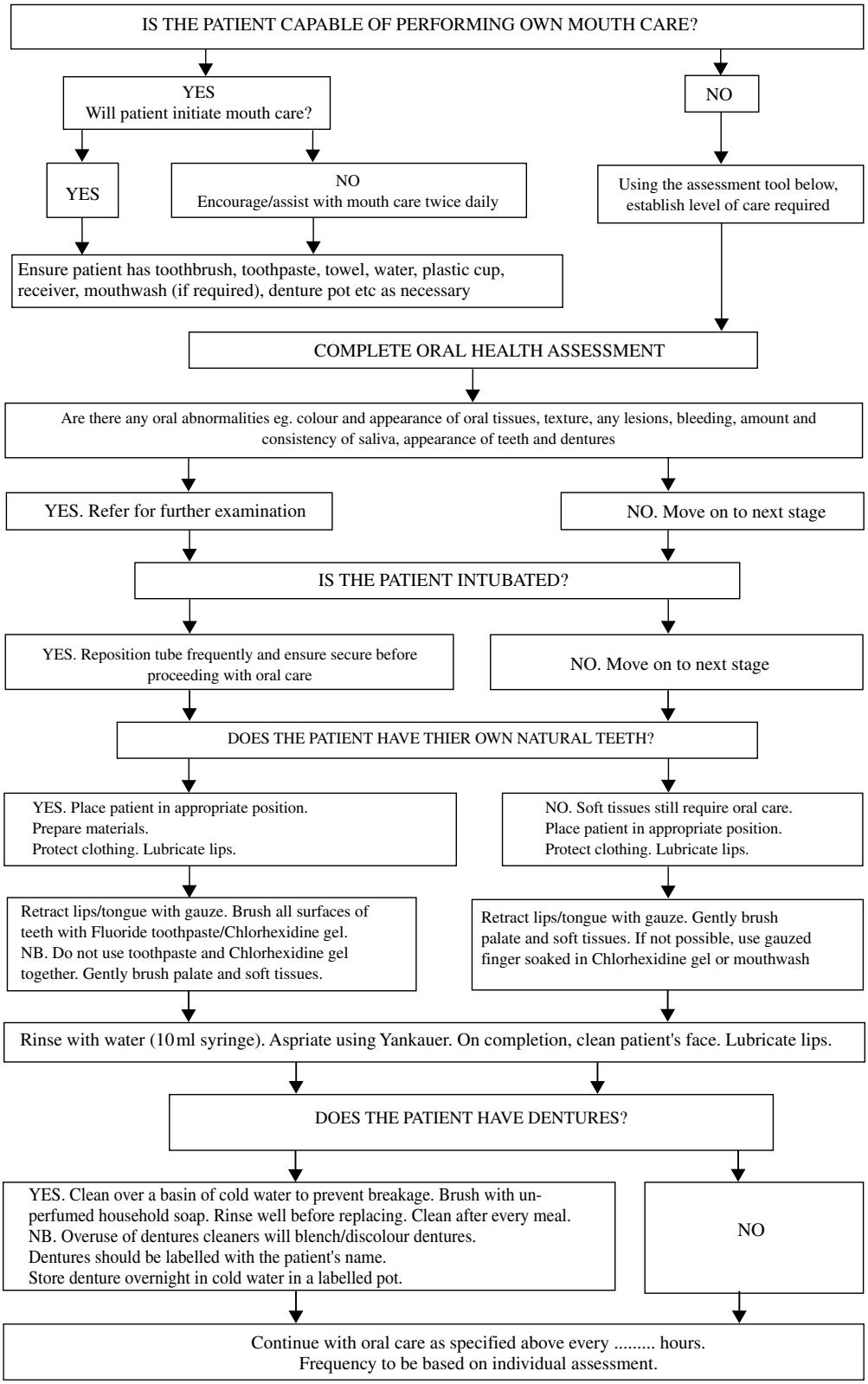


Figure 21 The fit surface of the lower denture which is anchored by the Dolder bar and helps to maintain denture stability (By courtesy of A. Ali)

Over-dentures that cover retained roots and suitably adapted crowns are beneficial in retaining proprioceptive feedback and tactile sensation. Modifications or attachments to the existing teeth help locate the denture and improve stability with obvious consequences for patient satisfaction (Figures 20 and 21). Good oral hygiene must be maintained particularly at the fit surface of the over-denture. If extraction and progression to full dentures is proposed, it should, if possible, be carried incrementally by first providing a training appliance to allow gradual acclimatization before progressing to the edentulous state and complete dentures (Figure 22). Immediate addition of teeth to the training appliance when natural teeth are extracted can provide uninterrupted function and gentle adaptation. If a more rapid transition is required, extractions followed by insertion of immediate complete dentures may be indicated. Pre-extraction models permit a more accurate copy of the previous dentition both in terms of anatomical position of teeth and appearance.

Table 3 Oral Assessment Guide (Griffiths and Lewis, 2002)



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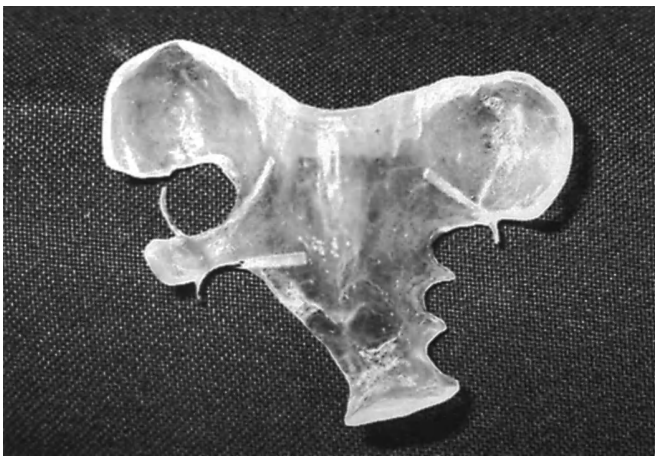

Figure 22 Clear acrylic partial training appliance constructed for a 58-year-old male with cerebral palsy and intellectual impairment

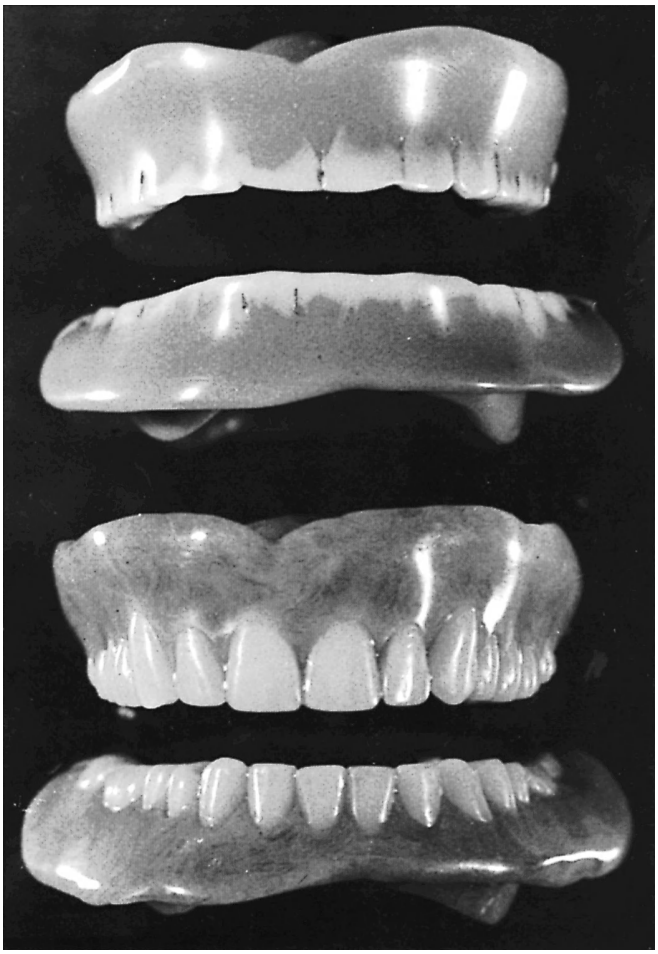

Figure 23 Old worn acrylic resin dentures showing gross occlusal wear and abrasion (above) and new dentures (below)

For the edentulous patient, complete dentures can restore function and aesthetics. Patients frequently do not complain about ill-fitting dentures because of gradual adaptation to progressive oral changes; therefore, it may be difficult for the older denture wearer to adapt to new dentures (Figure 23). In the absence of major defects, ill-fitting dentures can be relined. Temporary linings allow a more even distribution of occlusal forces and allow damaged soft tissue to recover before permanent reline or replacement. Permanent soft linings of silicone or plasticized acrylic resin may improve comfort if the mandible is atrophic. However, these materials lose their plasticity and should be replaced at regular intervals.

Contrary to popular belief, denture construction requires considerable skill and a significant level of cooperation. Impression taking can be distressing and requires compliance to obtain an accurate functional record. The copy technique provides a less invasive method of replacing dentures, while maintaining the contours to which the patient has become habituated but eliminating unsatisfactory features such as wear, poor occlusion or loss of fit due to alveolar resorption. It involves taking an impression of an existing denture. Therefore, a previous set of dentures, however old or unsatisfactory, is essential. Denture retention relies upon the size and shape of alveolar ridges. Gross alveolar resorption reduces retention and stability. Anatomical features that interfere with retention can be eliminated with preprosthetic sulco-plasty or surgical removal of the mylohyoid ridges and benefit healthy patients who can tolerate the procedure. Assessment of the patient's motivation to wear dentures is essential before considering surgery.

Reduced salivation impairs retention and causes discomfort; saliva substitutes provide symptom relief and may improve retention. Pilocarpine is effective in stimulating salivary flow post irradiation and may provide relief for drug-induced xerostomia. However, some patients fail to adapt to new dentures in spite of good anatomical features for success. An upper "social" denture may satisfy the needs of patient or family in restoring appearance and speech. Older people who lose teeth in later life and have difficulty retaining and controlling dentures may benefit from implant-supported dentures provided that wound healing is not compromised by other medical problems.

Denture hygiene is a significant problem. Many denture wearers do not clean their dentures effectively. Nurses lack information on effective methods for denture hygiene (Barber *et al.*, 2002). Denture-related stomatitis may resolve with good denture hygiene, removal at night, and by ensuring adequate oral lubrication. Candidal infection is the most common pathogen in denture stomatitis (*see also* **Chapter 23, Oral Disease**); antifungal therapy may be necessary in conjunction with the above measures. When immediate or new dentures are fitted, patients are advised to wear them continuously for a limited period but with regular removal to allow scrupulous cleaning. After a period of acclimatization, patients should be advised to routinely remove dentures at night.

Denture cleaning procedures should be simple, consistent, and carried out after meals and at night. Cleaning over a sink of cold water reduces the risk of accidental fracture. Recommendations are summarized in Table 4; with the exception

Table 4 Care of dentures (Gloves should be worn when handling a patient's dentures)

Denture hygiene techniques	Acrylic resin (plastic)	Metal and acrylic resin	Temporary soft linings	Permanent soft linings
Rinse after every meal with cold water	√	√	√	√
Remove debris by brushing with soft brush using	Unperfumed household soap and water	Unperfumed household soap and water	Do not brush. Rinse well in cold water	Unperfumed household soap and water
Soak in alkaline hypochlorite solution (Milton or Dentural)	20 min	10 min	20 min	20 min
OR				
Soak in alkaline peroxide solution (Steradent) using hand hot warm water	15 min	15 min. Do not use acid cleaners	Do not use alkaline peroxide cleaners	
Rinse well with cold water before insertion	√	√	√	√
Store in cold water over night	√	√	√	√

of temporary soft linings which are easily damaged, brushing is the most effective method of cleaning dentures. Effervescent cleaning tablets can be confused with sweets and were implicated in the accidental death of an elderly inpatient (Mackenzie, 1982). Hard calculus deposits cannot be removed by brushing and require professional attention. Immersion in an ultrasonic cleaning bath is effective but care must be taken to ensure dentures are labeled to avoid possible confusion (Figure 24). Clear advice about denture management and hygiene, both verbal and written, should be provided to patient and/or carer. Advice should cover expectations, limitations and lifespan, pain management, problems with speech and salivation, denture hygiene, and labeling.

Soft tissues need oral care in the dentate and edentulous (Tables 2 and 3). Gentle brushing with a soft toothbrush will remove plaque and food debris which tend to accumulate mainly in the buccal sulci. A sweeping action with a gauze-covered finger using chlorhexidine gluconate gel or mouthwash may be substituted if brushing cannot be tolerated. There is little scientific value in the use of foam mouth sticks except for uncooperative and terminally ill patients (Bowsher *et al.*, 1999).

Recommendations are made for routinely naming dentures particularly on admission to residential or continuing care (Barber *et al.*, 2002; Fiske *et al.*, 2000). Few dentures are marked in construction despite long-standing recommendations; when asked, patients are generally in favor of having them *named*. There are additional benefits in identification at postmortem or of unconscious or amnesic persons. In the author's experience of working in acute and continuing care hospital services most referrals for replacement of lost dentures are from acute wards. The emotional distress of being without dentures for several weeks while new dentures are being made cannot be quantified. Denture construction is both labor intensive and costly; it involves a minimum of five visits and presupposes the patient's mental and physical ability to cooperate with treatment. In a number of cases, this is a contraindication to treatment.

Naming dentures is a cheap and simple procedure using a proprietary marking kit. Results are not as durable as laboratory methods and renaming should be carried out at regular intervals. If carried out on admission, it can reasonably be assumed that the dentures are the patient's property. It would help reduce the problem of confused patients wearing the wrong denture or when dentures have been erroneously collected "en masse"' for cleaning. The British Society for Disability and Oral Health (BSDH) recommends a policy for denture care that includes labeling and responsibility for the cost of replacement dentures (Fiske *et al.*, 2000). Naming dentures does not prevent loss, but if found, they can be returned to the owner (Table 5).

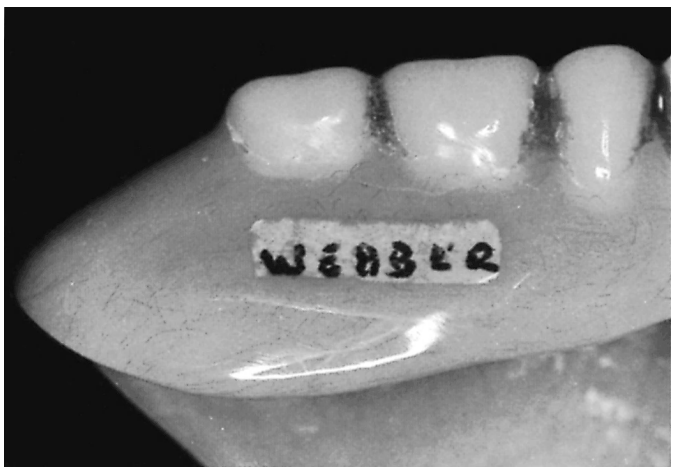

Figure 24 Labeled denture

PEOPLE REQUIRING SPECIAL CARE

Functionally independent healthy adults make up the majority of the older population; they will have increasing expectations about maintaining good oral health and appearance, and many will have the resources to take advantage of advances in cosmetic dentistry (BDA, 2003). However, frail and functionally dependent older people will largely fall within the remit of special care dentistry, which is evolving as a speciality concerned with the oral health needs of specific groups. Special care is defined as

"*those who by virtue of illness, disease and/or its treatment, disability, lifestyle or cultural practices, who are at greater risk of poor*

Table 5 Recommendations to develop local standards for oral health in residential and continuing care

1. Liaison between health, social, and voluntary agencies to identify residential and continuing care establishments without a dental service or with inadequate access to dental services.
2. Screening programs to identify baseline data for dental service planning and oral health promotion strategies appropriate to residents' needs.
3. Oral assessment criteria on admission to identify
   (a) risk factors for oral health;
   (b) individual oral care needs and develop an oral care plan;
   (c) appropriate oral hygiene equipment;
   (d) preventive and palliative measures;
   (e) need for and access to dental services.
4. A policy on the care and safe-keeping of a resident's dentures to include
   (a) denture labeling on admission with the resident's consent;
   (b) responsibility for the cost of replacement dentures if lost or mislaid.
5. Dental input to multi/inter-disciplinary assessment where appropriate including
   (a) procedures for access to pain relief, appropriate general and specialist dental services, oral hygiene advice, and support;
   (b) support for health professionals and carers in oral care;
   (c) procedures for ensuring continuity of dental care on discharge.
6. Training for health care professionals in
   (a) the scientific basis of oral health and disease;
   (b) oral assessment criteria and tools for oral assessment;
   (c) identification of risk factors and stressors for oral health;
   (d) current oral care practices appropriate to individual needs;
   (e) practical oral care to motivate, encourage, support, and assist residents to carry out oral, dental, and denture hygiene;
   (f) eligibility for free or partial exemption for the cost of NHS dental care;
   (g) accessing local dental services.
7. Oral health advice and support for residents, family, and carers, appropriate to their needs.
8. Oral health education and promotion for residents, carers, and health professionals which address
   (a) the oral health needs of residents;
   (b) dietary issues in the context of healthy eating for oral and general health.
9. Facilities for privacy, dignity, and comfort for personal oral hygiene and on-site dental screening, assessment, and treatment.
10. Negotiated standards and procedures for oral health which promote structure and process for putting theory into practice and which can be monitored/audited (Fiske *et al.*, 2000)

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oral health, for whom the management of dental care poses other health risks or who experience barriers to the access and receipt of dental care" (Griffiths, 2000).

Gerodontology is a well-established specialty developed in response to the oral health needs and provision of care for older people with chronic debilitating physical or mental illness, pharmacology, and psychosocial problems. Both specialities are raising awareness of the oral health needs of frail and functionally dependent older people in residential care and in the community. Identification of those in the community presents the greatest challenge and it is therefore essential that the dental profession works closely with statutory and voluntary agencies to ensure people are aware of oral health care services available to them, and address the training needs of personal and professional carers.

A comprehensive assessment is essential at the start of any health intervention. Oral assessment is necessary at the first episode of care to identify existing oral health needs, risk factors, and appropriate preventive measures. During an acute phase of illness, the need for oral care requires monitoring and later during the phases of recovery and rehabilitation. There is no single assessment tool that weighs the different factors, quantifies risk status and subsequently translates into the degree and type of intervention required. Assessment tools which alert health professionals to problems can be adapted to different client groups and assist in the development of an oral care plan (Table 6) (Griffiths, 2002). More complex assessments require training to recognize the signs and symptoms of oral pathology. Furthermore, assessment facilitates the identification of individuals who might benefit from services.

Key areas that give an indication of oral health status and point toward objectives for care include

- *presence of existing symptoms and signs of oro-dental disease including early changes to dental and soft tissues;*
- *current mouth care practices and preventive behaviour, including dental service attendance patterns;*
- *presence of risk factors including systemic disease, medication, impairment, and disability;*
- *presence of key stressors for oral health* (Griffiths and Boyle, 2005c).

Oral assessment with consideration of the likely prognostic course of the disease at an early stage will help alleviate later problems and permit gradual adjustment to changes in dental status. Oral health assessment should be incorporated into routine assessment. It need not be confined to

Table 6 Oral health assessment by health professionals provides a mechanism for opportunistic identification of clients who have oral and/or dental problems, are not receiving regular dental care and/or are at risk of poor oral health. Subjective indicators include the ability to speak, smile or eat without pain or discomfort. This example of an Oral Health Assessment may be adapted to suit any client group or adapted for self-assessment. It is recommended that risk assessments are used in collaboration with local dental services in order to facilitate access to an appropriate dental service. The Community Dental Service is best placed to fulfill the role of facilitator. A response in a highlighted area signifies a need for further investigation or action (Griffiths and Lewis, 2002)

1. Does the client have natural teeth?	☐ NO	☐ YES	☐ Don't Know
2. Does the client wear dentures?	☐ NO	☐ YES	☐ Don't Know
	Specify	☐ Upper	☐ Lower
(a) YES, are dentures labelled?	☐ YES	☐ NO	☐ Don't Know
(b) If YES, how old are dentures?	☐ >5 yrs	☐ **<5 yrs**	☐ **Don't Know**
3. Does the client have any problems? e.g. pain, discomfort, difficulty eating, decayed teeth, denture problems, ulcers, dry mouth, halitosis etc. If YES, describe the problem.	☐ NO	☐ **YES**	☐ **Don't Know**
4. Does the client smoke or have a past history of smoking?	☐ NO	☐ **YES**	☐ **Don't Know**
5. Is the client taking medication? Check the British National Formulary for oral side-effects	☐ NO	☐ **YES**	☐ **Don't Know**
6. Is urgent dental treatment required?	☐ NO	☐ **YES**	☐ **Don't Know**
7. Date of last dental treatment?	☐ >1 yr	☐ **<1 yr**	☐ **Don't Know**
8. Registered for dental care? If Yes, record name and address of dentist.	☐ YES	☐ **NO**	☐ **Don't Know**

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professional carers but should be incorporated into wider assessment by members of the multiprofessional team. Organizational links between health professionals and the dental profession facilitate the provision of appropriate dental care and preventive measures at the earliest opportunity to the benefit of patient and carer. These objectives can be best achieved by including dentistry within the multidisciplinary team (Fiske *et al.*, 2000).

There is a need to establish dental fitness at diagnosis for people with continuing health care needs, particularly when cognitive faculties deteriorate. Most oral and dental problems in Alzheimer's disease result from a progressive diminution in self-care (*see also* **Chapter 93, Clinical Aspects of Alzheimer's Disease**). The same principles apply to stroke and other neurological disorders which cause physical disability, and in particular, conditions which affect oro-facial musculature causing paralysis or sensory loss, impaired oropharyngeal reflexes, and a reduction in neuromuscular control (Griffiths, 2002) (*see also* **Chapter 71, Acute Stroke**; **Chapter 81, Muscle Disorders**). The dental team can make a significant contribution to the process of rehabilitation and quality of life. The effect of early advice and support should help to alleviate the stress and psychological morbidity among carers.

Advice on the potential oral side effects of medication, methods of overcoming manual limitations in oral hygiene techniques, instruction in techniques, which overcome disability and modifications to toothbrushes before the onset of poor or deteriorating oral hygiene, may help to motivate patient and/or carer. Information on chemical plaque control and preventive measures is essential. The dental hygienist is best qualified to deliver this under the guidance and prescription of a dentist who has examined the patient.

Oncology patients are at risk of distressing and potentially life-threatening symptoms and oral side effects (*see also* **Chapter 128, Cancer and Aging**; **Chapter 129, Oncological Emergencies and Urgencies**). Oral tissues are more prone to inflammation and infection. Patients may complain of disturbance of taste, dysphagia, soreness, and dry mouth. Xerostomia due to irradiation of the salivary glands encourages excessive plaque formation, which leads to characteristic decalcification of the enamel encircling crowns (Figure 25); this is particularly difficult to restore. Reduced salivary flow on thin and atrophic mucosa creates greater susceptibility to irritation. Dentures may cause discomfort or trauma. Detailed guidance for the oral care of oncology patients receiving radiotherapy, chemotherapy or bone marrow transplantation may ameliorate the serious oral side effects associated with treatment (Fiske and Lewis, 2001). A high standard of oral hygiene should be maintained together with necessary preventive or palliative measures. To maximize comfort, oral assessment, oral hygiene instruction, and preventive measures should be provided at diagnosis and

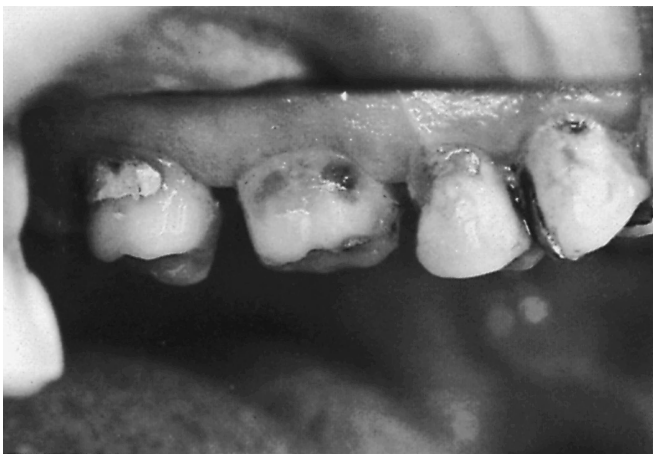

Figure 25 Post-radiation cervical caries encircling the teeth

repeated at intervals during treatment. Information on the anticipated oral side effects of treatment may be helpful to enable the patient to cope with discomfort and encourage greater attention to oral hygiene and acceptance of routine preventive measures.

Severely or terminally ill patients require increased daily attention to oral care and comfort (*see also* **Chapter 170, Management of the Dying Patient**). Standards of mouth care in professional care settings are inadequate and are based on the use of inappropriate tools and materials (Rawlins and Trueman, 2001; Fiske *et al.*, 2000; McNeill, 2000; Bowsher *et al.*, 1999). A high prevalence of oral symptoms and denture-related pathology affect the quality of life in terminally ill patients (Aldred *et al.*, 1991). Denture wearers experienced difficulties and more than half wore dentures at night. Candidal carriage is higher in terminally ill subjects; a clinical diagnosis of oral candidosis was made in 70% and isolated in 79% of the sample. More than half complained of oral dryness, which must be viewed in the context of pain relief by opiate derivatives that exacerbate xerostomia. Improved denture hygiene to reduce microbial contamination, removing dentures at night, temporary relines, and maintaining oral lubrication provide some relief. The dentist, hygienist, and nursing staff should collaborate to establish appropriate individual oral hygiene to minimize oral discomfort in acute illness and the final stages of life. However, it is the day-to-day responsibility of nursing staff to deliver appropriate oral care. An oral assessment guide for patients who are dependent, dysphagic, or critically ill will facilitate the identification of appropriate oral care (Table 3) (Griffiths and Lewis, 2002).

DENTAL SERVICES

Provision and improvement of dental services for the older population has been a matter of professional concern for many years. There have been major changes in the delivery of dental services in recent decades and changes in the organizational structure of the NHS. There will continue to be major changes in the delivery of primary dental care due to the current pace of legislative changes. Clinical governance, clinical guidelines, and new care pathways will also impact on how dental services are delivered within all dental services.

Responsibility for dental services has devolved from central government to Primary Care Trusts and Local Health Boards. As a result of local commissioning, traditional differences between general dental services and salaried services are likely to change. The role of the Community Dental Service (CDS) in monitoring levels of dental health in all sections of society and in identifying and providing services to patients requiring "special care" dentistry is being eroded by pressure to provide care for the general population who are unable to access NHS dental care. One in five adults in Britain claim that they experience difficulty finding an NHS dentist (McGrath *et al.*, 2001).

The BDA monograph makes comprehensive recommendations for dental services to meet the needs and requirements of the growing population of older people in the United Kingdom (BDA, 2003). The supply of dental services will need to change and be more accessible to people with restricted mobility. Local commissioning of dental services will need to be fully integrated within the NHS. While general dental services will be at the heart of providing primary dental care, health authorities will need to provide support for dental services to frail older people in residential care and within the community. It is essential that the role of the CDS is protected and developed as a provider of specialist care and advice for older patients in order to deal with the increased complexity of treatment demands. It is likely that responsibility for demanding contracts for dental services for older people will continue to lie with the dental profession and relevant pressure groups. Barriers to dental care need to be researched in the light of changes in the organization of NHS dental services and the availability of dental care.

Initiatives to increase service utilization by frail older people are recommended. People in residential care settings can be identified with relative ease as compared with those within the community. Assessment of risk factors can be carried out by nondental personnel. Functional assessment by health care teams is well recognized, particularly for people aged over 75 (*see also* **Chapter 132, Function Assessment Scales**; **Chapter 74, Stroke Rehabilitation**). Implementation of the "Single Assessment Process" and "Unified Assessment" provide an opportunity to include a basic oral health risk assessment into a comprehensive holistic assessment process (DoH, 2001a; WAG, 2002). An oral health care assessment is now a fundamental requirement in all health and social care settings in Wales (WAG, 2003). A simple questionnaire can highlight risk factors and alert professional carers to oral and dental needs (Table 6) (Griffiths, 2002). Liaison between hospital and CDSs provide a mechanism for coordinating and ensuring that older people have access to dental services on discharge. Access to dental care should be included in hospital discharge policy with the CDS acting as a facilitator in this process (*see also* **Chapter 159, Systems of Health Care: the United Kingdom, the United States, and Australia**).

Within long-term care facilities, numerous problems mitigate against routine provision of oral health care and encourage neglect (Fiske *et al.*, 2000; Frenkel *et al.*, 2000). Many institutions do not support a policy for oral health care. Guidance on the wide ranging issues of the needs and demands of residents, knowledge and skills of care staff, screening and oral assessment, diet and nutrition, oral health education and promotion, and access to oral hygiene equipment and dental services is designed to develop local standards for oral health care (Fiske *et al.*, 2000) (Table 5). Changes in nursing practice are slow to be addressed nationally although there is increasing interest in oral hygiene in the nursing press. Changes at a local level require the support of the relevant manager (Griffiths and Boyle, 2005d). Standards for oral health care in residential care facilities must be included in registration criteria by the Social Services Inspectorate.

Dental care in hospital is generally the responsibility of the hospital dental service; however, variation exists in service delivery throughout the United Kingdom. Where dental surgeries exist on hospital premises, quality of care also depends upon the adequacy of the facilities and equipment. A controlled area such as a clear treatment room can satisfy basic requirements. Procedures that generate aerosol droplet infection should not be carried out at the bedside because of the risk of aerosol spread of medically resistant bacteria and proximity of patients vulnerable to infection. Self-drive mobile dental units have been advocated but they are quite unsuitable for patients who are very frail or dependent. Acceptance of the dental team as recognized members of the multidisciplinary team serves to increase oral and dental health awareness with a potential for improved oral health for patients.

Domiciliary dental care has been available for many years for "*patients whose condition precludes attendance at a dental surgery*". Whereas most housebound patients have medical or mobility problems, there may be other social or psychological reasons for providing care at home. Domiciliary care is not widely known, neither is it offered routinely by general dental practitioners. Demand for this service is increasing as a result of demographic population changes, greater awareness of legislation to support equal opportunities for disabled people, increasing public awareness and the increase in the dentate population. Treatment usually comprises typically inexpensive, short duration procedures such as examination, hygiene procedures, denture provision and simple extractions. The development of atraumatic restorative techniques and materials have widened the scope of treatment that can be provided.

Limitations to providing dental care out of a clinical environment include health and safety issues such as manual handling and cross-infection control, the scope of dental procedures and lack of diagnostic radiography. Most of the current need is prosthetic, is noninvasive and requires very little in the way of complex equipment so can be provided in the home environment with minimal difficulty. Invasive procedures require portable equipment and the quality or complexity of care may at times be affected by the "unusual clinical circumstances". Cost of domiciliary equipment is prohibitive and purchase is generally confined to CDSs. Once dental fitness has been established or treatment completed, patients may be transferred to general dental practitioners for periodic domiciliary assessment, continuing care and prevention; withdrawal from NHS coverage makes this increasingly unlikely. Dentate patients may need domiciliary advice and support from a hygienist to maintain oral hygiene.

Surgical procedures carried out at home are confined to simple uncomplicated extractions. The support of family, carer or a medical ancillary worker may be required to provide after care for patients who have little support or live alone. The decision to proceed with any surgical procedures must include a thorough appraisal of the medical history and suitability of the domestic environment. Practicalities of cross-infection control must be evaluated before proceeding with surgical techniques. A mobile dental unit overcomes some of the disadvantages, permitting more complex restorative care while avoiding the stress of traveling to a dental surgery. The drawbacks of the initial expense must be weighed against the flexibility that a self-drive mobile unit provides in reaching a variety of isolated populations who might otherwise not receive treatment.

Domiciliary dental care is time consuming and the cost of purchasing portable equipment may be a financial disincentive to the general dental practitioner. The CDS is currently the major provider of domiciliary dental care in the United Kingdom. Liaison with local medical and dental practitioners, and health care professionals in developing a time efficient service is a function that the CDS is best able to provide. Screening, diagnosis, and advice at home may, in many cases, reduce inconvenience to the housebound, particularly if care cannot be provided at home and referral is necessary. The limitations and disadvantages for clinicians must be weighed against the advantages and benefits for the patient. The role of the CDS in providing domiciliary care must be protected and developed together with financial incentives to encourage general dental practitioners to provide domiciliary care. If these issues are not addressed, older frail or disabled people living in nonresidential settings will be at risk of being denied access to continuing oral health care services.

ORAL AND DENTAL HEALTH PROMOTION

Improvements in dental services will not alone improve the oral health of older people. Oral and dental health education programs that address the specific needs of the target group are more effective. A participative approach that encourages self-empowerment with an emphasis on informed decision-making is advocated. Programs need to be designed specifically for older people and adapted to address the needs of people who are physically or mentally impaired.

Key messages include dietary control of extrinsic sugars, effective plaque control, benefits of fluoride, care and use of dentures, smoking cessation, and regular dental attendance. This might, where relevant, include the use of sugar-free medicines and oral side effects of medication, and any other oral problems associated with specific conditions. Chair-side oral health information is considered to be more effective than mass media campaigns, and should be backed up with written information. However, this relies on dental attendance. For those who are not in regular contact with dental services, other mechanisms must be evaluated to deliver the key messages and provide advice on the local availability of dental services. Daytime television is suggested as an effective communication medium (BDA, 2003). Information must be provided in accessible formats and in a range of languages.

All health personnel should receive additional training to support the concept of primary oral health care (*see also* **Chapter 149, Geriatric Medicine Education in Europe**; **Chapter 157, Nursing (UK)**). This includes care providers in voluntary and social care settings. Training

programs need to stress how poor standards of oral hygiene can pose a serious health threat in relation to general health and aspiration infections (*see also* **Chapter 60, Aspiration Pneumonia**; **Chapter 61, Respiratory Disease in the Elderly**). With adequate training, there is no reason why people without nursing qualifications would be any less proficient in the identification of oral health problems and dental needs than the nursing professionals; however, high staff turnover and accommodating shift patterns can make this type of training difficult to organize successfully (BDA, 2003). There are conflicting reports of the effectiveness of oral health education programs. Improvements in the knowledge of care staff are reported (Frenkel *et al.*, 2001) but evaluation of a carers' training program after a year demonstrated that there had been no changes in practice and no measurable improvement in residents' oral health (Simons *et al.*, 2000). Local standards for oral health care and cascade training may help to overcome this serious barrier to promoting the oral health of frail or dependent older people. Pre and postregistration nurse training must address this historical lack of oral and dental health education.

Individual oral hygiene instruction, and continued supervision should be allocated to a dental hygienist, who is trained in communication skills, and has a major role to play in residential and community settings in educating patients and their carers. The attachment of a hygienist to continuing care facilities enables direct support to improve oral health and hygiene at a local level, reinforce standards for oral health and facilitate earlier identification of oral pathology.

Oral health should not be considered in isolation from general health but integrated into general health promotion and include strategies to facilitate contact with dental services. It should be an essential part of the curriculum for all health professionals as well as members of the dental team.

PROFESSIONAL TRAINING

Changing clinical needs and demands of the older population require changes in training for the whole dental team (BDA, 2003). Following guidance from the General Dental Council, gerodontology is receiving greater attention in the undergraduate curriculum (Thompson *et al.*, 2001) (*see also* **Chapter 150, Education in Geriatric Medicine in the United Kingdom**). The dental profession will need increased clinical skills to deal with the challenges of restorative care. Greater attention to communication skills will be essential, particularly for patients with cognitive impairment. Effective postgraduate and postregistration training programs are essential for dentists and professions complimentary to dentistry (therapists, hygienists, and dental nurses). It is recommended that by the time age discrimination legislation is put into effect in 2006, all members of the dental team will have received awareness training as it applies to patient care, as part of their curricula (BDA, 2003).

The paternalistic model of care is being challenged. Exposure to different client groups does not alone change attitudes or negative stereotypes. Appropriate teaching and experience of services for frail older people may help to overcome negative attitudes and the evolution of a five-year curriculum which is taking place in many dental schools may provide a focus for structured changes in undergraduate education. Dental public health, behavioral science, and special care dentistry in the undergraduate curriculum provide a further focus for addressing the sociological and behavioral aspects of aging, and perhaps help to promote a multidisciplinary and patient-centered approach to dental care. Through experience and familiarity with the problems, the rewards of working with and for older people may be enjoyed. While the debate into specialist training continues, postgraduate and vocational training programs will continue to be necessary to meet the challenges of an aging population.

SUMMARY

Dental services must address the problem of a large and diverse older population with a variety of dental needs. While current treatment needs are primarily associated with edentulousness, increasing numbers in the upper age range, greater levels impairment and disability, and lower rates of edentulousness will pose new challenges to the dental profession to provide more complex restorative care and satisfy expectations. Key issues are covered in depth in the BDA monograph (BDA, 2003).

KEY POINTS

- Universal access to NHS oral health care with free NHS oral health risk assessment from the age of 60.
- Development of dental services that address the needs of the frail and functionally dependent older people, including greater availability of domiciliary dental care.
- Proper resourcing of the CDS to provide specialist services and clinical leadership in providing care for older people.
- Undergraduate, postgraduate and postqualification training for the dental team in gerodontology and special care dentistry.
- Recognition of special care dentistry as a specialty.
- Mandatory oral health education for all professionals involved with health or social care for older people.
- Dissemination of information in a variety of formats to facilitate informed choice and access to appropriate oral health care.

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23

Oral Disease

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INTRODUCTION

Many people now retain most of their natural teeth into the later decades of life. Once they become edentulous and wear complete dentures, the habit of regular attendance at their dentist is broken. Doctors rather than dentists, therefore, may have the opportunity of regularly examining the mouths of this group of elderly patients who often first consult their doctor rather than their dentist about oral symptoms. Gloves and mask should be worn for the oral examination. A better source of light than the average battery pencil torch is recommended – a headlight or a dental unit light are ideal. A pair of dental hand mirrors serves both to illuminate the oral cavity (by reflected light) and retract the cheeks, lips, and tongue. Subtle changes in the oral mucosa are better detected by drying the surface with a gauze square or with a dental air syringe.

A systematic examination of the lips, cheeks, sulci, teeth, gingivae, retromolar triangles and floor of the mouth, the ventral and dorsal surfaces of the tongue, palate, and oropharynx in turn will ensure that early lesions are not missed. Dentures should be removed and their fit and cleanliness checked and the mouth examined for denture stomatitis (see below), traumatic ulceration, or mucosal hyperplasia at the denture periphery. Any facial swelling or restriction in mouth opening should be noted and the masseter, pterygoid, and temporalis muscles examined for spasm or tenderness. The neck should be palpated for enlarged lymph nodes.

Age changes alone in the teeth, oral mucosa, and salivary glands have little effect on oral health, but the common microbial diseases, such as caries, periodontal diseases, and thrush, remain prevalent with advancing age. Oral ulceration, leukoplakia, and carcinoma are important diseases in the elderly.

Age Changes in Teeth

The enamel becomes increasingly cracked ("acquired lamellae") with age and the surface concentration of fluoride builds up. Attrition, abrasion, and erosion are common (see below). Owing to the deposition of secondary (posteruptive) dentine, teeth become yellower and less sensitive, the pulp recedes from the crown and the root canal becomes narrow and threadlike. Starting at their periphery, the dentinal tubules become progressively obliterated by deposition of calcified peritubular dentine by the odontoblast processes. As a result, the teeth become less sensitive and their roots become translucent and more liable to fracture during extraction.

The odontoblast layer lining the pulp chamber becomes irregular and discontinuous. The pulp tissue is less vascular and cellular (Murray *et al.*, 2002) and undergoes a patchy fibrosis, or features pulp stones composed of dentine and fine calcific deposits. The layer of cementum on the roots becomes progressively thicker.

Tooth Wear

Excessive wearing away of the teeth is commonly the result of a combination of accelerated attrition, abrasion, or erosion.

Attrition

The incisal edges and cusps, and to a lesser extent the approximal surfaces, of the teeth are worn away during chewing. On the usual soft Western diet, the loss of tooth tissue is not clinically significant, unless the teeth are habitually ground together or clenched, often during sleep (nocturnal bruxism).

Abrasion

Misdirected and overenthusiastic horizontal toothbrushing produces substantial grooves at the necks of the teeth and sometimes gingival recession. Dentine exposed by this

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abrasion is often sensitive, toothbrushing may be inhibited, and a plaque-caries sequence initiated. A soft toothbrush with a small head should be used and the technique corrected, with a demonstration by a dentist or dental hygienist (*see* **Chapter 22, Oral Health**).

Erosion

Excess consumption of grapefruit, lemon juice, or other soft drinks of low pH may demineralize the surface of the enamel and the underlying dentine. Eventually, shallow concavities appear on the labial surfaces and incisal edges of the maxillary incisors and the characteristically imbricated enamel surface becomes smooth and thin. By contrast, oral regurgitation of gastric acid due to repeated vomiting or in gastroesophageal reflux will progressively dissolve the palatal surfaces of the teeth. The margins of fillings appear raised above the adjacent eroded tooth surface.

Dental Caries

Older people in good general health generally enjoy better dental health than dependent chronically sick patients living in institutions, who may have more missing teeth or denture problems. People remain at risk from tooth decay in later life, often occurring at the margins of fillings and particularly on root surfaces exposed by receding gums. Xerostomia resulting from medication or other factors (see below) or a failure of toothbrushing or dental flossing or cleaning of partial dentures may also contribute to root caries. Sucrose-containing drinks, sweets, or snacks between meals or last thing at night may be a factor in caries susceptibility at all ages. Regular toothbrushing with a fluoride toothpaste and flossing and application of a topical fluoride gel by a dentist or a hygienist can have surprisingly good results in preventing or arresting caries in this situation. A 0.2% chlorhexidine mouthwash is an effective adjunct to mechanical measures in prevention of the accumulation of dental plaque.

GINGIVAE AND PERIODONTAL LIGAMENT

Age Changes

The gingivae (gums) recede slowly in adult life with minor loss of the periodontal ligament attaching the teeth to the alveolar bone, even in people with good dental plaque control. The changes are slight and do not usually cause tooth loss and "getting long in the tooth" may be regarded as a physiological aging process (Burt, 1994; Streckfus *et al.*, 1999).

Even in old age, only a minority of the population with risk factors such as poor dental hygiene, tobacco smoking, or diabetes mellitus have inflammatory periodontal disease severe enough to cause tooth loss (Burt, 1994) (see the following text).

Localized Gingival Swelling (Epulis)

The fibrous epulis, a localized chronic inflammatory hyperplasia of the gingiva, is a common reactive lesion, a response to an irritant such as dental plaque, calculus, or a cavity margin. The cause should be eliminated, followed by excision of the swelling.

Generalized Gingival Enlargement

Generalized enlargement of the gingivae may represent a chronic inflammatory hyperplasia induced by dental plaque. Medication is an important cause of a generalized swelling of the gingivae, associated with antiepileptics such as phenytoin (dilantin) or sodium valproate, the immunosuppressive cyclosporine, calcium channel blockers (nifedipine, diltiazem, nitrendipine, felodipine, verapamil), or tranexamic acid (Scully and Cawson, 2002).

Leukemia

Leukemic infiltration of the gingivae results in a dramatic enlargement in a matter of weeks, in contrast with the insidious increase in other types of swelling. This clinical feature of leukemia is more characteristic of the acute monocytic or myelocytic varieties.

There are gingival hemorrhages, which are spontaneous, free, and generalized, unlike the localized and limited bleeding typical of chronic gingivitis, which occurs only after eating or toothbrushing. In leukemia, mucosal purpura, and ecchymoses are also commonly found, or occasionally ulceration of the interdental gingival papillae resembling an acute necrotizing ulcerative gingivitis (Vincent's infection) may occur.

Scurvy

The hemorrhagic and erythematous gingivae in scurvy is an uncommon cause of enlarged gingivae. The body stores of vitamin C are often marginal ($<23\,\mu mol\,l^{-1}$) or as low as those found in clinical scurvy ($<1\,\mu mol\,l^{-1}$). Only dentate subjects show this scorbutic gingivitis, and the institutionalized elderly and alcoholics are most at risk.

Chronic Gingivitis and Periodontitis

Chronic periodontal disease may be more important than root caries as the major cause of tooth loss in older people. This commences as a gingivitis initiated by the accumulation

of dental plaque (biofilm) at the necks of the teeth. The gingivae, which are normally pink and stippled and firmly applied to the teeth, become dark red, edematous and glazed, and bleed easily. Only a minority of people are susceptible to progression to periodontal disease associated with specific anaerobic bacteria. The gingival sulcus becomes pathologically deepened to form a pocket from which an inflammatory exudate seeps, causing an offensive taste, halitosis, and bleeding. Gradually, the collagen fibers of the periodontal membrane are destroyed and the alveolar supporting bone resorbed. Eventually, the teeth may become loose, making eating difficult. Less commonly, an acute periodontal abscess may supervene.

In some older patients, there is a good response to instruction in toothbrushing and flossing to remove plaque, and to a course of scaling and polishing of the teeth. A dental hygienist, the patient's relatives or health carers, can be involved in supervising or even giving this home care. Loose, painful, useless teeth should be extracted. For teeth, particularly with deep residual periodontal pockets, regular scaling combined with root planing under local anesthesia can be beneficial in selected elderly patients. Discomfort from exposed root dentine is an indication for application of topical fluoride by a dentist or dental hygienist, or home use of a desensitizing toothpaste containing fluoride or strontium chloride (Sensodyne).

AGE CHANGES IN THE ORAL MUCOSA

Studies of the oral epithelium have not consistently shown any changes with age, when hematological, nutritional or other systemic factors have been carefully discounted (Mackenzie *et al.*, 1996). Fibroblasts in the lamina propria may synthesize less collagen with age and the collagen fibers are thicker and coarser. No loss of functional capacity of the gingival or oral mucosa to withstand normal masticatory forces has been shown, however. Similarly, the sense of taste to sour or sweet substances remains remarkably intact with advancing years (Bartoshuk and Weiffenbach, 1990).

The ectopic sebaceous glands become more prominent in the mucosa of the lips and cheeks of old people (Fordyce's spots).

Multiple varicose veins resembling caviar on the ventral surface of the tongue ("caviar tongue") or lips are also common. The foliate papillae representing leaflike folds of the mucosa covering accumulations of lymphoid tissue (lingual tonsil) situated bilaterally on the posterolateral margins of the tongue may concern elderly people who fear cancer. Owing to the atrophy of the adipose tissue of the cheeks and lips, the minor labial salivary glands become palpable to the alarm of elderly ladies with cancerophobia.

The vermilion border of the lower lip is subject to solar irradiation and may become irregularly mottled (actinic cheilitis), due to alternating atrophy and hyperkeratosis. There is actinic "elastotic" degeneration of the collagen and lamina propria. Crusted nodules representing actinic keratoses or early invasive squamous cell carcinomas may subsequently develop and require excision and, occasionally, the whole of the unstable vermilion border may need to be removed, in a "lip-shave" operation.

To summarize, the morphological changes in the epithelium or lamina propria of the oral mucosa with advancing age, are insufficient to account for the dry, burning sensation of the lips and tongue which troubles some elderly women (see below).

INFECTION OF THE ORAL MUCOSA

Candidosis

Candidosis is the only common oral mucosal infection in older patients. The most important systemic factors promoting oral candidosis in patients over 70 years of age are listed in Table 1. Local factors are also important. The wearing of complete dentures, particularly continuously day and night, boosts oral candidal populations. Smoking significantly increases the candidal carrier rate (Arendorf and Walker, 1980) and most patients with chronic hyperplastic candidosis have had a history of cigarette smoking.

Salivary flow is a further local factor that limits proliferation of candida. Patients with xerostomia due to Sjögren's syndrome have high oral candidal populations (Tapper-Jones *et al.*, 1981) and are susceptible to thrush.

Oral candidosis takes the following forms:

Thrush (Acute Pseudomembranous Candidosis)

The creamy white plaques, resembling milk curds, on the oral mucosa with an inflammatory surround, can be easily wiped off (Figure 1), a point of distinction from leukoplakia.

Denture Stomatitis (Chronic Atrophic Candidosis)

Denture stomatitis is a symptomless inflammation of the palate caused by candida, and possibly anaerobic bacteria, in the microbial plaque on the fitting surface of the upper denture (Figure 2). Continuous night-and-day denture wearing is a key factor.

Table 1 Factors in oral candidosis

A. *Systemic*	
1. Dehydration	
2. Diabetes mellitus	
3. Drugs	– steroids or other immunosuppressives
	– cytotoxic agents
	– antibiotics
4. Malignant disease	
5. Anemias, iron deficiency, neutropenia	
6. Postoperative states	
7. HIV (uncommon in this age group)	
B. *Local*	
1. Denture wearing (particularly continuously)	
2. Tobacco smoking	
3. Xerostomia	

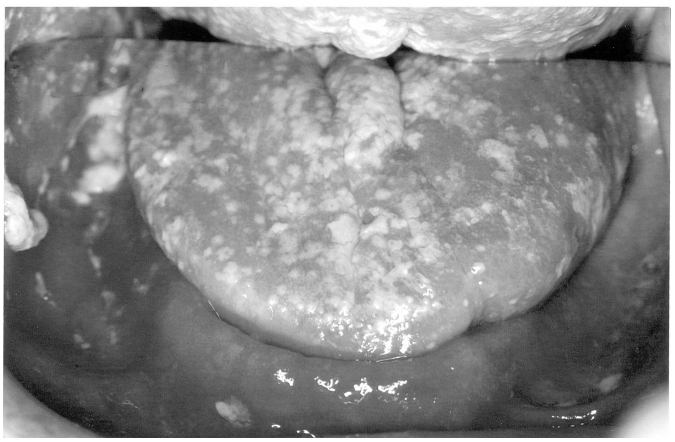

Figure 1 Acute oral pseudomembranous candidosis (thrush). The white plaques could be easily detached

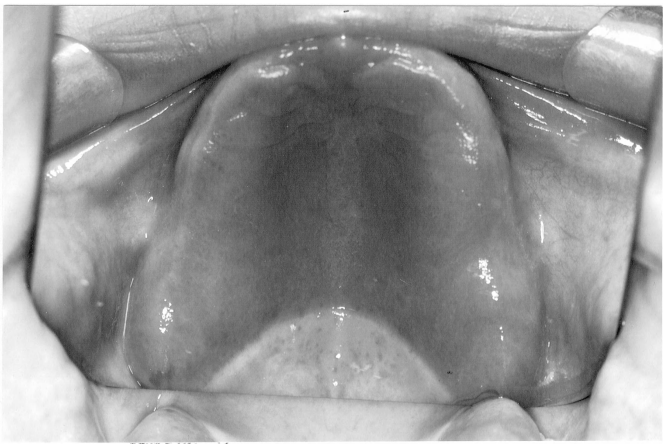

Figure 2 Denture stomatitis in an edentulous patient wearing her dentures continuously day and night. A heavy growth of *Candida albicans* was cultured from the fitting surface of the upper denture

The yeast is carried in the saliva to the other sites, where it may also initiate an angular stomatitis (cheilitis). Dentures should not be worn overnight but instead be immersed in a dilute hypochlorite solution such as dilute Milton or Dentural. Miconazole 2% gel (Daktarin) oral gel may be applied to the fitting surface of the upper denture. Allergy to the acrylic resin of the denture base is only very rarely a cause of denture stomatitis.

Antibiotic Sore Mouth (Acute Atrophic Candidosis)

After broad-spectrum antibiotic therapy the tongue becomes sore, red, and the filiform papillae are lost, whereas the remaining fungiform papillae become prominent.

Chronic Hyperplastic Candidosis (Candidal Leukoplakia)

This appears as chronic nodular or speckled white plaques on the mucosa of the tongue, cheeks, or palate (see below).

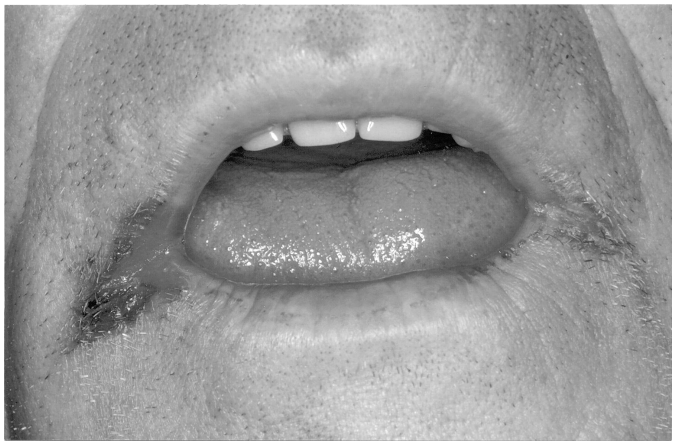

Figure 3 Bilateral angular cheilitis secondary to candidal denture stomatitis

Angular Cheilitis

The skin lateral to the commissures is erythematous, fissured, or eroded (Figure 3). This is commonly due to candida, secondary to a denture stomatitis which should be managed as described above. Old dentures in which the vertical dimension has been substantially reduced owing to excessive wear of the teeth may contribute to angular cheilitis and a dental opinion is advisable. Angular cheilitis may be a feature of iron deficiency anemia, when papillary atrophy of the tongue is usually also present, sometimes as part of the Patterson-Kelly (Plummer-Vinson) syndrome.

Median Rhomboid Glossitis

An elliptical depapillated red area of mucosa, often irregularly keratinized, develops in the midline of the dorsum of the tongue, in its middle or posterior third. It may cause intermittent soreness or more commonly is an incidental finding. It appears to be an acquired chronic oral candidosis rather than, as was previously supposed, a developmental anomaly. Tobacco smoking and denture wearing, and HIV infection in younger patients, have been found to be associated factors.

Amphotericin lozenges (10 mg) dissolved orally three times a day will relieve any symptoms but the condition is otherwise harmless.

Management of Candidal Infections of the Mouth

Attention to local factors such as denture hygiene and continuous denture wearing, tobacco smoking, and predisposing systemic factors (see above) is essential.

Topical antifungal agents such as amphotericin lozenges (10 mg) or suspension (100 mg/ml) or 2% miconazole oral gel are well tolerated. Systemic antifungals such as fluconazole or itraconazole are reserved for profoundly immunocompromised patients with neutropenias or HIV-AIDS (Zegarelli, 1993).

Black Hairy Tongue

The filiform papillae in the posterior third of the tongue become longer and discolored by pigment-forming bacteria and possibly by tea and tobacco and other dietary constituents. The long "fur" may prove nauseating or alarming.

Antibiotics, poor oral hygiene, smoking, alcohol, and mouthwashes have been blamed for black hairy tongue. However, the cause is essentially unknown but reassurance that it is not a serious infection, is important. Recently, oral retinoids have been used to treat the condition. Most simply, the patient can scrape off the long papillae with a stiff toothbrush or spoon.

ULCERATIVE AND BULLOUS LESIONS OF THE ORAL MUCOSA

The range of ulcerative and erosive conditions of late onset to affect the mouth is relatively narrow (see Table 2). Failure to recognize erosive lichen planus, mucous membrane (cicatrizing) pemphigoid, or pemphigus presenting as recurrent "mouth ulcers", delays instituting the appropriate treatment.

Recurrent Oral Ulceration

Traumatic Ulcers

Traumatic ulcers are the most frequent. They arise in the sulci at the periphery of ill-fitting dentures or in the buccal mucosa as a result of cheek biting. The ulcers are typically shallow and shelving with an irregular or linear outline, and once the local cause is eliminated, healing is swift. A chlorhexidine gluconate mouth rinse is helpful. Leaflike hyperplastic folds (denture-associated hyperplasia) at the periphery of the denture result from denture trauma in the long term.

Table 2 Ulcerative and bullous conditions of the oral mucosa in the elderly

Recurrent oral ulceration
Traumatic ulceration
Lichen planus
Drug-induced ulceration
Hematological
Neutropenia
Leukemia
Iron, B_{12} or folate deficiency
Behcet's syndrome
Associated with inflammatory bowel disease
Chronic ulcerative stomatitis
Persistent oral ulcer
Squamous cell carcinoma
Bullous disorders
Mucous membrane (cicatrizing) pemphigoid
Herpes zoster
Pemphigus vulgaris and pemphigus vegetans
Angina bullosa hemorrhagica

Lichen Planus

In oral lichen planus, the characteristic lesions are white striae or papules forming a reticular lacelike pattern on the buccal mucosa or lateral margins of the tongue, often with a bilaterally symmetrical distribution (Figure 4). These may cause a burning sensation or discomfort. Only a minority of patients may have skin lesions.

Atrophic changes in lichen planus present as red areas. Confluent white plaques may be a feature on the tongue. The gingivae may become red and atrophic (desquamative gingivitis). Bullous lichen planus may present as recurrent oral ulceration.

The ulceration or erosive form of lichen planus may have a protracted course, sometimes taking 10 years or more to remit. There may be an association with hepatitis C infection or liver disease. Occasionally the lesions heal as a white

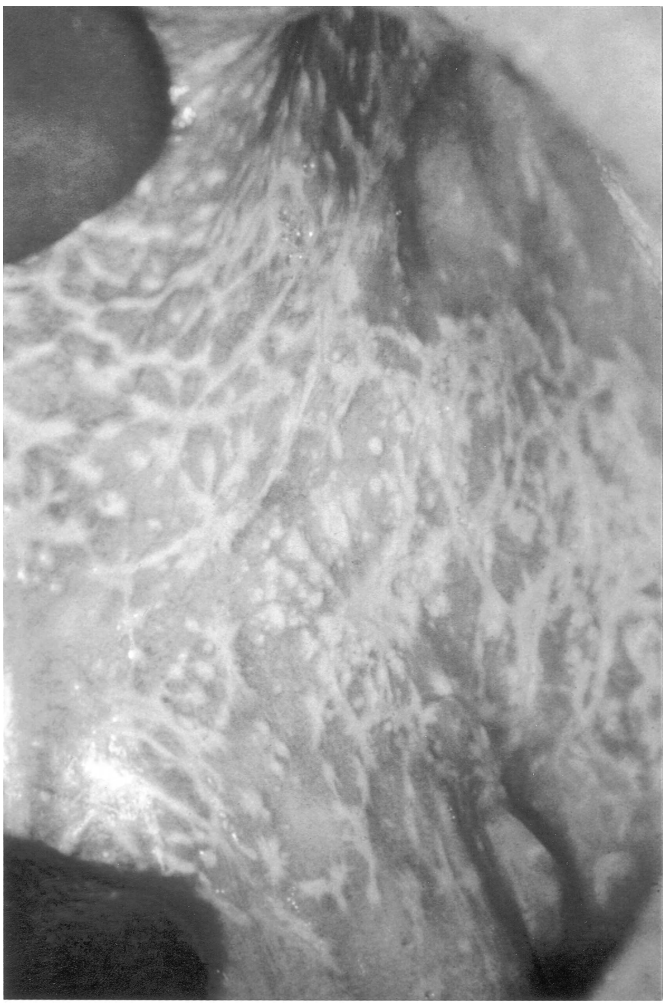

Figure 4 White striae and papules in a reticular pattern on the buccal mucosa in oral lichen planus

mucosal plaque or as localized areas of depapillation of the tongue. The keratinized white margins of the erosions usually serve to distinguish lichen planus from those due to mucous membrane cicatrizing pemphigoid. A biopsy of the intact keratinized margin will confirm the diagnosis and exclude any epithelial dysplasia. A subgroup of women with lichen planus affecting the gingivae, vulva, and vagina has been delineated.

In most cases of oral lichen planus, no cause can be isolated. Drugs may, however, induce a lichenoid reaction that may be clinically and histologically indistinguishable from lichen planus. These include gold salts, beta-blockers, captopril, thiazide diuretics, oral hypoglycemics, antimalarials, antituberculous drugs, antidepressants, and nonsteroidal anti-inflammatory analgesics.

Lichenoid reactions to the mercury content of dental amalgam fillings may occur, particularly in cases when the lesions are restricted to mucosal surfaces in the cheek in contact with the fillings. In such selected cases, replacement of amalgams with alternative materials may be rewarded by resolution. An oral lichenoid reaction may be a feature in graft-versus-host disease.

Topical corticosteroids will help relieve any burning sensation or soreness of the involved mucosa. These involve 0.05% clobetasol or 0.05% fluocinonide or 0.1% triamcinolone acetonide in an adhesive paste: Topical tacrolimus (Vente *et al.*, 1999) has been under trial recently. A tetracycline mouth bath used three times daily for 3 days will relieve symptoms due to secondary bacterial infection in the erosive form. For this, a 250-mg tetracycline capsule is opened and the powder contents dissolved in 15-ml warm water, and this mouth bath held in the mouth for 2 minutes and then spat out.

In severe forms, where eating and swallowing have become intolerable to the point of weight loss and the patient's life has become miserable, a limited course of systemic corticosteroids is justified, for example, prednisone, 5 mg four times a day for 1 month, reducing gradually to a maintenance dose of 5–10 mg daily. Usually the systemic therapy can then be tailed off and discontinued within 3 months.

Cyclosporine mouthwashes, retinoids, or tacrolimus have also been used more recently (Chan *et al.*, 2004). Patients with oral lichen planus of long standing, usually of 10–15 years duration have a slightly increased risk of oral cancer with an estimated incidence of 1–4%.

Drug-induced Ulceration

Aspirin ill-advisedly held in the cheek to relieve toothache results in an erosion covered by necrotic epithelium. Cytotoxic agents regularly cause ulceration, either directly by their effect on the oral epithelium or indirectly as a result of neutropenia.

Gold salts, nonsteroidal anti-inflammatory analgesics and occasionally other drugs (Scully and Cawson, 2002) have occasionally been implicated in mouth ulceration. Neutropenic ulceration occurs regularly in bone marrow transplant recipients and usually resolves when the blood neutrophil count rises above 0.5×10^9 cells/l. Recombinant human granulocyte-colony-stimulating factor (rHuG-CSF) elevates blood neutrophil counts with a reduction in oral ulcers (Dale, 1995) in a variety of neutropenias, especially due to chemotherapy but also in congenital and idiopathic and cyclic neutropenia.

Behcet's Disease

The oral ulceration in Behcet's disease may persist into later life. Clinically these ulcers are similar to minor or major aphthae or herpetiform ulceration. To fulfill the current diagnostic criteria for Behcet's disease, the patient should also have two of the following four changes: eye lesions, skin lesions, genital ulceration, and a positive pathergy test (International Study Group for Behcet's Disease, 1990). Topical steroids (see above) or a tetracycline, mouthwash can give some relief for the mouth ulcers. Thalidomide (not to be used for women who could become pregnant) or colchicine 0.5 mg twice daily can control more severe ulceration. Many patients with extraoral manifestations will need corticosteroids such as prednisolone with or without azathioprine (*see* **Chapter 135, Skin Disorders in the Elderly**).

Mouth Ulceration Secondary to Inflammatory Bowel Disease

Mouth ulceration of aphthous type may infrequently be an oral manifestation of inflammatory bowel disease, such as Crohn's disease, ulcerative colitis, or coeliac disease. Diffuse thickening of the lips, cheeks, and lower face may also be a feature of Crohn's disease, with characteristic noncaseating granulomas. Malabsorption of iron or other hematinics may be a factor in this type of mouth ulceration. Pyostomatitis vegetans (Ficarra *et al.*, 1993) or the oral equivalent of pyoderma gangrenosum are other occasional associations.

Persistent Oral Ulcer: Squamous Cell Carcinoma

A solitary enlarging oral ulcer with indurated raised margins in the elderly, persisting for more than 3 weeks despite treatment, particularly in a patient with risk factors for oral cancer (see below) should be regarded as a squamous cell carcinoma until proved otherwise and a biopsy is mandatory.

Bullous Lesions

Mucous Membrane Pemphigoid (MMP) (see Chapter 135, Skin Disorders in the Elderly)

This is a chronic autoimmune blistering disorder with a target antigen in the lamina lucida of the basement membrane. Junctional separation of the epithelium from the lamina propria results in a bulla. It tends to occur in older

people, usually women. The oral mucosa is almost invariably affected, together with the nasal mucosa and conjunctiva in most cases.

Subepithelial bullae arise on the maxillary gingivae, hard and soft palate, and buccal mucosa. The bullae are generally clear, measuring a few millimeters to a centimeter in diameter, and take some hours to rupture, leaving painful erosions (Figure 5). Atrophic erythematous sore gingivae (desquamative gingivitis) in patients whose natural teeth are still present is a typical finding. In severe forms, lesions of the pharynx and esophagus may cause dysphagia, and hoarseness may result from laryngeal involvement. The anus, penis, vulva, and skin may occasionally be affected. An association with rheumatoid arthritis has been reported. The buccal and labial sulci become reduced in depth, due to scarring. As a consequence, dentures become unstable and need frequent adjustment.

Mucous membrane pemphigoid (MMP) is now recognized to be a heterogeneous group of subepithelial blistering disorders involving mucous membranes, particularly of the mouth and eyes. At least five subsets of MMP have been distinguished by their clinical features and the antigenic specificity of the autoantibodies detected in biopsies and serum by direct and indirect immunofluorescence (Scully *et al.*, 1999).

The milder forms of MMP can be treated with topical corticosteroids, such as fluocinonide 0.025% in Orabase or a 5 ml mouthrinse of dexamethasone 0.1 mg ml^{-1} held in the mouth for minutes and then spat out, three times daily. In more severe forms, or where there is eye involvement, a short systemic course of prednisone, 1–2 mg kg^{-1} day^{-1}, tapering to a level just sufficient to retain control. Dapsone and azathioprine have been used in combination with prednisone for their steroid sparing effects (Fine, 1995) but each has potent adverse effects. Topical antifungals such as amphotericin B lozenges can be useful in preventing thrush with such regimes. The tetracycline minocycline, sulphapyridine, and cyclosporine mouthrinses (very expensive) have also been used.

Figure 5 Mucous membrane pemphigoid in an 82-year-old man presenting with "mouth ulcers"

Herpes Simplex

Recurrent herpes simplex may be severe on the lips (herpes labialis) in elderly patients receiving chemotherapy for leukemia or other malignancies and its incidence can be reduced by prophylactic aciclovir.

Herpes Zoster (see Chapter 145, Infectious Diseases; Chapter 148, Infections of the Central Nervous System Chapter 135, Skin Disorders in the Elderly)

Reactivation of varicella zoster virus infection affects middle-aged and elderly patients, in particular, and may involve the sensory ganglion of the trigeminal nerve.

After a prodromal phase of severe facial pain, which may be mistaken for toothache, cutaneous hyperesthesia, erythema, and unilateral grouped mucocutaneous vesicles appear in a dermatome distribution on the skin of the cheek, lower eyelid, and lip in maxillary nerve lesions, with erosions on the ipsilateral mucosa of the upper lip and palate as far as the midline. In mandibular division involvement, the rash is commonly situated on the chin in the distribution of the mental nerve, and on the buccal mucosa and ipsilateral half of the tongue. Trigeminal zoster may occur without vesicles (sine herpete). Geniculate ganglion involvement manifests as a lower motor neurone facial nerve palsy, vesicles in the external ear and fauces, loss of taste on the side of the tongue (Ramsay-Hunt syndrome). Aciclivir, valaciclovir, and famiciclovir are effective and limit postherpetic neuralgia.

Pemphigus Vulgaris and Pemphigus Vegetans (see Chapter 135, Skin Disorders in the Elderly)

This serious bullous eruption, appears in the mouth on average 4 months before the skin is affected, although occasionally it remains restricted to mucosal surfaces. Its onset is commonly in middle age, but the geriatrician will see patients in whom pemphigus first occurs in later life. It is an autoimmune disorder with IgG_1 and IG_2 autoantibodies against the desmosomal glycoprotein, desmoglein-I, the major antigen (or Dsg-3) producing intraepithelial blisters. The oral blisters usually rupture quickly, leaving erosions. To confirm the diagnosis, biopsies of the intact oral lesion or perilesional mucosa are needed (a) a formalin-fixed specimen for light microscopy (b) an unfixed specimen for direct immunofluorescence, and (c) a blood sample (no anticoagulant).

If pemphigus vulgaris can be recognized at an early stage, where the lesions are confined to the mouth, it can usually be controlled with a relatively lower dose of systemic steroids such as 40–60 mg prednisolone daily (Harman *et al.*, 2003). Paraneoplastic pemphigus should also be considered. Regular toothbrushing with a soft toothbrushing and a chlorhexidine gluconate (0.2%) mouthrinse is essential and any thrush treated. In the oral lesions of pemphigus vegetans, the mucosa heals with a granular surface, men are more frequently affected and the clinical course is generally milder than in pemphigus vulgaris.

Angina Bullosa Hemorrhagica

Young or middle-aged women are mainly affected. During meals, a subepithelial hemorrhagic bulla forms rapidly in the subepithelial region of the mucosa of the soft palate or cheeks. Occasionally the palatal swellings may enlarge to the point where the patient fears asphyxiation. The extravasated blood soon ruptures spontaneously, forming a painful erosion. A tetracycline mouthbath made up freshly by dissolving the powder contents of a 250 mg capsule in a 15 ml warm water and held in the mouth for 5 minutes three times daily, relieves soreness from secondary bacterial infection. Rarely, similar oral lesions can be a marker of thrombocytopenia.

DENTURE-INDUCED HYPERPLASIA

This is a benign mucosal hyperplasia seen as leaflike folds of tissue at periphery of a denture, with sometimes superimposed traumatic ulceration. The dentures need to be trimmed back and, if necessary, replaced.

WHITE LESIONS OF THE ORAL MUCOSA

Most white mucosal patches are due to the irritant effect of tobacco smoking or friction from the teeth, often in combination, and these changes are usually reversible and nondysplastic. A leukoplakia has been defined as a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; a minority of leukoplakias will transform into cancer (Axell *et al.*, 1996). A number of white lesions of thrush, lichen, planus, and aspirin burns, and so on (Table 3) are thus excluded by this definition. Malignant change is more frequent in speckled (nodular), red, or verrucous leukoplakias.

Tobacco-associated Leukoplakia

Many patients presenting with oral white mucosal lesions are pipe or cigarette smokers. In a pipe smoker there are umbilicated white papules on the soft palate due to thickened palatal epithelium at the openings of minor salivary glands. There is no epithelial dysplasia and this is not a premalignant lesion. If the patient stops smoking, the mucosa generally returns to normal within a year.

Table 3 White lesions of the oral mucosa

Benign	***Potentially malignant***
Ectopic sebaceous glands	Dysplastic leukoplakia
Thrush	Tobacco-associated leukoplakia
Aspirin burn	Lichen planus
Frictional Keratosis	Oral submucous fibrosis
Oral epithelial nevus	Chronic hyperplastic candidosis
Leukedema	Discoid lupus erythematosus
Oral hairy leukoplakia	Tertiary syphilis
Darier's disease	
Red lesion of the oral mucosa	
Erythroplasia	

Frictional Keratosis

A frictional keratosis is a linear white lesion where the upper and lower teeth meet in the cheek mucose, lips, or lateral margins of the tongue. Sharp teeth or faulty dentures may be responsible. Smoking often seems to be a coirritant. If the causes are eliminated, the mucosa returns to normal.

Tertiary Syphilis

Syphilitic glossitis, one of the oral manifestations of tertiary syphilis is now rare. The tongue is blunt and fibrosed with keratosis and atrophy of the anterior dorsum. Syphilitic leukoplakia of the tongue or elsewhere in the mouth carries a significantly increased risk of oral cancer.

Chronic Hyperplastic Candidosis

Chronic hyperplastic candidosis appears as speckled white plaques on the buccal mucosa, tongue, or palate. A biopsy is needed to show the candidal hyphae in the superficial epithelial layers, with occasionally epithelial dysplasia. Topical or systemic steroid therapy or immunosuppressive medication, diabetes mellitus, or iron deficiency, are predisposing factors. Tobacco smoking and denture wearing, particularly continuously day and night, may be local promoting factors. The management will include attention to predisposing factors, a course of antifungal therapy of fluconazole, often for several months, and excision of any residual dysplastic white plaques. The risk of cancer is now thought to be low.

Oral Hairy Leukoplakia

This was first described in North American homosexuals with HIV infection. White plaques with a corrugated surface on the lateral margin of the tongue are the usual presenting factors. Histologically, koilocytes in the upper spinous epithelial layer are markers of Epstein-Barr virus infection. Oral hairy leukoplakia has since been reported in transplant recipients receiving immunosuppressive therapy. Some lesions respond to acyclovir but there is no dysplasia and oral hairy leukoplakia is not potentially malignant. It is uncommon in the elderly.

Sublingual Keratoses

There are supple, wrinkled, well-demarcated white plaques on the ventral surface of the tongue, or on the floor of the

mouth, often symmetrically distributed about the midline. A report that the lesions frequently underwent malignant change has not been subsequently confirmed.

Oral Epithelial Nevus

Oral epithelial nevus (white folded gingivostomatosis) is a rare disorder due to a cytokeratin gene mutation, usually of autosomal dominant inheritance. The mucosa of the gingivae, cheeks, lips, and sometimes the soft palate has a white shaggy appearance, and sheets of the surface epithelium are easily wiped off. Vaginal or rectal mucosa may also be affected. The biopsy findings are diagnostic. There is no dysplasia and this is a harmless condition.

Erythroplakia

The bright red velvety mucosal plaque is an uncommon but sinister lesion, which is disproportionately frequent in older patients. Severe dysplasia or carcinoma *in situ* are common biopsy findings. It is often asymptomatic and detected during a routine examination of the mouth. Up to half the patients may develop oral carcinoma.

Management of White and Red Lesions of Oral Mucosa

Tobacco smoking, betel quid use or trauma from the teeth or dentures or thrush should be attended to. Any remaining white patches should be biopsied to confirm the diagnosis and to identify any epithelial dysplasia and its severity. The correlation between the assessment of different pathologists on the presence and severity of oral epithelial dysplasia has been shown, however, to be poor. This subjective variation in histological evaluation of leukoplakia has prompted alternative methods such as ploidy analysis of DNA content which promise to provide a more objective and reliable way of predicting the risk of cancer (Sudbo *et al.*, 2001). In the future, DNA analysis of mutations or other molecular methods will probably prove a more accurate guide to malignant potential. The place of other diagnostic techniques, such as exfoliative cytology, brush biopsy, or vital staining with tolonium chloride mouth rinses, remains uncertain.

Leukoplakias with biopsy-proven moderate or severe dysplasia are generally excised where clinically practicable. However, no random controlled trials are available of the effectiveness of surgery, laser, or cryotherapy in preventing oral cancer developing in these lesions (Lodi *et al.*, 2002). A careful follow-up, therefore, is essential.

ORAL CANCER

Although oral cancer accounts for only 2% of malignant tumors registered in developed countries, approximately 50% of the patients still die from intraoral tumors (all stages, all grades) such as cancer of the tongue. The incidence of oral cancer rises steeply after 50 years, and 70% of patients presenting with the disease are over 65 years. Rather more men are affected than women.

Etiology

Tobacco (smoked, chewed or used as snuff) and heavy alcohol drinking, are the major risk factors for mouth cancer in most industrialized countries and interact with a supermultiplicative effect (Johnson, 2001). In the Indian subcontinent, betel quid containing areca nut and slaked lime and often tobacco, or areca nut (betel) chewing alone, are carcinogenic. Areca nut is also important in the etiology of oral submucous fibrosis, a potentially malignant condition. Lip cancer is usually due to excessive exposure to ultraviolet light, particularly in outdoor workers.

Dietary Deficiency

A low intake of fresh fruit and vegetables carries an increased risk of oral cancer. Prolonged iron deficiency leading to the Patterson-Kelly (Plummer-Vinson) syndrome predisposes to cancer of the pharynx and the mouth (Walker *et al.*, 2003).

Other Factors

Oncogenic types of HPV-16 and 18 virus have been implicated in a small subset of oral cancers, particularly tumors of the posterior tongue and tonsils. The evidence for a link between herpes simplex and oral cancer is less convincing. Syphilis is now only rarely implicated in oral cancer. Dental sepsis or trauma from teeth or dentures have not been convincingly shown to be etiological factors. Genetic polymorphisms controlling the metabolism of tobacco and alcohol or DNA repair may explain the predisposition to lip and oral and pharyngeal cancer in some families but concordance studies in twins indicate that environmental exposure to carcinogens is more important.

Clinical Appearances of Oral Cancer

On the lower lip, a persistent crusted lesion at the vermilion border, often superimposed on a diffuse solar cheilosis, should be regarded as a squamous cell carcinoma until proved otherwise, and the diagnosis established by biopsy.

Within the oral cavity, the cancers arise in a horseshoe-shaped area on the lateral margins of the tongue, floor of the mouth, mandibular alveolus, and lower buccal sulcus. The carcinomas may appear as a raised nodule, an ulcer

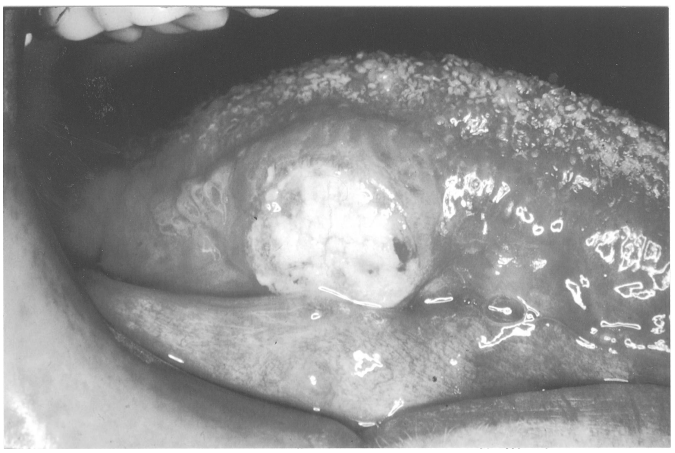

Figure 6 Squamous cell carcinoma with a raised indurated margin on the ventral surface of the tongue

with indurated margins (Figure 6), or an indurated or fissured white plaque. Limitations of tongue movements, severe pain, restricted mouth opening and lymph node involvement are all late signs.

A biopsy is essential. Unrecognized oral cancers are still treated with topical medicaments or antibiotics for long periods with distressing consequences. The stage of the disease is the most important prognostic factor. Metastatic involvement of even a single lymph node is associated with a 50% reduction in survival rates. With improved control of loco-regional disease, distant metastases are becoming clinically more important.

The site of the cancer also affects the outcome. In contrast to lip tumors, which are usually curable, most intraoral cancers in the elderly are advanced at presentation with 5-year survival rates only approximately 50%. Other prognostic factors such as patient gender, tumor grade, and modality of treatment are less important. Poor general health has an adverse effect on outcome.

Treatment

Oral cancer is usually treated by surgery including in some cases neck dissection or radiotherapy or a combination. The place of adjuvant chemotherapy remains to be established. With advances in ablative and reconstructive surgery, better control of the primary tumor and neck nodes is now possible. Distant metastases or a second primary tumor in the upper aerodigestive tract, often also associated with tobacco and alcohol are further problems.

THE JAWS AND MUSCLES OF MASTICATION

Age Changes

The structure and the size of the alveolar processes of the jaws are dependent upon the presence of the teeth which they support. The alveolar bone forms as the teeth develop and erupt and is resorbed after extractions, and the resultant loss of facial contour and height accentuates the appearance of aging. As in other bones, the jaws of the elderly are subject to generalized osteoporosis, and the thickness and bone mass of the mandibular alveolus becomes reduced. Progressive periodontal disease results in inflammatory resorption of alveolar bone which is accelerated in women with generalized osteoporosis (Geurs *et al.*, 2003) and conversely may be retarded by biphosphonates.

Atrophy of the edentulous alveolus after extractions may make dentures unstable, particularly in the lower jaw. Modern surgical procedures, such as insertion of subperiosteal osseointegrated titanium implants can stabilize removable dentures or even retain single teeth, but such preprosthetic surgery in patients aged over 70 years is not to be undertaken lightly. The muscle mass and maximal biting force of muscles of mastication such as masseter and medial pterygoid muscles, is reduced in elderly people (Newton *et al.*, 1993) and is further reduced in the edentulous, but most complete denture wearers do not have problems in chewing the average Western diet.

Swellings of the Jaws

Unerupted Teeth, Roots, and Cysts

A dental abscess from a nonvital tooth is the commonest cause of a sudden swelling of the jaw, irrespective of age. In the elderly subject presenting with a swelling of longer duration, sometimes causing a loss of fit of dentures, radiographs will often reveal a residual dental cyst or an unerupted tooth, sometimes with an associated dentigerous cyst. Unerupted teeth may become more superficial (and then infected) due to resorption of the overlying alveolar bone. Frequent hot salt water mouth baths, a chlorhexidine mouthwash twice daily, analgesics and an antibiotic such as amoxicillin prescribed, for example, 500 mg together with metronidazole 200 mg three times daily or in patients allergic to penicillins, clindamycin 300 mg 6 hourly and the patient instructed not to wear dentures meanwhile. Fluctuant collections of pus need to be incised. After an interval of at least 2 weeks the tooth or cyst should then be removed.

Retained roots may become infected and require removal, but asymptomatic roots buried deeply in the jaws are common radiographic findings and can be safely left, unless a cyst has formed.

Ameloblastoma

This is the commonest odontogenic neoplasm. It arises centrally in the jaws, particularly in the third molar region or the angle of the mandible. It may present as a jaw swelling, loss of fit of a denture or loosening of teeth. A multilocular radiolucency is the characteristic X-ray appearance, although some tumors are monolocular. Ameloblastoma typically presents in about the fifth decade but older patients can

be affected. The tumor is locally invasive and resection with a margin of uninvolved bone with bone grafting is needed.

Paget's Disease

This osteodystrophy involves the facial skeleton in a minority of cases and the maxilla is more affected than the mandible in both the polyostotic and also the rare monostotic form. The vault of the skull is a frequent site for Paget's disease and the deformity imparts an inverted triangle shape to the head.

In the jaws, pain and facial deformity are the usual presenting features. The maxilla is usually diffusely enlarged with a tendency to obliteration of the vault of the palate, or loss of fit of dentures.

A craggy hypercementosis of teeth may make extractions difficult. Severe infection of the sockets may follow extractions where the bone is sclerotic in elderly patients, whereas postextraction hemorrhage is a feature of the vascular osteoporotic phase. Calcitonin injections or bisphosphates may give some relief of pain. Sarcoma, as a complication, is very rare in the jaw lesions.

SALIVARY GLAND DISORDERS

Age Changes in Salivary Glands

With age, an increasing proportion of the secretory acini of the major and minor salivary glands tissue are replaced by fat and fibrous tissue. The cytoplasm of some of the epithelial cells becomes granular and eosinophilic. Ultrastructurally, this oncocytic change is due to many swollen mitochondria. Most investigations, however, have not shown a corresponding drop in salivary flow rates with age (Baum, 1996).

Dry Mouth

A complaint of a dry burning mouth is not uncommon in older people but is not due to age changes in salivary glands. Patients presenting with a complaint of dry mouth can be grouped into those with normal salivary flow and those with reduced salivation (Table 4). Salivary flow rates (unstimulated) can be assessed most simply by asking the patient to first swallow and then drool into a plastic preweighed cup over 5 minutes. The stimulated salivary flow rate is assessed similarly while the subject chews paraffin wax. Values of $<0.1\,\mathrm{g\,min^{-1}}$ unstimulated salivary flow rates and $<0.5\,\mathrm{g\,min^{-1}}$ stimulated flow rates are suggestive of a dry mouth, allowing for the wide range found in asymptomatic healthy people.

In true xerostomia, there may be difficulty in swallowing, speaking, or a taste disturbance. Angular cheilitis, often a marker of chronic candidosis, a smooth tongue with a fissured "cobblestone" appearance, adherent glazed buccal mucosa, widespread cervical dental caries at the gum margins (Figure 7) and an absence of the usual pool of saliva in the floor of the mouth are characteristic findings.

Table 4 Causes of complaint of dry mouth

A. With reduced salivary flow

1. *Salivary gland disease*
   - Radiotherapy
   - Sjögren's syndrome
   - Sarcoidosis
   - Amyloid
   - Hemochromatosis
2. *Generalized disorders*
   - Diabetes mellitus
   - Dehydration
     - Fluid deprivation or loss
     - Prolonged diarrhea, vomiting, HIV, hepatitis C
3. *Medication*

Atropinics	Clonidine
Benzhexol	Opiates
Benztropine	Orphenadrine
MAO inhibitors	Ipra troprium
Phenothiazines	Antihistamines
Selegiline	Amphetamines
L-dopa	DDI
Lithium	Fluoxetine
Retinoids	

B. With normal salivary flow

Psychological
- Anxiety
- Depression

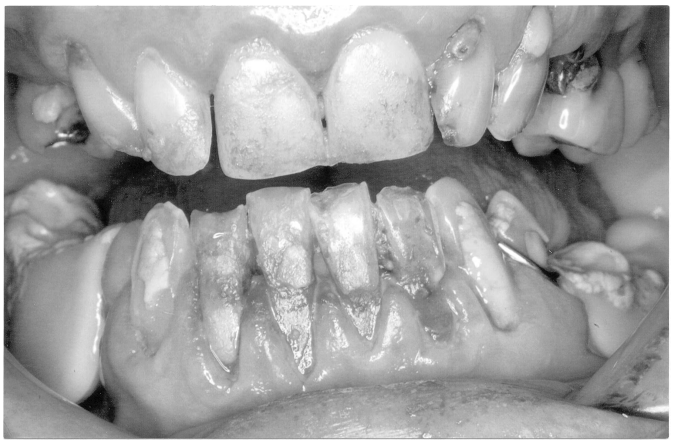

Figure 7 Recurrent dental caries at the necks (cervical margins) of teeth in a patient with a profound xerostomia in Sjögren's syndrome

A dry burning feeling (burning mouth sensation) of the lips or mouth (see below) is a distressing complaint in elderly people, predominantly in women but the salivary flow rates usually prove to be normal and the oral mucosa is clinically healthy.

Dehydration

This may occur in senile dementia when patients no longer drink enough fluid.

Drug-induced Xerostomia

Medication rather than age changes is an important factor in dryness of the mouth in the older person and elderly patients can be particularly sensitive to the anticholinergic action of drugs.

Antidepressants, antihypertensives, or antidepressants are relatively commonly incriminated in drug-induced xerostomia, but a wide spectrum of medication is said to reduce salivary flow (Sreebny, 1996).

Sjögren's Syndrome

Sjögren's syndrome is a chronic slowly progressive autoimmune destruction of exocrine glands, particularly the salivary and lacrimal glands, resulting in dryness of the mouth and eyes. The xerostomia and xerophthalmia may occur in isolation (primary Sjögren's syndrome) or associated with rheumatoid arthritis, systemic lupus erythematosus, scleroderma, primary biliary cirrhosis, vasculitis, or chronic active hepatitis (Moutsopoulos, 1998). Middle-aged women are predominantly affected.

The diagnostic criteria are listed in Table 5.

Autoantibodies: Ro (SS-A), La (SS-B), antinuclear factor, and rheumatoid factor are diagnostically useful. Fodrin and muscarinic acetylcholine receptor antibodies are now claimed to be both more sensitive and specific.

For the minor salivary gland biopsy, minor glands are removed under local anesthesia via an incision in the mucosa of the lower lip. More than 1 focus of 50 or more lymphocytes and plasma cells per 4-mm gland sectioned is diagnostic for Sjögren's Syndrome.

Fatigue is a general complaint. The oral changes of xerostomia are as detailed above. The major salivary glands, most noticeably the parotid glands, may be persistently enlarged in half the patients. Typically the swelling is firm, diffuse, and bilateral. Intermittent painful swellings of the parotid gland may be due to retrograde bacterial infections of the ducts. A B cell lymphoma in the parotid gland is another complication.

Table 5 Diagnostic criteria for Sjögren's syndrome

Eye symptoms	Dry eyes everyday for >3 months, gritty sensation, or use of tear substitutes >3 times daily
Eye signs	Positive Schirmer test (<5 mm per 5 min) positive Rose-Bengal score of >4
Oral symptoms	Daily symptoms of dryness
Minor salivary gland biopsy: >1 focus score per 4 mm^2	
Salivary gland function	Positive result in one or more of the following tests: Salivary scintigraphy, parotid sialography, reduced salivary flow (<1.5 ml per 15 min)

Oral Effects of Radiotherapy and Chemotherapy: Xerostomia, Mucositis, and Osteoradionecrosis

The xerostomia due to the salivary gland atrophy and fibrosis induced by radiotherapy may result in caries affecting the roots and crowns of the teeth. There are effective cariostatic topical fluoride regimes (see below) (Dreizen *et al.*, 1977).

In the mucositis which may follow 12–15 days after radiotherapy or 7–14 days after chemotherapy, the oral mucosa becomes ulcerated, with or without a pseudomembrane on an erythematous base (Scully *et al.*, 2004). A bland soft diet and avoidance of smoking, alcohol, tea, and coffee is advised. Lozenges containing polymyxin E, tobramycin, and amphotericin B can be helpful. For pain control, nonsteroidal anti-inflammatory analgesics or in severe cases opioids may be needed. Topical lignocaine (lidocaine) before meals and benzydamine mouthrinses are useful. Granulocyte-macrophage colony-stimulating factor has been administered subcutaneously for chemotherapy mucositis.

The jaws, particularly the mandible, gradually become hypovascular, hypocellular, and hypoxic after radiotherapy and extractions or even trauma from a denture, may be complicated by osteoradionecrosis. This is difficult to treat and the emphasis should be on prevention, getting the patient dentally fit before radiotherapy. A dentist is a valuable member of the multidisciplinary team managing head and neck cancer patients.

Management of Dry Mouth

The problem of replacing the normal 1500 ml or so daily salivary secretion for a patient with severe xerostomia has not yet been solved. Diabetic sugar-free chewing gum or pastilles help stimulate salivary flow. Saliva Orthana (Nycomed) aerosol spray containing mucin and xylitol, available with fluoride ($4.2\,mg\,l^{-1}$) or in pastille form and Glandosane (Fresenius) spray are approved for the relief of dry mouth in Sjögren's syndrome but are relatively expensive and many patients resort to frequently lubricating their mouths with tap water (should be fluoridated) from a small plastic spray bottle. Pilocarpine 5 mg orally three times daily may increase salivation but palpitations, sweating, flushing, or abdominal cramps may limit patient acceptability.

Sodium fluoride gel (1.23%) applications to the teeth and regular scaling, polishing, and instruction in effective toothbrushing with a standard fluoride tooth paste twice daily and a neutral high concentration toothpaste (5000 ppm F-) once daily are important for caries prevention in profound xerostomia. Topical antifungal preparations, such as amphotericin suspension (Fungilin) or miconazole oral gel (Daktarin), should relieve the discomfort due to chronic candidal infection, which is frequently present.

HYPERSALIVATION (PTYALISM)

Hypersalivation may occur transiently as a response to local causes, such as wearing dentures for the first time

or oral ulcers or wounds. Prolonged ptyalism may be an adverse reaction in iodism or medication with a parasympathomimetic effect, or in poisoning by mercury or other heavy metals (Table 6).

In most patients complaining of "too much saliva," the measured salivary flow rates are within normal limits. The affected individual seems to have become overaware of what is in fact a normal volume of saliva but does not swallow it as usual. This may be an obsessional trait and explanations and reassurances are usually unavailing. Lack of coordination between (normal) saliva production and swallowing seems also to be responsible for the "hypersalivation" in Parkinsonism and in Down's syndrome. Drooling from one corner of the mouth is a feature of unilateral facial paralysis.

Table 6 Causes of hypersalivation

A. With increased salivary flow	
Local	
	New dentures
	Oral ulceration
Medication	
	Anticholinesterases
	Iodides
	Pilocarpine
	Buprenorphine
	Haloperidol
	Niridazol
B. With normal salivary flow (False ptyalism)	
	Psychogenic
	Parkinson's disease
	Facial paralysis
	Bell's palsy or other lower motor neurone lesion
	CVA

CVA, cerebrovascular accident.

FACIAL PAIN

Dental Causes

As in younger patients, a dental cause such as a carious tooth is the commonest explanation for facial pain (Table 7). Exacerbation of the pulpitis by hot or cold drinks is characteristic. A transient hypersensitivity to hot, cold, or sweet substances can be due to dentine exposed at the necks of the tooth by toothbrush abrasion or by periodontal disease. A transient pain produced by biting on hard food can be due to a filled tooth whose crown has cracked more or less vertically. An orthopantomogram radiograph is useful for screening the jaws in facial pain.

The pain of an infected socket may be very severe and continuous. On examination the usual blood clot is missing and the alveolar bone lining the socket is exposed. The surrounding gingiva is inflamed and tender. Syringing the socket with warm chlorhexidine 0.2% solution, insertion of an obtundent dressing Alvogel, and adequate analgesics (e.g. paracetamol-codeine) usually give relief. Unerupted teeth, jaw cysts, and retained roots are painful in the event of secondary bacterial infection.

Table 7 Causes of facial pain

1. Dental causes	
	Dental caries and periodontal disease
	Cracked tooth
	Infected socket
	Retained roots, unerupted teeth
	Infected jaw cyst
2. Temporomandibular joint pain	
3. Trigeminal neuralgia	
4. Postherpetic neuralgia	
5. Periodic migrainous neuralgia	
6. Giant cell arteritis	
7. Myocardial ischemia	
8. Ocular causes	
9. Atypical (psychogenic) facial pain	
10. Burning mouth sensation	
11. Trotter's syndrome	

Temporomandibular Joint Pain

Significant pain from the temporomandibular joint pain is uncommon in old people. Although erosions, lipping, flattening, and other degenerative changes of osteoarthritis have been identified histologically or radiologically in surveys of older people, most patients remain symptomless. Temporomandibular joint pain dysfunction is characterized by pain, clicking, limitation of movement, tenderness, and spasm of the pterygoid and masseter muscles but the temporomandibular joints are radiographically and histologically normal. Young women are predominantly affected and the condition is distinctly uncommon in older people. Patients should be reassured that they do not have arthritis, any abnormal biting or jaw posturing habit corrected and satisfactory dentures provided as necessary. An occlusal acrylic splint fitting over the existing teeth is usually helpful.

Arthritis as part of rheumatoid arthritis, psoriasis, gout, or ankylosing spondylitis may rarely involve the temporomandibular joint with destruction of the condylar head and marked restriction of mouth opening.

Trigeminal Neuralgia (*see* Chapter 64, Neurological Signs of Aging)

The patient is usually over 50 years of age at presentation. The diagnosis of idiopathic trigeminal neuralgia is made on the history in the absence of any physical signs. More females are affected than males. The patient complains of a paroxysmal pain of frightening intensity, arresting any activity. The pain is usually brief (<2 minutes) and confined to one or more divisions of the trigeminal nerve, most commonly both the maxillary and the mandibular divisions. It is almost invariably unilateral, particularly affecting the right side of the face. The pain may be provoked by washing or toweling the skin of the face or eating. It may occur several times daily for weeks or months and then remit spontaneously, only to recur with greater severity with increasingly brief remissions. A dental cause of pain

must always be excluded first by a detailed clinical and radiographic examination.

Medical management with carbamazapine, phenytoin, or baclofen is usually successful. A minority of patients will need ablative procedures such as peripheral neurotomy or cryotherapy, Gasserian ganglion injected or trigeminal nerve root decompression (*see* **Chapter 64, Neurological Signs of Aging**).

Usually some years after the onset of the disease, 3–4% of patients with multiple sclerosis will develop trigeminal neuralgia. A similar pain, secondary (symptomatic) trigeminal neuralgia, may be caused by intracranial tumors or other lesion but the pain rarely resembles primary trigeminal neuralgia. In unusual cases, Paget's disease of bone may also cause pain simulating trigeminal neuralgia.

Postherpetic Neuralgia

This can be particularly troublesome for the elderly patient who may become severely depressed as a result. It is a common sequel to herpes zoster reactivation in the trigeminal nerve. On examination there may be atrophic scars from the eruption with a segmented distribution. The skin is hyperesthetic or dysesthetic. Topical 0.075% capsaicin cream or lignocaine gel may give relief. Early treatment with amitryptiline is effective. Adequate analgesics should be prescribed, together with a reassurance that the pain will usually remit in time.

Periodic Migrainous Neuralgia (Cluster Headache)

The pain is usually unilateral and felt in or around the orbit. Young males are predominantly affected. The pain lasts from 15 minutes up to 3 hours. It tends to occur late at night or in the early hours of the morning, in a regular manner, daily for several weeks or months, and then remits for months, only to recur. There may be an ipsilateral lacrimation, conjunctival injection, rhinorrhea, and nasal stuffiness. The management is discussed in **Chapter 64, Neurological Signs of Aging**.

Giant Cell Arteritis

Middle-aged or elderly patients are affected (*see* **Chapter 64, Neurological Signs of Aging**; **Chapter 65, Headache in the Elderly**). They usually present with a headache but alternatively pain confined to the face may be a symptom of involvement of the superficial temporal or facial arteries. The pulses are typically absent and tender nodular thickenings may be palpable along the course of the vessel. Alternatively, the lumen of the affected artery may be merely narrowed and pain during mastication results from the ischemia of masseter and temporalis muscles. There is a good response to systemic prednisone therapy. Sudden blindness, which is sometimes bilateral, can follow ophthalmic artery involvement and an early ophthalmic opinion is advisable in all cases of giant cell arteritis.

Myocardial Ischemia

Although anginal pain may radiate to the mandible, it is only rarely confined to the jaw.

Ocular Causes

In acute glaucoma, the pain is felt in the globe of the eye itself and visual disturbances, photophobia and lacrimation are frequent. The eye is characteristically red, hard, and tender to palpitation.

Psychogenic (Atypical) Facial Pain

The patients are usually elderly or middle-aged women. Often there is a history of recent bereavement or retirement from a busy job, when for the first time the patient is alone in the house for long periods. The complaint is of a continuous diffuse pain affecting both jaws, spreading across the midline (unlike toothache) and the pain is not confined to the territory of any of the branches of the trigeminal nerve. The pain, however, does not usually keep the patient awake or interfere with daily activities and can be described by the patient with a composed or even cheerful facial expression. Often, previous dental treatment such as extractions is blamed. Mastication or taking cold or hot sweet foods have no effect on the pain in contrast to that from pulpitis. Clinically and radiographically, there are no abnormalities in the mouth, teeth, or jaws. Frequently, the patient has had previous dental extractions because of the pain. In many patients there are features of anxiety and depression or of an obsessional trait. Analgesics are unhelpful. Treatment with a psychotropic drug, particularly antidepressants, for example, prothiaden or amitryptiline, is beneficial in some patients but the relapse rate is high. Requests for the extraction of sound teeth should be resisted.

Burning Mouth Sensation

Middle-aged or elderly women are usually affected. They complain of a diffuse, dry burning sensation of the tongue, cheeks, and lips. Local causes such as faulty dentures should be excluded. Candidal infection or lichen planus (see above) or a true xerostomia should be excluded. Glossitis, stomatitis, or mucosal ulceration may be indicators of iron, folate, or vitamin B_{12} deficiency, even in the absence of symptomatic anemia (Field *et al.*, 1995). Lack of other nutritional factors or perimenopausal estrogen deficiency have been suggested, but not substantiated, as causes of burning mouth syndrome,

and a "scalded mouth" sensation is an occasional adverse effect of ACE inhibitors such as enalapril or lisinopril.

However, no such local or systemic organic causes can be identified. Psychological factors such as depression or anxiety or obsessional traits seem to be common in this group. Cognitive behavior therapy, but not antidepressants or hormone replacement therapy, has been found to be effective.

Trotter's Syndrome

Pain from a nasopharyngeal carcinoma can be referred in the mandibular or maxillary divisions of the trigeminal nerve. An ipsilateral conductive deafness and immobility of the soft palate and an enlarged cervical lymph node are characteristic.

DENTAL CARE OF THE ELDERLY (*see* Chapter 22, Oral Health)

General Consideration

A lot can be done to prevent and relieve pain from the teeth and mouth in older people. Retaining at least some natural teeth into middle and old age is becoming the norm but many people aged 65 or more wear partial or complete dentures. Prostheses are often erroneously regarded by their wearers as permanent life-long fixtures. Once patients are rendered edentulous, the habit of regular dental attendance is usually lost and thus many oral malignancies in old people are unfortunately advanced, and early detection of oral cancer in this group is the exception.

Since mastication with dentures is considerably less efficient than with natural teeth, older complete denture wearers living independently may choose a diet significantly lower in most nutrients, fruit, and vegetables (Sheiham and Steele, 2001).

The dental treatment of old people poses particular problems. Brittle, broken down teeth, often with gross abrasion and attrition, are more difficult to restore satisfactorily, the more so because few elderly patients can tolerate lengthy sessions in the dental chair. A significant proportion have difficulty in visiting a dentist because of transport problems, or because they are bedridden or confined to a wheelchair or cannot manage the stairs of a dentist's premises. Some dentists, however, will provide treatment on a domiciliary basis. The expense involved is another reason why some old people may not seek dental care. Others are simply afraid of dental treatment. Institutionalized, house-bound or dependent patients, particularly those in poor general health, are known to be, in particular, dental need (Peltola *et al.*, 2004).

Elderly patients living independently and retaining some natural teeth may have difficulty in keeping their teeth clean. Root caries and periodontal disease are common but may cause surprisingly few symptoms. The zealous eradication of all dental disease may not be appropriate. Root caries can be arrested by topical fluoride application, using either a 1% sodium fluoride gel in a customized applicator tray provided by the dentist or hygienist, and in toothpaste used at home by the patient professionally instructed in efficient toothbrushing.

DENTAL TREATMENT OF THE MEDICALLY COMPROMISED

Cardiovascular diseases, cerebrovascular disease, asthma, and obstructive airways disease are common in older people, and local anesthesia for dental treatment is always preferable to general anesthesia where possible. Effective sedation is important before dental treatment for the anxious cardiac patient. Patients at moderate or high risk of infective (bacterial) endocarditis should have antibiotic prophylaxis before dental procedures likely to cause a bacteremia. The indications and recommended antibiotic regimes are detailed elsewhere (Dajani *et al.*, 1997; Ramsdale *et al.*, 2004).

Dental treatment is also complicated by concurrent medication. Patients who have taken corticosteroids over the previous 2 years may have adrenocorticortical suppression, and a booster intramuscular injection of hydrocortisone immediately prior to dental treatment is advisable, even in patients on low doses of steroids.

Elderly patients receiving cytotoxic or immunosuppressive therapy are at increased risk from infections following surgical procedures in the mouth. A full blood count and platelet count should be performed immediately prior to any oral surgery to exclude a drug-induced anemia, neutropenia, or thrombocytopenia, and most dental surgeons prescribe antibiotics prior to extractions or other surgical procedures in the immunocompromised. In patients taking anticoagulants who need extractions, the dose will have to be stopped or reduced until the International Normalized Ratio is 2–2.5 to avoid a postextraction hemorrhage (Scully and Cawson, 2002). A close liaison between the patient's physician and dentist is essential.

Systemic Effect of Oral Disease

Bacteremias of oral origin may result in bacterial endocarditis in patients with prosthetic heart valves, valvular heart disease or other cardiac disorders carrying an increased risk of endocarditis (see above). Recent evidence also indicates that periodontal disease is a risk factor for cardiovascular disease (Desvarieux *et al.*, 2003), and in pregnancy for premature low birth weight babies. Glucose control in diabetes may be adversely affected. Other confounding factors such as smoking, hypertension, hyperlipidemia, and diabetes may explain this apparent association (Tuominen *et al.*, 2003) and more research is needed. Oropharyngeal (including periodontal) pathogens can be aspirated into the lungs to cause pneumonia in the elderly (Shay, 2002).

KEY POINTS

- Although age changes do occur in otherwise healthy teeth, gingivae, oral mucosa, jaws, and salivary glands they do not cause any functional problems.
- Candida is the commonest cause of oral mucosal infection and successful management involves attention to systemic and local factors
- A systematic examination with a good light source of the whole mouth is needed if potentially malignant epithelial lesions are to be detected at an early potentially curable stage.
- Dryness of the mouth is not a symptom of aging but usually due to medication or salivary gland disease in older people.
- There is growing evidence of the systemic adverse effects of oral disease.

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Epidemiology of Nutrition and Aging

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INTRODUCTION

According to WHO (2002), population aging is one of humanity's greatest success story. It is also one of the greatest challenges to cope with it in social-economic and health policies. Worldwide, the proportion of people 60 years and over is growing faster than any other age-group. In addition, it is foreseen that decreasing fertility rates and increasing longevity ensure the continued "graying" of the world's population. The extra years are not always spent in good health; therefore, often the question is raised, "How do I get old healthy?"

Analyses of the major causes of death clearly show that the burden of noncommunicable diseases has rapidly increased. In 2001, these noncommunicable diseases accounted for almost 60% of 56.5 million deaths annually and for 47% of the global burden of diseases. Figure 1 shows the 20 leading risk factors for disease disability and death in developed and developing countries. Only few of these risk factors – underweight and unsafe sex (Human Immunodeficiency Virus (HIV)) – explain the much lower life expectancy in developing countries. This differs from developed countries, where the most important risk factors are associated with noncommunicable diseases and include high blood pressure, high concentrations of serum cholesterol, low intake of fruits and vegetables, being overweight, alcohol and tobacco use. Five of these global risk factors are closely related to diet and inactivity and may lead to cardiovascular disease, type 2 diabetes and certain types of cancer. Other diseases also related to diet and physical inactivity, such as dental caries and osteoporosis, are widespread causes of morbidity. These global epidemiological data have prompted WHO (World Health Organization) and Food and Agriculture Organization (FAO) to set up a Joint WHO/FAO Consultation on Diet Nutrition and the Prevention of Chronic Disease. The recent report of this group provides an update of dietary recommendations including the following guidelines (WHO, 2003):

- limit energy intake from fat and shift consumption away from saturated fats and trans-fatty acids toward unsaturated fat;
- increase consumption of fruits and vegetables as well as legumes, whole grains, and nuts;
- limit the intake of "free" sugars;
- limit salt (sodium consumption from all sources) and ensure that salt is iodized;
- achieve energy balance for weight control.

The guidelines are evidence based for younger adults and may not have the same impact in older adults. In old age, frailty is likely to develop as a consequence of the aging processes, combined with one or more chronic conditions. There are numerous factors that may lead to frailty (Figure 2). These factors make that in old age the role of nutrition may expand from the prevention of diseases to the supply of specific nutrients and the maintenance of food intake (Schürch and Scrimshaw, 2000). This food intake should be sufficient to combat frailty and to maintain quality of life. Frail is defined here as an age-related physiologic vulnerability resulting from impaired homeostatic reserve and reduced capacity of the organism to withstand stress. In view of a desired adaptation of the dietary guidelines to health priorities in older adults, we will discuss in this chapter epidemiological evidence for this age-group on:

- body weight, body composition, and health;
- changes in dietary intake: differences within and between populations;
- risk nutrients;
- healthy diet scores, all-cause mortality, coronary heart disease (CHD), and cancer mortality;
- nutrition supplements and health indices;
- dietary guidelines in old age.

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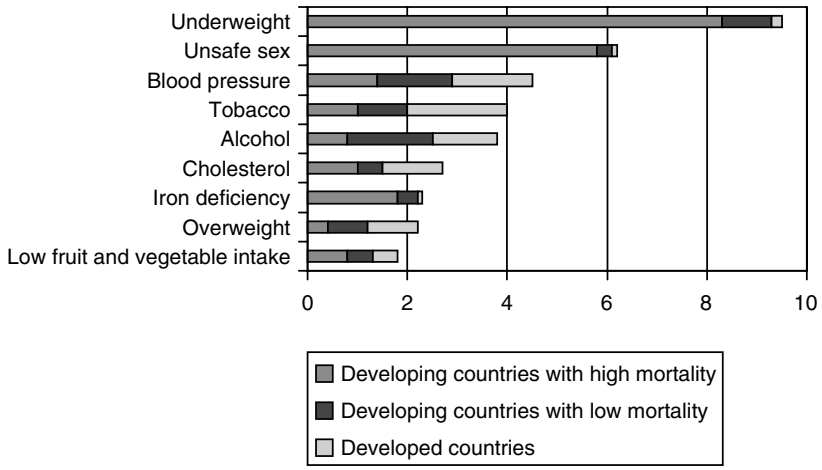

Figure 1 Global distribution of burden of disease attributable to 20 leading selected risk factors for disease disability and death, nine factors are presented here (Reproduced by permission of World Health Organization, 2002)

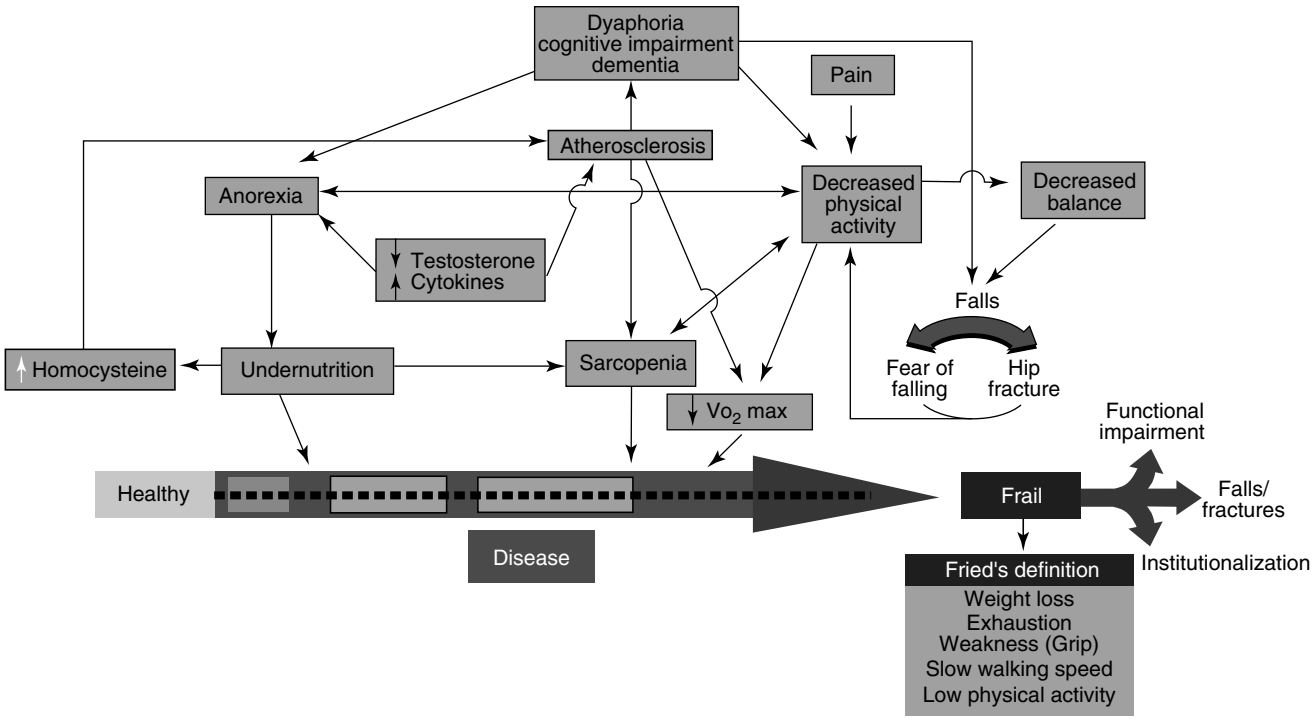

Figure 2 The pathophysiology of frailty (Reproduced by permission of Morley, 2001) www.cyberounds.com/conferences/geriatrics/

BODY WEIGHT, BODY COMPOSITION, AND HEALTH

Epidemiology of Body Weight Change, Changes in Body Composition, and Usual Aging

In cross-sectional studies, the prevalence of high body weight or obesity (Body Mass Index (BMI) $>30\,\mathrm{kg\,m^{-2}}$) increases with age up to about age 60 years, remains stable until about 70 years and then declines (Baumgartner *et al.*, 1995; Seidell and Visscher, 2000). These studies indicate that both weight loss and weight gain are associated with adverse health outcomes, such as decreased functional status, institutionalization, and increased mortality (Newman *et al.*, 2001; De Groot *et al.*, 2002).

In considering changes in body mass and health, changes in body composition have to be included. A decline in lean body mass occurs already in the third decade (Baumgartner *et al.*, 1995). This loss in lean body mass, much of which may

be due to a sedentary lifestyle, tends to be offset by gains in fat mass that continues until age 65 to 70. At any given BMI, older people will be considerably fatter, than younger adults of similar body weight because the fat-free mass diminishes by as much as 70% between the ages of 30 to 70. Studies in very healthy elderly people indicate that only very small decrements in weight ($0.1-0.2\,kg\,year^{-1}$) appear to occur in association with normal aging. Therefore, weight loss should never be dismissed as part of the aging process.

Most of the studies on BMI in the aged have been conducted in the United States (Baltimore Longevity Study; New Mexico Study and the older age-group of the NHANES III (National Health and Nutrition Examination Survey)) or in Europe (SENECA (Survey in Europe on Nutrition and the Elderly a Concerted Action)). Available data indicate that demographic changes are even more dramatic in the less developed countries (Solomons, 2000). One study including other demographic groups is the International Union of Nutrition Societies (IUNS) cross-cultural study on "Food Habits in Later Life." In this study, people of 70 years and older from communities in Australia, Greece, China, Japan, the Philippines, and Sweden were involved. The results show that on average BMI for Caucasian men and women is about $25\,kg\,m^{-2}$, with the highest for the Greek women ($30\,kg\,m^{-2}$). Filipino and Chinese had average BMIs between 20 and $22\,kg\,m^{-2}$. The estimated fat mass showed as expected: a large gender difference with on average 43 to 50% for women and 25 to 35% for men, but differences in fat mass between ethnic groups were less striking (Wahlqvist *et al.*, 1995).

Aging and the Association between BMI, Weight Loss, and Health

Many studies have documented that the relative risks of a high BMI may become less pronounced with aging. Several explanations for this phenomenon have been forwarded, such as selective survival, cohort effects, and/or a ceiling effect of mortality rates (Seidell and Visscher, 2000). Also, it might be possible that an excess of fat mass is less detrimental at old age. The most important explanation might be that BMI is not a good indicator of body composition. The U-shaped relation between BMI and mortality in younger adults may be the result of a positive association between body fat mass and mortality and an inverse linear association between fat-free mass and mortality. As stated above, the ratio between the two compartments changes with aging and the BMI does not measure this. Finally, kyphosis in old age makes it difficult to measure height and, therefore, may result in unreliable estimates of BMI.

At the other end of the scale reflecting body weight, prospective studies have shown that weight loss, a decline in BMI, can be both a marker of and an independent contributor to adverse health outcomes (Wallace and Schwartz, 2002). Weight loss in elderly subjects is likely to reflect sarcopenia, a loss of lean body mass and particularly muscle mass. The latter may contribute to the increased mortality, especially if the initial body weight is relatively low. Incidence rates of 5 to 15% have been reported in studies of involuntary weight loss in community-dwelling older adults (Wallace and Schwartz, 2002; De Groot *et al.*, 2002). In frail elderly people, often dependent on professional care, rates of over 25% up to 40% have been observed. The degree of weight loss used to define "weight losers" has been variable in the different studies. Although no clear consensus exists in practice, mostly involuntary weight loss of 5% or more in one month or 10% and more in 6 months is applied to clinical diagnoses of malnutrition based on weight loss (Dempsey *et al.*, 1998).

It is considered helpful to inquire if weight loss was voluntary, nevertheless, two studies have suggested that intentional or not intentional, weight loss was similarly associated with increased mortality (Wallace and Schwartz, 2002). Suggested explanations for this finding are that weight loss per se is due to loss of lean body mass with all consequences of impaired function. Further, nutritional deficits are associated with low energy intake as is shown in Figure 3; (De Groot *et al.*, 1999).

Central Adiposity and Health

Redistribution of body fat with aging further limits the applicability of BMI as risk indicator in older adults. There is evidence in younger adults that those who have the majority of their adipose tissue around their waist (high waist-to-hip ratio) have a higher prevalence of diabetes mellitus, hypertension, and coronary artery disease than those who have predominantly hip adiposity. Folsom *et al.*, (1993) examined the role of body fatness on mortality in a random sample of 41 837 Iowan women aged 55 to 69 years, followed for 5 years. Waist-to-hip ratio was positively correlated with mortality, also after correction for smoking, alcohol, and estrogen use. Waist-to-hip ratio is, however, increasingly difficult to interpret with advancing age. Whereas the waist measures abdominal fatness, hip circumference may reflect also variation in pelvic width and gluteal muscle. In elderly people, narrow hips may reflect peripheral muscle wasting, which may correlate with chronic conditions (Seidell and Visscher, 2000; Visscher *et al.*, 2001).

Comparative data on the impact of abdominal fatness on mortality in younger and older adults come from the Baltimore Longitudinal Study on Aging. This study showed that increased abdominal depth (sagittal diameter) was related to increased all-cause mortality and CHD in men aged 55 and younger, but the same diameter was not related to either endpoint in older men. Explanations include again selective survival and cohort effects, but it may also be that the increased abdominal fat mass is less hazardous in older than in younger men (Seidell and Visscher, 2000).

The question arises, how useful in addition to BMI a measurement is of the waist-to-hip ratio, or waist circumference only. Visscher *et al.*, (2000) used data from the seven-country

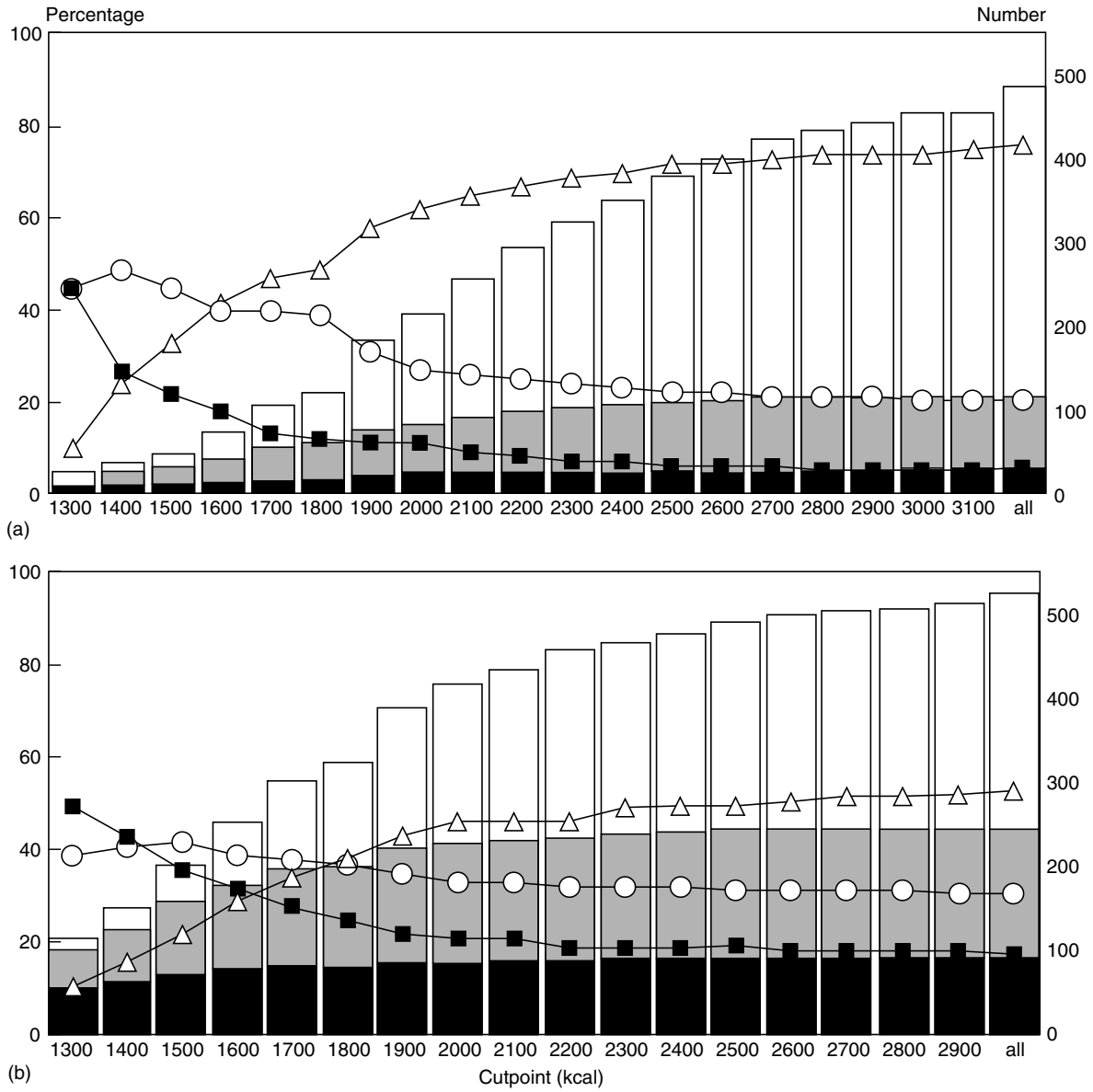

Figure 3 Number and percentage of **a** men and **b** women with an inadequate intake of no nutrients (□ and △), one nutrient (■ and ◯) and at least two nutrients (■ and □) for groups with energy intakes under different cut points (Reproduced from De Groot *et al.*, (1999) by permission of Oxford University Press)

study and showed that a large waist circumference was a better predictor of higher 5-year mortality than waist-to-hip ratio or BMI. Low BMI was a better predictor of mortality than low waist circumference. It is very likely that low lean body mass is better reflected by a low BMI, whereas increased fatness is better reflected by increased waist circumference.

The Importance of Weight Stability and the Need for Data on Body Composition

Weight stability within acceptable range as described above, or even a slight increase in weight seems to result to the lowest mortality (De Groot *et al.*, 2002). However, a stable weight or BMI may mask loss of lean body mass replaced by fat mass. There is a greater need for body composition data in epidemiological studies. How far waist circumference as an indicator of body fatness is of practical use in clinical situations should be studied further.

Fluid Status and Dehydration in the Elderly

Older adults are at risk for dehydration because of both reduced fluid intake and increased fluid losses (Weinberg and Miraker, 1995). Even in healthy, successful aging, there is a reduction in thirst in response to water deprivation, which is evidenced both in a lower self-reported thirst score during

dehydration and ingestion of less water after the dehydration period. Dehydration is a common and potentially lethal problem in both institutionalized and community-dwelling elderly people. In the United States, about 1.5% of community-dwelling people are hospitalized with dehydration each year (Reyes-Ortiz, 1997), but a British study found lower rates of 0.3% (Long *et al.*, 1991). The most common causes of dehydration were infection, altered level of consciousness, cognitive impairment, and use of diuretics. In hospitals, mortality rate was 54% in those older adults with dehydration (Long *et al.*, 1991). In a recent review, Allison and Lobo (2004) concluded that dehydration is a common problem in nursing homes often due to failures in detection of dehydration and appropriate management. They point to the fact that overload of water and salt is also common and may result in impaired recovery from surgery or perioperative mortality and morbidity. For the elderly, it is advised to take about 1.51 fluid per day.

Aging, Bone Loss, and Nutrition

Bone loss commences around the age of 40 years and is on average between 0.5% and 1% per year in men, and in women, the rate of bone loss accelerates around the menopause to about 2% per year. When bone density falls below 2.5 SD of the mean bone mineral density (BMD) of young adults, WHO (1994) speaks about osteoporosis. Osteoporosis is a multifactorial disease and defined also as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures" (Consensus, Osteoporosis, 1993). Biological, environmental, and genetic factors as well as lifestyle factors may play an important role in the onset and development of osteoporosis. Incidence of osteoporosis varies widely between countries and between and within ethnic groups. For instance, the NHANES III (Broussard and Magnus, 2004) showed that low BMD is most common among elderly non-Hispanic white women (21% osteoporosis) and among Mexican American women (20% osteoporosis) and lower in non-Hispanic black women (18%). Prevalence data are lower depending on diagnostic criteria applied.

Although a low percentage of the bone mass can be explained by nutritional factors (less than 20%), it can still have a large impact on bone health. Dietary therapy of vitamin D and calcium, and especially the combination of these two, is promising, as most of the times supplementation of both nutrients shows beneficial effects on BMD, bone turnover, and a reduced risk of fractures without side affects. Vitamin D requirement may be higher in regions where calcium intake is low. Vitamin D also has a beneficial effect on the risk of falling, explained by improvement of muscle function. Evidence for associations between optimal protein intake and bone mass is diverse, whereby positive, negative, and no associations have been found. Other dietary factors such as vitamin K, vitamin A, caffeine, fluoride, phosphorus, and zinc are subjects of current bone research as well, and are under debate whether important and truly associated with bone health.

CHANGES IN DIETARY INTAKE: DIFFERENCES WITHIN AND BETWEEN POPULATIONS

Changes in Energy and Macronutrients over Time

Population-based nutritional surveys have shown a gradual decline in energy intake at old age (De Groot *et al.*, 2000; (Figure 4 NHANES III)). Cross-sectional studies and longitudinal studies starting at middle age suggest that this decline in intake is accompanied by an increase in the percentage of energy from carbohydrates, whereas relative contributions

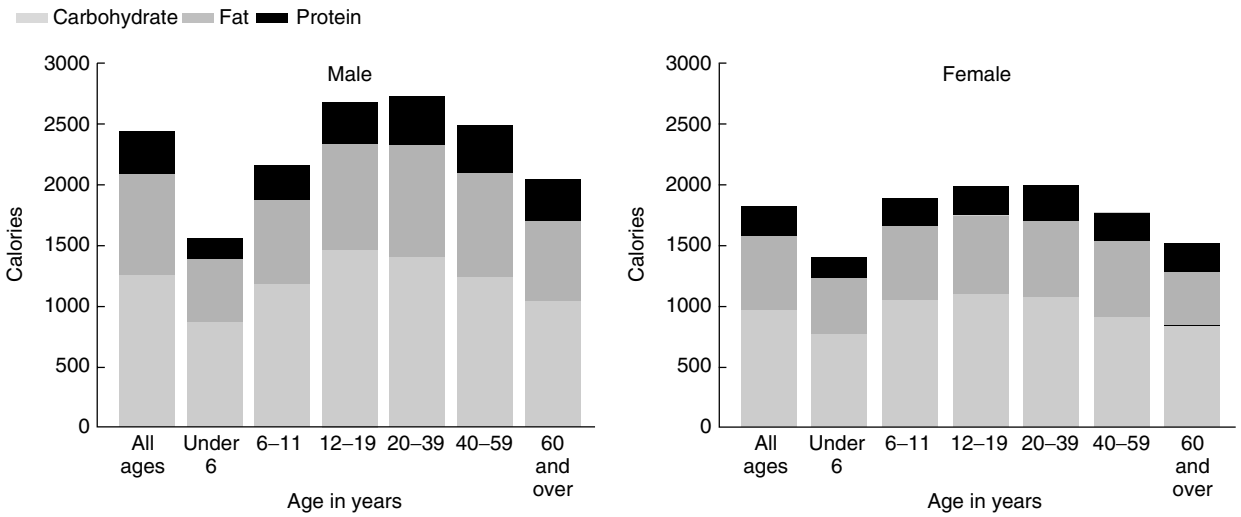

Figure 4 Total calorie intake and major sources of calories for US population, NHANES 1999–2000. (*Source*: http://www.cdc.gov/nchs/nhanes.htm U.S. Department of Health and Human Services Centers for Disease Control and Prevention National Center for Health Statistics)

of fat to energy intake decrease (Morley, 1997; Wakimoto and Block, 2001). In the SENECA (Survey in Europe on Nutrition and the Elderly, a Concerted Action) study in relatively healthy elderly people, thus starting at older age and covering shorter time spans, such shifts in macronutrient intakes did not emerge, despite the tendency of a reduction in total energy intake (Table 1, Moreiras *et al.*, 1996). This suggests that changes related to aging are small after the age of 70 years.

The macronutrient composition appears to vary considerably between populations. Across studies, intakes range from 12 to 18% energy from protein, from 20 to 42% energy from fat, and 38 to 65% of energy from carbohydrates. Low percentages energy from fat and high from carbohydrates are especially found in the Japanese and Chinese older communities (Wahlqvist *et al.*, 1995; Stookey *et al.*, 2000, Moreiras *et al.*, 1996).

The implication of macronutrient composition of the diet for health has been studied less than that of insufficient energy intake. One study that related macronutrient composition with survival revealed that decreasing protein and fat intake were increasingly related with mortality, while carbohydrates show a threshold effect on frail elderly patients (Frisoni *et al.*, 1995).

Table 1 Contribution of protein, fat, and carbohydrates (energy %) to daily energy intake in SENECA's follow-up study and longitudinal changes (1993 vs 1989)

	Men ($n = 155$)		Women ($n = 585$)	
	1993	Change	1993	Change
Energy (MJ day^{-1})	8.9 ± 2.4	-0.6 ± 2.5	7.0 ± 2.1	-0.4 ± 2.0
Energy % from:				
Protein	14.5 ± 2.8	-0.1 ± 2.8	15.4 ± 3.2	0.0 ± 3.3
Fat	35.8 ± 8.4	0.6 ± 7.6	38.1 ± 9.7	0.7 ± 8.6
Carbohydrates	45.0 ± 8.7	-0.2 ± 8.4	46.2 ± 9.5	-0.4 ± 8.9

Source: Reproduced from Moreiras O *et al.*, 1996. Copyright Nature Publishing Group.

Meal Patterns

As part of the culture, there are numerous factors that may influence the share of energy in the diet coming from various energy sources. These include, for example, the meal pattern and the use of food between meals. In Europe, large differences exist in the number of meals eaten per day; the median ranges from six in Denmark to three in the South of France. Meal-based nutrient intake data suggest that the cooked meal in the South of Europe mediates the beneficial effects of the Mediterranean diet (Schlettwein-Gsell *et al.*, 1999).

Vulnerable Groups

Within older populations, there are some subgroups, such as the socially isolated, the lonely, the institutionalized, or the economically deprived people, more likely to be consuming an imbalanced diet. Regarding the socially isolated, there are hardly any data, however, food consumption data of elderly *people living alone* show an adverse impact neither in the United States nor in Europe (Gerrior *et al.*, 1994; Pearson *et al.*, 1998).

Institutionalized elderly people tend to have a lower energy intake – mainly due to a lower fat intake – and a lower protein intake. Furthermore, nutrient inadequacy was more prevalent in the institutionalized elderly than in the community-dwelling groups as is shown in Table 2 (Van der Wielen *et al.*, 1996; Nowson *et al.*, 2003). At the same time, no clear differences in food patterns were observed. Therefore, the main cause of the higher prevalence of nutrient inadequacy in the dependent elderly people is most likely the low level of total food intake. An exception might be the group with a *poor state of dentition*. In the NHANES III as well as the SENECA, a lower quality of the diet was observed due to avoidance of food groups such as meat, fruit, and vegetables (Fontijn-Tehkamp *et al.*, 1996; Sayoun and Krall, 2003).

Table 2 Percentage of elderly people in different categories receiving *less* than the recommendations (RDA)[a] or less than the mean minimum requirements (Minimum need)[a] from diet alone

		Females			
		Nursing homes		Free-living	
Nutrient	Reference value	Resident $n = 40$	Admission $n = 11$	SENECA $n = 68$	4-day marches $n = 32$
Thiamin	RDA 0.12 mg MJ^{-1} and >1.0 mg day^{-1}	88^{A}	91^{AB}	71^{AB}	44^{B}
	Minimum need 0.07 mg MJ^{-1} and >0.8 mg day^{-1}	55^{A}	45^{A}	31^{A}	6^{B}
Riboflavin	RDA 1.3 mg day^{-1} (females); 1.5 mg day^{-1} (males)	62^{A}	45^{AB}	26^{B}	12^{B}
	Minimum need 1.1 mg day^{-1}	45^{A}	36^{AB}	19^{B}	9^{B}
Vitamin B6	RDA 0.02 mg g^{-1} protein[b]	90^{A}	91^{AB}	66^{B}	38^{C}
	Min. need 0.015 mg g^{-1} protein and >1.0 mg day^{-1}	58^{A}	45^{AB}	31^{B}	6^{C}
Vitamin C	RDA 70 mg day^{-1}	72^{A}	64^{A}	16^{B}	3^{B}
	Minimum need 50 mg day^{-1}	48^{A}	45^{AB}	12^{BC}	0^{C}

Source: Reproduced from Van der Wielen *et al.*, (1996). Copyright The Gerontological Society of America Reproduced by permission of the publisher.
[a]Requirements according to the Netherlands Food and Nutrition Council (1992). [b]Intakes should be at least 1.0 mg day^{-1} and 1.1 mg day^{-1} for females and males respectively (aged 65 years and older).
[ABC]On each row, values sharing the same capital letter are not significantly different (Fisher's exact test for 2×2 tables, $p < 0.01$).

Table 3 Main items in three diet scores: Healthy Eating Index (HEI), the Mediterranean Diet Score(MDS) and the Healthy Diet Index HDI

HEI[a]	MDS[b,c]	HDI[d]
Grains	Cereals	Complex carbohydrates, dietary fiber, mono and disaccharides
Vegetables	Vegetables	Vegetables and fruits
Fruits	Fruits and nuts	
	Legumes	Pulses, nuts, seeds
	Alcohol	
Meat poultry, fish, eggs, dry beans, nuts	Meat and meat products	Protein
Milk	Dairy and dairy products	
Energy % of:	Ratio mono-unsaturated/saturated fat	Ratio Saturated/polyunsaturated fat; cholesterol
total fat		
saturated fat		
Salt intake		
Variation score		

[a]For calculations of the index see http//www.cnpp.usda.gov. [b]Recently, this score has been changed with alcohol as a separated recommendation and fish introduced in the core pyramid. Also, daily physical activity obtains attention. Oldways Preservation and Exchange Trust 1999 to 2003. [c]For calculation of the score see Trichopoulou *et al.*, (1995). [d]For calculations of the score see Haveman-Nies *et al.*, (2001).

Institutionalized people are often frail and suffer from functional as well as *cognitive impairment*. In addition to an overall inadequate food intake, several studies have pointed to more specific nutrients and cognitive decline. Examples are increased serum homocysteine levels, as a result from a shortage of folic acid, vitamin B12, or B6 (Morris *et al.*, 2001; Eussen *et al.*, 2002), vitamin C and E as antioxidants, and specific fatty acids (Kalmijn, 2000). However, up till now, studies regarding these relations are either contradictive or valid trials are lacking.

Economically deprived people also may consume an unhealthy diet. In the United States, 21% of the older independently living people below the poverty index had a poor diet based on the Healthy Index (for description see Table 3), while amongst those above the poverty level, this was 11% (Federal Forum, 2000). In the SENECA study, those subjects who reported difficulty in budgeting for their food purchases were found to have a significantly lower intake of three out of five nutrients analyzed, than those subjects who reported no such difficulty. It should be added that the former subjects also reported four times more often to have poor health as the SENECA participants without budget problems (Schlettwein-Gsell *et al.*, 1999).

Park *et al.*, (2003) reviewed dietary intake data in *rural and urban elderly people* in Korea. She observed that urban elderly people with a low income had energy intakes about 400 kcal or 1.7 MJ below the all-income (no separation between low and high income) elderly groups, and this resulted for the low income group in an inadequate supply of micronutrients. The low energy intake was related to a lower body weight and BMI ($24\,kg\,m^{-2}$ vs $22\,kg\,m^{-2}$). In the rural elderly group, BMI was also rather low ($22\,kg\,m^{-2}$), but their energy intake was as high as the all-income group. Similar results were obtained in a Chinese study (Stookey *et al.*, 2000).

HIGH-RISK NUTRIENTS

Even with an apparently adequate food intake, an adequate supply of some nutrients is hard to achieve. Below we discuss some specific high-risk nutrients not directly related to a low energy intake.

Atrophic gastritis reduces the absorption of several nutrients, which leads, especially for *vitamin B12,* to a deficiency state. Van Asselt *et al.*, (1998) found in the Dutch SENECA cohort a prevalence of 24%, which only partly could be explained by dietary intake or atrophic gastritis. As yet, there is no evidence that vitamin B12 is handled differently in old age once the vitamin is absorbed. Therefore, other factors responsible for the cobalamin deficiency need to be sought.

Low *vitamin C* levels have been associated with increased risk for coronary artery disease and senile cataract (Nyssonen *et al.*, 1997). Nevertheless, based on current knowledge, requirements for vitamin C in older people do not differ from those of younger people ($60-100\,mg\,day^{-1}$). Unfortunately, vitamin C is readily lost from foods during storage and preparation. For Dutch and Danish diets, such vitamin C losses amounted to approximately 45% of vitamin C content of the diet, and consequently, about 30% of the subjects had too low intakes. Results from the NHANES III study showed that average intake serum levels were normal in the Americans, but smokers, those not taking supplements, and non-Hispanic black males had higher risks. Low serum levels for the latter group were mainly due to low intakes of fruits and vegetables (Hampl *et al.*, 2004).

Vitamin A is of worldwide concern as a risk nutrient, but probably due to lower requirements in old age (Russell, 1997), has not been observed as a specific problem for the elderly people. An exception might be the observation of very low intakes in Korea (Park *et al.*, 2003).

Approximately one-third of the *vitamin D* requirements can be obtained from the diet. The rest is synthesized in the skin under the influence of sunlight. As a result of limited sunlight exposure and a fourfold reduced capacity of the skin to produce vitamin D, deficiencies may occur in homebound elderly people (Lips, 2001). However, also in relatively healthy older people, low vitamin D levels are often observed (Van der Wielen *et al.*, 1995; Newmark *et al.*, 2004). Surprisingly, in the SENECA Southern survey towns, lower values were found than in the Northern towns. This could be explained by reduced sunlight exposure and

by problems performing activities of daily living. Using sunlamps and/or vitamin D supplements was particularly prevalent in the Northern SENECA towns, and such use was associated with a higher serum 25-hydroxyvitamin D concentration.

Calcium is a risk nutrient in elderly people with no or little dairy products in their diet. This might happen within many cultures and was particularly observed in some Asian centers (Park *et al.*, 2003; Wahlqvist *et al.*, 1995).

DIETARY PATTERNS, HEALTHY DIET SCORES, AND SURVIVAL

Healthy Diet Scores

In addition to single dietary components or nutrients, measures of overall dietary patterns are important in investigating diet and health status (Kant, 1996 and Trichopoulou *et al.*, 1995). To make dietary patterns operational, two common methods are cluster analysis and calculation of diet scores. Cluster analysis explores the categorization of persons into groups on the basis of similarity in food intake (e.g. alcohol drinkers or fish and grain eaters). Diet scores are based on dietary guidelines and are applied to identify groups with good or poor nutritional status. In the United States and Europe, existing measures of overall dietary quality include the Healthy Eating Index (HEI), Mediterranean diet score, and the healthy diet indicator. These diet scores differ in diet components, scoring rates, and definition of cut-off values (Table 3). In spite of these differences, diet scores as well as cluster analysis have been shown to be useful tools to identify groups with different nutritional status. Haveman-Nies *et al.*, (2001) evaluated dietary quality of European and American elderly subjects using cluster analysis, the healthy diet indicator, and two versions of the Mediterranean diet scores MDS. These measures were tested for associations with lifestyle and nutritional status in an elderly population, aged 70 to 77 years from the Framingham study and from the SENECA. Table 4 shows food group intake and results of the scores by the five dietary pattern clusters observed. In general, Southern European Centers and Framingham had better mean diet scores than Northern European Centers. Cluster analysis revealed that the meat, eggs, and fat pattern coincided with significantly lower average dietary quality, as measured with all three scores, compared to all other clusters except the alcohol cluster. The cluster characterized by a relatively high fish and grain intake had a significantly better MDS than all other clusters. High-quality diets were associated with less body fatness, greater physical activity, and nonsmoking.

Healthy Diet, Other Lifestyle Scores, and Mortality

As a next step, Haveman-Nies *et al.*, (2002) examined the relationship between three modifiable lifestyle factors and 10-year survival in the SENECA study. The factors included the quality of the diet as measured with the MDS, smoking, and physical activity. The results are shown in Figure 5. Even at age 70–75 years, the unhealthy lifestyle behaviors having a low-quality diet, smoking, and being physically inactive were singly related to an increased mortality risk (hazards

Table 4 Mean (s.d.) food group intake of 70–77 years elderly of the Framingham Heart Study and SENECA's baseline study, by dietary pattern cluster

	Sugar $n = 526$	Fish and grain $n = 307$	Meat, eggs, and fat $n = 659$	Milk and fruit $n = 525$	Alcohol $n = 93$
Northern center (n) (total = 782)	101	18	511	129	23
Southern center (n) (total = 500)	28	187	55	191	39
Framingham, MA (n) (total = 828)	397	102	93	205	31
Energy (MJ)	8.0 (2.5)	8.0 (3.1)	8.7 (2.5)	7.6 (2.6)	9.1 (2.7)
Energy (kcal)	1911 (605)	1903 (735)	2084 (595)	1826 (613)	2185 (641)
Food/nutrient groups (g):					
Grains	172 (86)	310 (176)	183 (80)	169 (92)	171 (93)
Alcoholic beverages	61 (100)	99 (159)	126 (176)	74 (129)	911 (423)
Milk and milk products	200 (169)	218 (175)	289 (213)	403 (293)	142 (147)
Fruit and fruit products	179 (129)	216 (149)	163 (126)	349 (251)	165 (148)
Eggs	12 (11)	10 (11)	18 (22)	10 (11)	15 (15)
Meat and poultry	97 (46)	87 (48)	142 (63)	92 (53)	103 (57)
Fish/shellfish	26 (21)	58 (43)	24 (24)	42 (49)	46 (52)
Vegetables	261 (131)	217 (138)	287 (132)	294 (191)	256 (143)
Total fat	70 (30)	59 (27)	96 (35)	65 (28)	66 (28)
Legumes/nuts/seeds	29 (28)	13 (16)	7 (12)	17 (20)	17 (24)
Sugar and sugar products	94 (68)	28 (24)	44 (34)	34 (35)	42 (50)
Diet scores:					
Healthy diet indicator	3.4 (1.3)[b]	3.4 (1.3)[b]	2.4 (1.1)[a]	3.4 (1.3)[b]	3.2 (1.3)[b]
Greek mediterranean diet score	2.8 (1.3)[b]	3.3 (1.2)[c]	2.1 (1.2)[a]	2.9 (1.3)[b]	2.2 (1.2)[a]
FS-mediterranean diet score	4.2 (1.4)[b]	4.6 (1.2)[c]	3.1 (1.3)[a]	4.1 (1.5)[b]	3.4 (1.2)[a]

[a,b,c]ANOVA followed by the multiple comparison test was used to test differences in diet scores between dietary clusters. Means within rows with different letter superscripts (c > b > a) are significantly different, $P \leq 0.05$.

Source: Reproduced from Haveman-Nies A *et al.*, 2002. Copyright Nature Publishing Group.

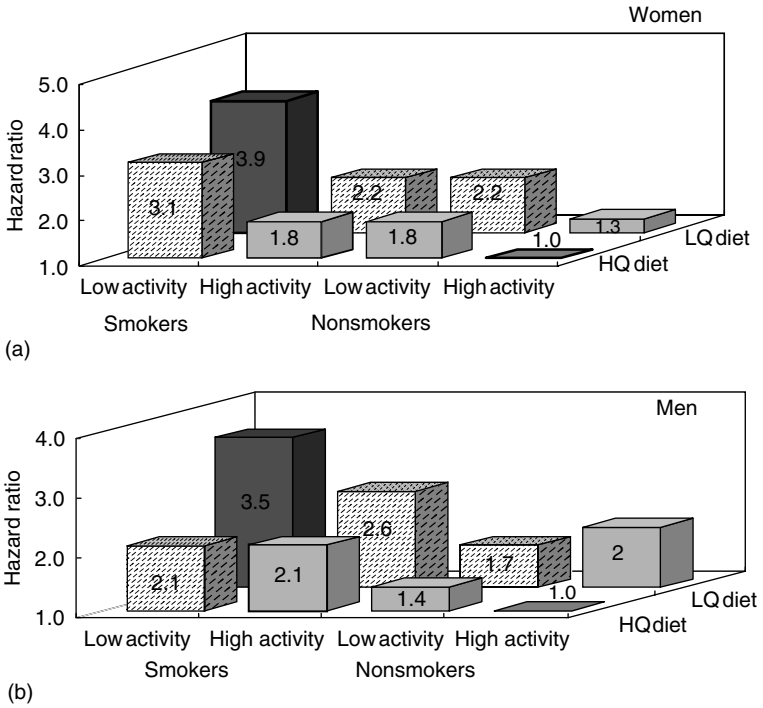

Figure 5 Hazard Ratios for single and combined effects of the lifestyle factors diet, smoking, and physical activity in European women (5a) and men (5b) born between 1913 and 1918, The SENECA Study, 1988 to 1999 (Reproduced by permission of Oxford University Press)

ratios ranged from 1.2 to 2.1). The risk of death was further increased to a three- or fourfold risk for all combinations of an unhealthy lifestyle. Numbers in the SENECA study were too low to examine associations with cause-specific mortality. Therefore, Knoops *et al.*, (2004) merged the data set of SENECA with three centers of the seven-country study (centers in Finland, Italy, and the Netherlands). Since important features of design and methods were similar, the merging of data did not lead to spurious results. Preliminary data show that, also in these groups (1507 apparently healthy men and 832 women aged 70–90 years), adherence to a Mediterranean diet and healthy lifestyle is associated with >50% lower rate of all-cause mortality; similar results were obtained for mortality of CHD, cardiovascular disease, and cancer. The results regarding the diet score confirm earlier data published by Trichopoulou *et al.*, (1995) for the Greek population and by Kouris-Blazos *et al.*, (1999) for Anglo–Celts and Greek Australians.

EFFECT OF NUTRITIONAL SUPPLEMENTS ON HEALTH INDICES IN ELDERLY PEOPLE

There are many ways to improve the nutritional situation in old age, mostly aimed at improving nutrient intake either in terms of quantity and or quality. In order to assess the efficacy of nutrition-related interventions, a number of studies have been conducted. A literature review (Wouters-Wesseling, 2002) examining the literature between 1985 and 2002 divided the studies into multinutrient supplements and single nutrient supplements. Studies conducted in the elderly with specific diseases such as Alzheimer disease were excluded.

Regarding the multiple nutrient studies, only nine were found with a placebo-controlled double-blind design. Six studies were carried out in institutionalized elderly and three studies in home-dwelling elderly. The number of participants varied between 30 and 130, and the duration of the studies between 1 month and 1 year. One study had a duration of 2 years and included a large number of 180 patients (Girodon *et al.*, 1999). The supplements varied in composition and also outcome measures varied. Nevertheless, the results of the studies are more or less in the same direction: improvement of body weight and biochemical parameters of the nutritional status such as serum vitamin levels and functional biochemical parameters, for example, serum homocysteine. Beneficial effects were more convincing when the intervention was conducted during a longer period and when the patients had more serious functional impairments. Studies also showed improvement of the immune status; especially humoral response improved after supplementation with both trace elements and antioxidants, meanwhile, antioxidants only had no effect (Girodon *et al.*, 1999).

Twelve placebo-controlled studies with a single nutrient intervention were found; three in institutionalized elderly people and nine in home-dwelling elderly. The nutrients included selenium, zinc, β-carotene (2 studies), vitamin D, E (4 studies), C, B1, and folic acid. The amount and duration

of the supplementation varied according to the multinutrient intervention. The supply of these single nutrients resulted in improvement of indices of the status related to the single nutrient supplement. Furthermore, the recommended daily doses of either a zinc or selenium supplement improved the immune status according to some, but not all immune status parameters. This occurred also with a high dose (400–800 mg) vitamin E, on the other hand, such an intervention also has shown an unfavorable effect on respiratory infections (Graat *et al.*, 2002).

The literature search shows that in frail elderly people, a combination of macronutrients and micronutrient (enriched or fortified foods) might be preferred. Such an intervention affects several aspects of the nutritional and health status of this group. Again, the doses should not exceed the recommended daily intakes, because adverse affects of such doses on organ systems have been reported (Palmer *et al.*, 2003).

In addition, other types of intervention studies provided evidence for improvement of the nutritional status and quality of life with different approaches to increase food intake. These are, amongst others, (van Staveren *et al.*, 2002):

- stimulation of physical activity,
- improving meal ambiance, and
- flavor enhancement of the cooked meal.

In sum, intervention studies have shown that in frail elderly, dietary interventions improve the nutritional status and that combining these interventions with other interventions such as extra physical activity give complimentary effects on health outcome variables.

DIETARY GUIDELINES

In this chapter, we started with the dietary guidelines for the prevention of chronic diseases of WHO (2003).

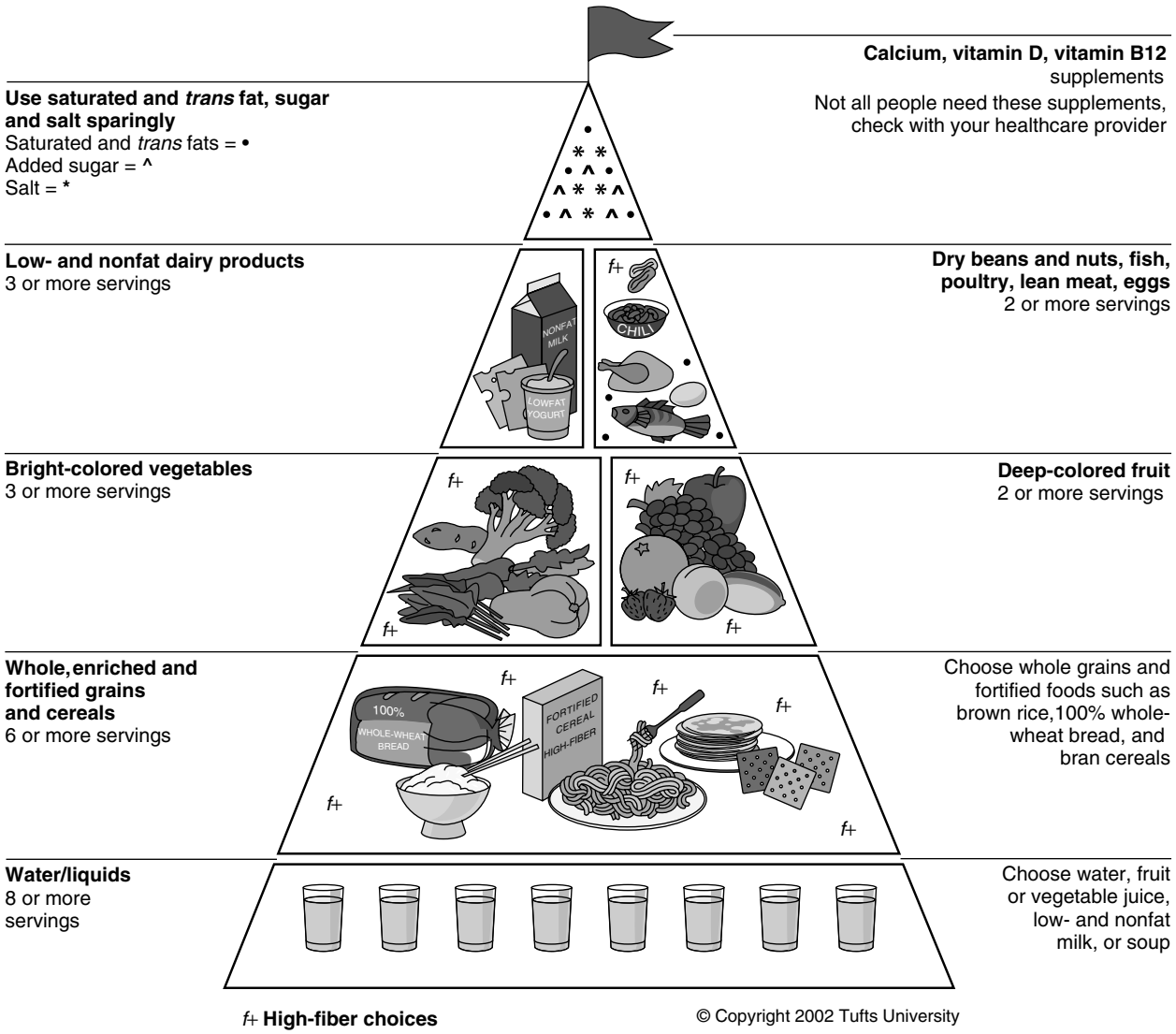

Figure 6 Food guide pyramid for older adults (Copyright Tufts University, Boston, USA)

Epidemiological studies on nutrition and aging show that the guidelines for elderly people are very similar to those formulated for younger adults. However, the priorities should be different. In the first place, it is recommended to aim for stable body weight and maintenance of fat-free mass by sufficient physical activity. Dietary recommendations are nicely depicted in the pyramid for elderly people (Figure 6). The healthy foods in the pyramid are the same foods that comprise the MDS. In addition, there is a basis of sufficient fluid (although the amount recommended is rather a maximum than an average), and attention is given to some supplements. For vitamin D, there is sufficient evidence that a supplement is required for groups of elderly people. Homebound elderly people are most at risk. Further, as explained above for elderly people with insufficient intake of dairy products, extra calcium is required and elderly people suffering from atrophic gastritis may benefit from a vitamin B12 supplement.

Frail elderly people with a very low energy intake may need enriched or fortified foods with vitamins and minerals added according to the dietary recommendations.

Finally, we like to conclude that although there are still many questions in the relationship between dietary patterns and health and in the effectiveness of supplement use, the epidemiology of nutrition and aging supplies us with sufficient evidence on the importance of adequate nutritional care and a healthy diet in old age.

KEY POINTS

- The relative risks of a high BMI become less pronounced with aging. A decline in BMI may reflect sarcopenia, which is related to decreased survival time.
- A low energy intake (<6.3 MJ/1500 kcal) goes together with an insufficient supply of micronutrients.
- High-risk nutrients independent of sufficient energy intake are vitamin B12 and vitamin D and for specific groups vitamin A, vitamin C, and calcium.
- Also in an elderly population, healthy dietary patterns are related to decreased total mortality and disease-specific mortality.
- Adequate nutritional care includes care for sufficient fluid intake.

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25

Absorption of Nutrients

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INTRODUCTION

Since the evolution of the first unicellular microorganisms, absorption of nutrients has been a challenge, that is, the ability to process and transfer energy from complex nonabsorbable forms stored in food to simpler and more usable forms across semipermeable biological membranes. In lower organisms this was generally easier as the unicellular organisms were bathed in the medium of nutrients they lived in. As more advanced multicellular organisms evolved, and as organisms were now living in environmental media that were outside of their food, it then became necessary to evolve a more complicated internal digestive and absorptive systems, with the various parts, that is, teeth, jaws, stomach reservoir, digestive enzymes, large absorptive surface areas in the intestine, and so on, all functioning as a system. Digestion of nutrients then became coupled to absorption of nutrients.

The small intestine is the most important site of nutrient absorptions. Structurally, it is constructed to provide maximum absorptive surface area within a limited space. The presence of Kerckring's folds, villi, and microvilli result in a 600-fold increase in surface area, compared to the surface area of a simple cylindrical tube. In humans, the surface area of the small intestine available for absorption is about 100 times larger than the human body surface area (Caspary, 1987).

Absorption of nutrients occurs across the plasma membranes of the intestinal epithelial cells. Nutrient molecules penetrate by various mechanisms that include simple passive diffusion, facilitated (carrier-mediated) diffusion, active transport, and pinocytosis (Caspary, 1992).

REGULATION OF NUTRIENT ABSORPTIONS

The amount of nutrients that is eventually absorbed into the body depends on several factors. Some of these are mechanical factors such as the amount of food ingested, masticating activities of the teeth, peristaltic activities of the gastric emptying and intestinal transit. Others are neuronal and hormonal factors, which control the secretions of digestive juices from the glands in the mouth, stomach, pancreas, and intestines. Still others are mucosal (especially of the small intestines) and intraluminal factors, which alter how nutrients are able to move from the intestinal lumen into the intracellular and interstitial spaces.

It has long been suspected that the composition of the food we eat, especially during our early days of formation may have effects on how we digest and absorb nutrients later on in life, that is, the phenomenon of intestinal adaptation and critical-period programming. Karasov *et al.* (1985) defined this as a biological mechanism, which is turned irreversibly on or off once during an individual's lifetime, in response to conditions prevailing at some critical stage.

Studies in rodents with hormones or peptides such as glucocorticoids, polyamines, growth hormone, insulinlike growth factors, proglucagon derived peptides, or by changing various components of the baby's diet have shown some acceleration of the rate of maturation of intestinal absorption (Tiesen *et al.*, 2000).

COMPOSITION OF DIET

The average diet consists of macronutrients (such as carbohydrates, proteins, fats), micronutrients (such as Vitamins B_{12}, C, A, E, D, K, niacin, thiamine, riboflavin, pantothenic acids, minerals), nonabsorbable fibers (such as hemicellulose, pectins), and water. Carbohydrates, especially polysaccharides account for at least 50% of the daily calories of adults living in western industrialized countries (Elsenhans and Caspary, 1987).

ABSORPTION OF MACRONUTRIENTS

After ingestion of carbohydrate, the enzyme alpha amylase acts on the polysaccharides of starch to convert them to

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short chain oligosaccharide. These are then acted upon by the membrane-bound enzymes of the epithelium of the small intestines to convert them into the monosaccharides of primarily glucose, galactose, and fructose, which are the absorbable forms of carbohydrates. The monosaccharides are then absorbed via transport routes that are both specific (e.g. sodium-dependent active transport and facilitated diffusion) and nonspecific (e.g. passive diffusion) (Elsenhans and Caspary, 1987) into the portal venous system. The main events of protein digestion occur with cleavage of polypeptides by pancreatic proteases such as trypsin, chymotrypsin, elastase, and carboxypeptidase. Large polypeptides are converted to oligopeptides. At the intestinal brush-border membranes, there is hydrolysis of oligopeptides into tripeptides, dipeptides, and some free amino acids, with subsequent transport by different specific amino acid and small peptide carrier systems into the cytoplasm of the intestinal epithelial cells where most dipeptides and probably all tripeptides are rapidly hydrolyzed to their constituent amino acids before they finally appear in the portal venous system (Caspary, 1992). About 90% of dietary fats consist of triglycerides, while the rest is made up of phospholipids, cholesterol, fatty acids, and fat-soluble vitamins (Glickman, 1983; Stremmel, 1987). Digestion of dietary fats begin with activities of upper gastrointestinal (GI) tract secretions, which bring about emulsification of fats into particles (mainly by bile salts), hydrolysis of lipid esters (mainly triglycerides by pancreatic lipase) converting them to fatty acids and monoglycerides. A water-suspension of mixed micelles consisting of bile acids, fatty acids, monoglycerides, cholesterol, lysophospholipids, and fat-soluble vitamins is presented to the intestinal mucosal cells (Stremmel, 1987; Carey *et al.*, 1983). Permeation of fatty acids through the microvillus membrane of the mucosal cells occur by a specific carrier-mediated energy dependent transport process driven by a transmembranous sodium gradient (Stremmel, 1987). Following absorption, intracellular, long chain fatty acids are reesterified into triglycerides. Then together with cholesterol, cholesterol esters, fatty acids, and fat-soluble vitamins, the lipids are reconstituted with apolipoproteins to form chylomicrons and very low density lipoproteins. These are then released into the interstitial spaces via a process of reversed pinocytosis or exocytosis and eventually into the lymphatic system and then the systemic circulation. Medium chain triglycerides are absorbed much more easily. They do not require bile salts for absorption and are not reesterified intracellularly. For this reason they do not require incorporation into chylomicrons, and are transported directly to the liver via the portal venous system (Caspary, 1992).

ABSORPTION OF MICRONUTRIENTS

Vitamins and minerals are readily absorbed from the gastrointestinal tract. Iron is mainly absorbed in the upper gastrointestinal tract and the absorption is enhanced in the presence of acid from gastric secretions. An acidic medium also enhances the absorptions of folate and calcium. Vitamin B_{12} is mainly absorbed in the terminal ileum. Malabsorption of fats will affect the absorptions of fat-soluble vitamins (A, D, E, K). Vitamin D is produced endogenously from the skin following exposure to sunlight (Moore and Iber, 1998). However, this amount is reduced with aging, making gastrointestinal absorption more important.

EFFECT OF AGING ON NUTRIENT ABSORPTION

The aging gastrointestinal tract has very few changes that substantially influence digestion and absorption of nutrients. The changes that do commonly occur have greater impact on the activity and pleasure of eating (Moore and Iber, 1998). The taste threshold for recognition and detection of flavors becomes elevated with aging (Stevens *et al.*, 1984). Medications and cigarette smoking can markedly alter taste thresholds. Similarly, zinc deficiency, which can occur in persons with diabetes mellitus or diuretic users, can cause an increase in taste thresholds. This means greater concentrations of substrate must be presented to the taste buds before they are detected. Loss of smell is also common with aging especially after the age of 80 years. Salivary flow is often diminished with aging, but it is usually related to disease or medications (Russell, 1992). Salivary volume secretion does not appear to be affected by aging per se (Baum, 1981). Chewing activities may be affected by aging because of loss of effective dentition, leading to restriction of food, malnutrition, and undernutrition. Reduced gastric acid production is common among the elderly. In one US population-based study, it was found to be about 31% in those over the age of 60 years (Samloff *et al.*, 1982). This was attributed to the high prevalence of Helicobacter pylori infection and atrophic gastritis in the elderly population.

Impaired gastric emptying and impaired esophageal motility are occasionally encountered with aging but they have little or no effect on nutrient absorption (Kupfer *et al.*, 1985). With aging, the blood flow to the gastrointestinal tract declines both absolutely and as a fraction of cardiac output (Blender, 1965). For a 65-year-old man, cardiac output decreases by 30% compared to young adults. This translates to a 50% decrease in gastrointestinal blood flow (Richey and Blender, 1977).

The liver size decreases with aging, and the portal blood flow also decreases significantly with aging. The activities of many glucuronyl transferase enzymes are diminished with aging (Iber *et al.*, 1994). The sensitivity of gallbladder contractions to cholecystokinin stimulation has been shown to be diminished in older people (Khalil *et al.*, 1985). Pancreatic enzyme secretions are slightly diminished with age. It is unclear if these changes have any significant effect on nutrient absorption under physiologic conditions. Morphological changes in the gastrointestinal tract such as number of crypts and villi, diverticulosis, intestinal brush-border membrane and its enzymes that occur with aging have been studied but there is no consensus if age-related changes

Table 1 Effect of aging on nutrient absorption

Nutrient	Age-related changes
Carbohydrates	Slightly reduced absorption at high doses
Protein	Slightly reduced absorption at high doses
Fat	Slightly reduced absorption at high doses
Thiamine	No change
Riboflavin	No change
Pantothenic Acid	Slightly reduced absorption
Niacin	No change
Folic Acid	Slightly decreased absorption
Vitamin A	Slightly increased absorption
Vitamin B_{12}	Slightly decreased absorption
Vitamin C	Slightly increased absorption
Vitamin D	Decreased skin synthesis
Vitamin E	Decreased antioxidant status
Vitamin K	No change
Calcium	Slightly decreased absorption
Magnesium	No change
Zinc	No change

significantly alter nutrient absorption (Warren *et al.*, 1978; Table 1).

DISEASE CONDITIONS INFLUENCING NUTRIENT ABSORPTION

Although impaired intake due to conditions such as depression and neurological diseases are the most common causes of reduced nutrient intake, a variety of gastrointestinal disorders can influence nutrient absorption. Chronic gastritis especially from Helicobacter pylori infection can lead to atrophic gastritis and achlorhydria with the consequence of malabsorption of iron (due to reduced gastric acid secretions) and of vitamin B_{12} (due to loss of intrinsic factor).

Small intestinal bacteria overgrowth, which is common in patients with long standing diabetes and diverticulosis, can be a cause of malabsorption of fats, vitamin B_{12} and folate, as the overgrown intestinal bacteria deconjugate bile salts and remove vitamin B_{12} from intrinsic factors. In severe cases, there may be extensive damage to the mucosal cells of the small intestine, leading to a more generalized malabsorption of nutrients (Holt, 1992). This condition can also be associated with an excessive gastrointestinal cytokine secretion leading to anorexia.

Celiac disease can result in damage to the intestinal absorptive surfaces due to gluten hypersensitivity with consequence of malabsorption of folate, vitamins A, D. This condition is worsened in the presence of wheat products, and may present with diarrhea. It is commonly associated with diabetes mellitus, and may present for the first time in older persons. Diseases of the pancreas can result in reduction of the exocrine function of the pancreas and pancreatic insufficiency with consequence of malabsorptions of fats, vitamins A, D, E, vitamin B_{12}, and calcium. Diseases of the terminal ileum such as regional ileitis can also result in malabsorption of fats, vitamins A, D, E, vitamin B_{12}, and calcium. Gastrointestinal surgeries that involve gastrectomy or vagotomy may result in malabsorption of iron, calcium, and vitamin B_{12}. Surgical removal of the terminal ileum may result in malabsorptions of vitamin B_{12} and fat. Pancreatic surgeries may also result in malabsorptions of fat, and fat-soluble vitamins. Surgical operations on the liver, gallbladder, or biliary tract generally have no effect on subsequent nutrition if the patient remains free of jaundice (Moore and Iber, 1998).

The work-up for malabsorption includes examining the stool for excess fat and meat fibers, and measuring circulating beta-carotene and vitamin A (Table 2).

DRUG–NUTRIENT INTERACTIONS

Drugs effect nutrient absorption by various mechanisms, among which are direct mechanisms such as drug-induced pH changes in the gastrointestinal tract (antacids), drug-induced changes in bioavailability (e.g. adsorption to drugs like kaolin, pectin), drug-induced retardation of absorption (charcoal), drug binding, or chelation (e.g. anionic exchange resins – cholestyramine, metal ions – iron, calcium). Drugs can also effect nutrient absorptions via indirect mechanisms, such as drug-induced changes in gut motility (e.g. anticholinergics), or drug-induced malabsorption syndromes (e.g. neomycin) (Thomas, 1995). The effect of drug–nutrient interactions are commonly seen in patients taking the same drugs daily for many months or years, as opposed to patients taking short courses of the drugs (Moore and Iber, 1998).

Table 2 Most common diseases modulating nutrient absorption

Disease	Impaired absorption	Mechanism
Chronic gastritis	Decreased vitamin B_{12}, iron	Reduced gastric acid secretion. Loss of intrinsic factor
Partial gastrectomy	Decreased vitamin B_{12}	Loss of intrinsic factor
Bacteria overgrowth	Decreased vitamin B_{12}, folate	Deconjugation of bile salts. Removal of vitamin B_{12} from intrinsic factor
Celiac disease	Decreased folate, vitamins A, D	Damage to intestinal absorptive surfaces
Pancreatic insufficiency	Decreased vitamins A, D, E, and calcium	Malabsorption of fats
Terminal ileum diseases	Decreased vitamins A, D, E, B_{12}, calcium, fats	Loss of absorptive surfaces
Alcoholism	Decreased folate, thiamine, macronutrients	Decreased intake. Damage to intestinal absorptive surfaces
Chronic liver and gallbladder diseases	Decreased vitamins A, D, E, K, fats	Malabsorption of fats

Table 3 Drug–nutrient interactions

Drugs	Effect on nutrient absorption	Mechanism
Methimazole, PTU, formaldehyde, CNS depressants	Decreased macro- and micronutrients	Impaired smell
Penicillamine, tetracycline, flagyl, captopril, cancer chemo, CNS depressants	Decreased macro- and micronutrients	Impaired taste
Erythromycin, digoxin, codeine, morphine, amphetamine	Decreased macro- and micronutrients	Suppressed appetite
Antacids, H2 blockers	Decreased vitamin B_{12}, calcium, iron	Cause pH changes
Kaolin. Pectin, charcoal, drug binder/chelations	Decreased calcium, iron	Impaired bioavailability
Anticholinergics	Malabsorption of macro- and micronutrients	Impaired gastrointestinal motility
Broad-spectrum antibiotics (neomycin)	Decreased vitamin K, folate	Affect intestinal bacteria flora
Anticholinergics	Decreased vitamins A, D, K, macronutrients	Impaired gastrointestinal secretions.

Examples of some commonly encountered clinical scenarios include folate deficiency or megaloblastic anemia in patients chronically on drugs such as phenytoin, phenobarbital, primidone, and phenothiazine. Vitamin B_{12} malabsorption occurs in patients on aminosalicyclic acid, colchicines, and trifluoperazine. Malabsorption of iron is present in patients chronically on antacids. Calcium malabsorption is associated with taking large amount of fibers. Niacin and pyridoxine deficiencies occur in patients chronically on isoniazide and penicillamine (Trovato *et al.*, 1991).

Chronic use of alcohol can result in injuries to the intestinal mucosal cells with resulting malabsorption syndrome that causes impaired absorption of both macro and micronutrients (Table 3).

CONCLUSION

In humans, absorption of nutrient is coupled with digestion of food and is regulated by a complex interaction of factors. Some of these are neurohormonal, while others are glandular, mucosal, and intraluminal factors. Normal aging brings about very few changes that substantially influence digestion and absorption of nutrients. The changes, however, have greater impact on the activity and pleasure of eating. Malabsorption of nutrients is often due to pathological gastrointestinal conditions of which those commonly seen in older adults include atrophic gastritis and achlorhydria, intestinal bacteria overgrowth, celiac disease, pancreatic diseases, previous gastrointestinal surgeries, and drug–nutrient interactions.

In summary the following apply:

KEY POINTS

- Physiological changes with aging have minimal impact on gastrointestinal absorption.
- Lack of production of intrinsic factor and achlorhydria can cause malabsorption of vitamin B_{12} and iron.
- Bacteria overgrowth in the intestine can lead to nutrient malabsorption.
- Medications are an important cause of micronutrient malabsorption.
- Celiac disease and pancreatic insufficiency are common causes of malabsorption in older persons.

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26

The Anorexia of Aging

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THE "PARADOX" OF UNDERNUTRITION IN OLDER PEOPLE

Over-nutrition is the major form of malnutrition in the developed world. A substantial proportion of older people in western countries are overweight or obese according to generally accepted body mass index (BMI weight[kg]/(height[m])^2) criteria. For example, in a 2000 study, 58% of Americans aged $\geq$65 years had a BMI of 25 kg m^{-2} or more (Flegal *et al.*, 2002), the World Health Organization cut-off for overweight. Weight loss is usually recommended for overweight and obese older adults in the same manner as in younger adults and at any given time, a substantial proportion of older people wish to lose weight. Furthermore, there is evidence from studies in species as varied as yeast, spiders, mice, and possibly primates, that long-term restriction of energy (food) intake by 30–60% compared to *ad libitum* intake, prolongs life (Lane *et al.*, 2004). It might seem, therefore, that reduced food intake leading to weight loss would be good for the majority of older people.

This is not necessarily the case, however. The effects of long-term voluntary energy restriction have not been tested in humans and the benefits observed in other species may not apply to ours. Even if such a restriction is beneficial, it may have to be started in childhood, with consequent inhibition of normal growth. Marked energy restriction in older adults is likely to lead to a substantial loss of beneficial lean body tissue as well as fat mass and increase the risk of vitamin, mineral, and other dietary deficiencies.

As indicated in the following text, (1) ideal weight ranges are almost certainly higher in older than young adults; (2) weight loss is often associated with adverse effects in the elderly, particularly if unintentional; and (3) undernutrition manifesting as low body weight and weight loss is common in older people and has significant adverse effects. For these reasons, caution should be exercised in recommending weight loss to people over 70 years and a high level of awareness needs to be maintained to detect unintentional weight loss and undernutrition in this age-group.

"IDEAL" BODY WEIGHT IN OLDER PEOPLE

There is increasing evidence that the adverse effects of being overweight or obese, as defined by standard BMI criteria, are not as great in the elderly as in younger adults. Ideal weight ranges based on life expectancy are higher for older than young adults. For example, in a 12-year study of 324 000 people in the American Cancer Society Cohort, for people under the age of 75 there was a significant and progressive increase in subsequent mortality as baseline BMI increased above 21.9 kg m^{-2}. These adverse effects of increasing body weight diminished, however, with increasing age above 45 years, and were absent altogether over 75 years (Willett *et al.*, 1999). Among 4736 people aged 60 or more followed for an average of 4.5 years in the Systolic Hypertension in the Elderly Program (SHEP) (Somes *et al.*, 2002), those whose baseline BMI was in the lowest quintile ($<$23.6 kg m^{-2}) had the highest subsequent mortality and those within the highest BMI quintile ($\geq$31 kg m^{-2}), corresponding to the conventional criteria of obesity, had the lowest mortality. Recommendations for ideal weight ranges in older people vary, but there is good evidence that BMI values below about 22 kg m^{-2} in people over 70 years of age are associated with worse outcomes than higher weights, and BMIs below 18.5 kg m^{-2} are a particular concern.

While optimum body weight for older people is probably higher than for young adults, they in fact tend to weigh less. The decline in body weight with age, as measured by BMI, has been well documented in population-based, cross-sectional, and longitudinal studies (Schoenborn *et al.*, 2002; Chumlea *et al.*, 1988). For example, in the 1997–1998 US National Health Interview Survey of 68 556 adults, more people aged 75 years and older than those aged 45–64 years were "underweight" (BMI $<$ 18.5; 5 vs 1.2%) and substantially less were "overweight" (BMI $>$ 25; 47.2 vs 63.5% (Schoenborn *et al.*, 2002)).

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WEIGHT LOSS IN OLDER PEOPLE

The lower average body weight of older than younger adults is not just because overweight people die earlier from obesity-related diseases, leaving the healthy, thin ones behind. On average, people over 75 years are more likely to lose than gain weight (Wallace *et al.*, 1995; Newman *et al.*, 2001), in part explaining why they weigh less than younger adults. For example, in a study that followed 247 community-dwelling American men aged over 65 for 2 years, on average these men lost 0.5% of their body weight per year and 13.1% of the group had involuntary weight loss of 4% per annum or more (Wallace *et al.*, 1995).

Numerous studies have shown that weight loss in the elderly is associated with poor outcomes, certainly if involuntary, but possibly even when deliberate. The prospective Cardiovascular Health Study (Newman *et al.*, 2001), for example, studied 4714 home-dwelling subjects over 65 years without known cancer. In the 3 years after study entry, 17% of the subjects lost 5% or more of their initial body weight, compared to 13% who gained 5% or more. The weight-loss group had significant increases in total ($2.09 \times \uparrow$ (95% confidence interval 1.67–2.62)) and risk-adjusted mortality ($1.67 \times \uparrow$ (1.29–2.15)) over the following 4 years compared to the stable weight group. The increased mortality occurred irrespective of starting weight and whether or not the weight loss was intentional. The weight gain group had no increase in mortality. In the SHEP study mentioned in the preceding text (Somes *et al.*, 2002), those subjects who had a weight loss of 1.6 kg year^{-1} or more experienced a 4.9 times greater death rate (95% CI 3.5–6.8) than those without significant weight change. Although mortality was also increased if weight increased more than 0.5 kg year^{-1}, the increase was less than that with weight loss (2.4-fold vs 4.9-fold increase). Of particular note, the adverse effects on mortality of weight loss were present even in the subjects who were heaviest at baseline (BMI $\geq$ 31) and were independent of baseline weight.

The combination of initially low body weight and weight loss is especially bad news for older people. In the SHEP study (Somes *et al.*, 2002), subjects with a low baseline weight (BMI $<$ 23.6 kg m^{-2} who lost more than 1.6 kg year^{-1} had a mortality rate of 22.6%, almost 20 times greater than the mortality rate of those with a baseline BMI of 23.6–28 kg m^{-2} whose weight remained stable. This interaction is a particular concern as the tendency for older people to lose weight is variable, with lean individuals probably most at risk (Rumpel *et al.*, 1993). In an older person, unintentional weight loss of 5% or more over 6–12 months is associated with an increased risk of adverse effects, while a loss of 10% or more very likely means protein-energy malnutrition.

There are many reasons why weight loss in older people has adverse effects. It some cases, weight loss is due to an illness, such as a malignancy, which is mainly responsible for the poor outcome and the weight loss is partly an "innocent bystander". Nevertheless, the weight loss and associated undernutrition is itself often a significant problem. This is because loss of body weight after the age of 60 is disproportionately of lean body tissue, that is, sarcopenia (Evans and Campbell, 1993) and individuals lose up to 3 kg of lean body mass per decade after the age of 50. Unlike loss of fat tissue, such a loss of lean tissue has adverse effects. Sarcopenia is associated with metabolic, physiologic, and functional impairments and disability including increased falls, and increased risk of protein-energy malnutrition.

UNDERNUTRITION IN OLDER PEOPLE

Prevalence

Protein-energy malnutrition is common in the elderly. Reported rates vary, in part because of differing methods used to diagnose this condition, but studies in developed countries have found that up to 15% of community-dwelling and home-bound elderly, between 23 and 62%, of hospitalized patients and up to 85% of nursing homes residents suffer from the condition (Morley, 1997).

Adverse Effects

Protein-energy malnutrition is associated with impaired muscle function, decreased bone mass, immune dysfunction, anemia, reduced cognitive function, poor wound healing, delayed recovery from surgery and ultimately increased morbidity and mortality (see Table 1). Epidemiological studies have demonstrated that protein-energy malnutrition is a strong independent predictor of mortality in elderly people regardless of whether they live in the community or in a nursing home, are patients in a hospital or have been discharged from hospital in the last 1–2 years (Cederholm *et al.*, 1995).

The increased mortality rate in elderly people with protein-energy malnutrition is further increased in the presence of other medical diseases, such as renal failure, cardiac failure, and cerebrovascular disease. For example, the 9-month mortality rate of 205 patients >70 years without cancer, admitted to a medical ward in Sweden, was 18% in 164 well-nourished patients without cardiac failure, 44% in 41 malnourished patients without cardiac failure, but 80% in 10 malnourished patients with congestive heart failure (Cederholm *et al.*, 1995).

CAUSES OF UNDERNUTRITION IN OLDER PEOPLE

Reduced Food Intake

Aging is associated with a decline in energy (food) intake. Energy intake decreases by approximately 30% between 20 and 80 years (Wurtman *et al.*, 1988). The elderly people on an average consume smaller meals more slowly, and

Table 1 Effects of weight loss and protein-energy malnutrition on function in the elderly

↓ Muscle function
↓ Muscle relaxation
↓ Muscle mass
↓ Muscle strength
↑ Risk of fracture
↓ Bone mass
↑ Incidence of falls
↓ Functional status
Immune dysfunction
↑ Increased risk of infection
↓ Delayed skin hypersensitivity
T-cell lymphocytopenia
↓ Synthesis of interleukin-2
↓ Cytolytic cell activity
↓ Response to influenza vaccination
Anemia
Poor wound healing
Fatigue
Pneumonia
Delayed recovery from surgery
↓ Cognitive function
↓ Cardiac output
↓ Intravascular fluid (dehydration)
↑ Incidence of pressure sores
↓ Maximal breathing capacity
↑ Hospital admission and length of stay
↑ Mortality

fewer snacks between meals (Morley, 1997), and consistently report that they are less hungry than young adults (Clarkston *et al.*, 1997). For example, the 1989 cross-sectional American National Health and Nutrition Examination Survey (NHANES III) study reported a decline in energy intake, between the ages of 20 and 80 years, of 1321 calories day^{-1} in men and 629 calories day^{-1} in women (Briefel *et al.*, 1995), a 7-year New Mexico longitudinal study of 156 persons aged 64–91 years, reported a decrease of 19.3 kcal day^{-1} $year^{-1}$ in women and 25.1 kcal day^{-1} $year^{-1}$ in men (Koehler, 1994), while a Swedish 6-year longitudinal study of 98 people found that between the ages of 70 and 76 years, there was a decrease in energy intake of 610 calories day^{-1} in men and 440 calories day^{-1} in women (Sjogren *et al.*, 1994).

The Physiological "Anorexia of Aging"

The age-related decline in food intake is not just due to the effects of illnesses that become more frequent with increasing age. Numerous studies have documented an age-related decline in appetite and energy intake in *healthy, ambulant noninstitutionalized* people (Wurtman *et al.*, 1988). Healthy older persons are less hungry and more full before, and become more rapidly satiated after eating a standard meal than younger persons. Much of this decrease in energy is probably a response to the decline in energy expenditure that also occurs during normal aging. In many individuals, however, the decrease in energy intake is greater than the decrease in energy expenditure, so body weight is lost (see the preceding text). This physiological, age-related reduction in energy intake has been termed *the anorexia of aging* (Morley, 1997).

Loss of Homeostasis

Old age is associated with diminished homeostatic regulation of many physiological functions, including the regulation of energy intake. For example, Roberts *et al.* (1994) underfed 17 young and old men by 3.17 MJ day^{-1} ($\approx$750 kcal day^{-1}) for 21 days, during which time both the young and old men lost weight. After the underfeeding period, the men were allowed to again eat *ad libitum.* The young men ate more than at baseline (preunderfeeding) and quickly returned to normal weight, whereas the old men did not compensate, returned only to their baseline intake and did not regain the weight that they had lost. Older people also have a reduced ability to detect and respond to dehydration.

The combination of age-related physiological anorexia and impaired homeostasis means that older people as well as young adults do not respond to acute undernutrition. Consequently, after an anorectic insult (for example, major surgery), older people are likely to take longer than young adults to regain the weight lost, remain undernourished longer, and be more susceptible to subsequent superimposed illnesses, such as infections.

Pathological Anorexia and Undernutrition in Older People

Protein-energy malnutrition is particularly likely to develop in the presence of other "pathological" factors, many of which become more common with increased age (Table 2). The majority are at least partly responsive to treatment, so recognition is important.

Poverty

One of the social factors that contributes to decreased food intake in the elderly is poverty, which is associated with an increased rate of hunger and food insecurity (Nelson *et al.*, 1998). Many older individuals have limited financial means, which makes it difficult to afford food of good nutritional quality.

Social Isolation

Older people are more likely to live alone than young adults. Social isolation and loneliness have been associated with decreased appetite and energy intake in the elderly (Walker and Beachene, 1991). Elderly people tend to consume substantially more food (up to 50%) during a meal when eating in the company of friends than when eating alone. The simple measure of having older people eat in company rather than alone may be effective in increasing their energy intake.

Table 2 Nonphysiologic causes of anorexia in older persons

Social factors
Poverty
Inability to shop
Inability to prepare and cook meals
Inability to feed oneself
Living alone/social isolation/lack of social support network
Failure to cater to ethnic food preferences in institutionalized individuals
Psychological factors
Depression
Dementia/Alzheimer's disease
Alcoholism
Bereavement
Cholesterol phobia
Medical factors
Cardiac failure
Chronic obstructive pulmonary disease
Infection
Cancer
Alcoholism
Dysphagia
Rheumatoid arthritis
Malabsorption syndromes
Gastrointestinal symptoms
– Dyspepsia
– Helicobacter pylori infection/atrophic gastritis
– Vomiting/diarrhea/constipation
– Parkinson's disease
Hypermetabolism (e.g. hyperthyroidism)
Medications
– Anti-infectives
– Antineoplastics
– Antirheumatics
– Nutritional supplements
– Pulmonary agents
– Cardiovascular agents
– CNS agents
– Gastrointestinal agents

CNS, central nervous system.

Depression

Depression, often associated with bereavement and the deterioration of social networks, is a common psychological problem in older people, present in 2–10% of community-dwelling older people and a much greater proportion of those in institutions (Evers and Marin, 2002). Depression is more likely to manifest as reduced appetite and weight loss in the elderly than in younger adults and is an important cause of weight loss and undernutrition in this group. Undernutrition *per se*, particularly if it produces folate deficiency, may further worsen depression, thus setting up a vicious cycle. Treatment of depression is effective in producing weight gain and improving other nutritional indices (Thomas *et al.*, 2003).

Dementia

Dementia may also contribute to reduced food intake in the elderly, because individuals simply forget to eat. Up to 50% of institutionalized dementia patients have been reported to suffer from protein-energy malnutrition (Sandman *et al.*, 1987).

Physical Factors

Many older people no longer have their own teeth. Poor dentition and ill-fitting dentures may limit the type and quantity of food eaten in older persons. For example, in one study, half of 260 nursing home patients, aged 60–101 years, in Boston, USA, complained of problems with chewing, biting, and swallowing. The patients with dentures were more likely to have poor protein intake than those with their own teeth (Sahyoun *et al.*, 1988). Immobility (e.g. stroke), tremor (e.g. Parkinson's disease), and impaired vision may also affect the capacity of an older person to shop for, prepare, and consume food. Common medical conditions in the elderly such as gastrointestinal disease, malabsorption syndromes, acute and chronic infection, and hypermetabolism (i.e. hyperthyroidism) often cause anorexia, micronutrient deficiencies, and increased energy requirements (Morley, 1997). Cancer and rheumatoid arthritis, which produce anorectic effects by releasing cytokines (see the following text), are also common in older persons.

Iatrogenic/Medications

The elderly are major users of prescription medications, a number of which can cause malabsorption of nutrients, gastrointestinal symptoms, and loss of appetite. For example, digoxin and some forms of chemotherapy can cause nausea, vomiting, and loss of appetite. Other medications can deplete the body's mineral stores; high doses of aluminum or magnesium hydroxide antacids deplete phosphate and potassium stores that can lead to muscle weakness and anorexia, while penicillamine induces zinc depletion that can lead to the loss of taste acuity and decreased food intake. The elderly often take multiple medications that increase the risk of drug interactions that can cause anorexia.

CAUSES OF THE PHYSIOLOGICAL ANOREXIA OF AGING

Declining Senses of Taste and Smell

Taste and smell are important in making eating pleasurable. The sense of taste probably deteriorates with age, although not all studies confirm this. Age-associated changes in taste may influence food choice in the elderly. There is strong evidence that the sense of smell declines with age, particularly after age 50. In one study, over 60% of subjects aged 65–80 and over 80% aged 80 or older exhibited major reductions in their sense of smell, compared to less than 10% of those aged under 50 (Doty *et al.*, 1984). The decline in the sense of smell is a cause of decreased food intake in the elderly because it makes eating food less enjoyable. It may also influence the type of food eaten; several studies have shown a strong correlation between impaired sense of smell and reduced interest in and intake of food. Consistent with this effect of aging on the types of food eaten is the

observation that aging is associated with a less varied, more monotonous diet.

Sensory-specific Satiety

Sensory-specific satiety is the normal decline in pleasantness of the taste of a particular food after it has been consumed. Sensory-specific satiety leads to a decrease in the consumption of a previously eaten food and a tendency to shift consumption to other food choices during a meal. This acts to promote the intake of a more varied, nutritionally balanced diet. Older people have a reduced capacity to develop sensory-specific satiety (Rolls and McDermott, 1991), perhaps because of reduced senses of smell and taste. Reduced sensory-specific satiety may in turn favor the consumption of a less varied diet and the development of micronutrient deficiencies.

HORMONES AND NEUROTRANSMITTERS: A SELECTIVE REVIEW (TABLE 3)

The remainder of this chapter will review, selectively, some of the emerging information about the control of food intake and why it declines with normal aging, with particular emphasis on endocrine factors. Recently discovered hormones with effects on feeding include leptin, ghrelin, and the orexins. At the time of writing, these discoveries had not yet led to evidence-based therapies, which still largely consist of nutritional supplements. The hope is that endocrine appetite stimulants or antagonists of anorexigenic hormones may have a future therapeutic role.

Table 3 Some endocrine factors influencing feeding and their possible contribution to the anorexia of aging

Effect of aging	
Factors that stimulate feeding	
Opioids	↓ activity; not proven in humans
Neuropeptide Y	no good evidence for role
Galanin	circulating levels unchanged sensitivity unknown
Orexins	no good evidence for role
Ghrelin	circulating levels possibly ↓ sensitivity unknown
Testosterone	stimulatory role unconfirmed (?indirect) ↓ activity with age possible effects via leptin, ghrelin and others
Factors that inhibit feeding	
CART[a]	possible ↑ central levels (rodents)
Cholecystokinin (CCK)	↑ circulating levels ↑ CSF levels ↑ sensitivity to satiating effects
GLP-1[b]	few data, possibly ↑ activity
Peptide YY	few data, no evidence for role
Insulin	effect on feeding unconfirmed, no evidence for role
Leptin	situation complex: circulating levels increase in men (↓ testosterone) BUT? leptin resistance
Cytokines	↑ activity likely

[a]CART, Cocaine-amphetamine-related transcript. [b]GLP-1, glucagon-like peptide I.

Overview of Appetite Regulation (Figure 1)

Central

The central feeding system is dependent on the stimulatory effect of neurotransmitters including the opioids, noradrenaline, Neuropeptide Y (NPY), the orexins, galanin, and ghrelin, and the inhibitory effect of corticotrophin-releasing factor, serotonin, cholecystokinin (CCK), and possibly insulin.

Peripheral (Gastrointestinal)

The short-term peripheral satiety system is largely driven by gastrointestinal mechanisms. In the longer term, factors such as leptin and cytokines (see the following text) become more important. Gastrointestinal sensory and motor functions are important in the regulation of satiation. Sensory signals induced by the distension by food contribute to initial sensations of fullness during a meal. These sensations are mediated via vagal mechanisms from mechanoreceptors situated within the stomach wall. In young adult humans, gastric distension, using a barostat, reduces food intake by up to 30%. Distension of the distal stomach (antrum) is related to increased sensations of fullness and is likely to

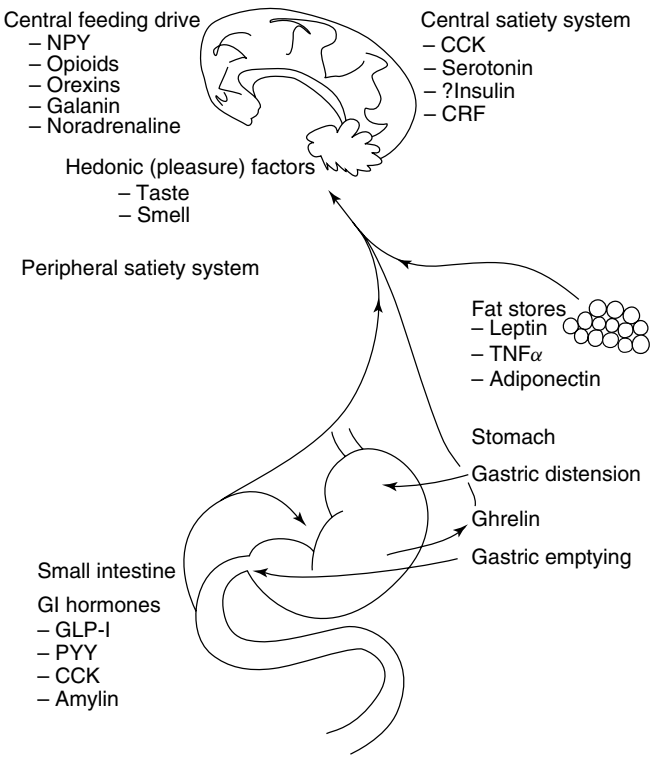

Figure 1 Overview of the mechanisms involved in appetite regulation

be more important than distension of the proximal stomach (fundus). After eating, the stomach relaxes by a process of receptive relaxation, resulting in decreased intragastric pressure and increased gastric volume. This relaxation is particularly marked in the proximal stomach and results in a proximal fundic reservoir where food is retained. Not long before it is emptied into the small intestine, food is propelled distally from the fundus into the antrum. The extent of antral filling and distension relates more closely to feelings of fullness and satiety than does proximal gastric distension.

Studies in animals and humans have demonstrated a relationship between postprandial satiety and the rate of gastric emptying. Slowing of gastric emptying may reduce appetite and food intake by increasing and prolonging antral distension and by prolonging the effect of small intestinal satiety signals. People with gastroparesis often exhibit symptoms of early satiety, loss of appetite, nausea, and vomiting, and studies in both animals and humans have shown that there is a relationship between postprandial satiation and the rate of gastric emptying.

Once food enters the small intestine, mechano- and chemoreceptors relay signals to the hypothalamus, resulting in the cessation of food intake. These signals are mediated by the release of gastrointestinal peptide hormones, including CCK, peptide YY (PYY), and glucagon-like peptide-1 (GLP-1). A number of gastrointestinal (GI) and pancreatic hormones, including CCK, GLP-1, and amylin have feedback effects on the stomach to slow gastric emptying, an effect associated with increased fullness and reduced food intake, by increasing and prolonging gastric distension and prolonging the effect of small intestinal satiety signals. Feedback signals from peripheral fat cells via leptin and, possibly, tumor necrosis factor-α as well as absorption of nutrients from the gut also contribute to satiation.

The Aging Gut

Aging is associated with cell loss in the myenteric plexus of the human esophagus and a decline in conduction velocity within visceral neurones. The consequent reduction in sensory perception may contribute to reduced food intake by inhibiting the positive stimuli for feeding. The elderly frequently complain of increased fullness and early satiation during a meal. This may also be related to changes in gastrointestinal sensory function; aging is associated with reduced sensitivity to gastrointestinal tract distension. If anything, reduced sensitivity to the satiating effects of distension might be expected to increase, not decrease, the food intake in older people. Nevertheless, proximal gastric distension has been found to have similar effects on food intake in healthy older and young adults, and the role, if any, of impairment of gastric sensory function in causing the anorexia of aging is unknown.

Aging is probably associated with impaired receptive relaxation of the gastric fundus. As a result, for any given gastric volume, there is more rapid antral filling and distension and earlier satiety. This impaired gastric accommodation response in the elderly may be because of altered fundic nitric oxide (NO) concentrations. Peripheral NO causes receptive and adaptive relaxation of the stomach, leading to dilation of the fundus and, ultimately, slower gastric emptying. The increase in NO with aging may therefore contribute to the slower gastric emptying observed in the elderly. Most, but not all studies indicate that gastric emptying slows slightly, but significantly, with increasing age. Clarkston *et al.* (1997) found that healthy older subjects were less hungry and more satiated after a meal than young subjects, and that postprandial hunger was inversely related to the rate of gastric emptying. The effects of aging on gastric emptying rate may require ingestion of a relatively large energy content, as small meals have not been shown to have different emptying rates in old compared to young individuals. Delayed gastric emptying in older people may, in part, result from enhanced release of small intestinal hormones such as CCK (see the following text).

In contrast, it seems that age has little, if any, effect on small intestinal or colonic motor function and orocecal and whole gut transit time are not affected in the healthy elderly. Healthy older people do have slower phase III migration velocities and more frequent "propagated contractions" in the small intestine, but no differences in duration of postprandial motility or amplitude or frequency of either fasting or postprandial pressure waves.

Central Neurotransmitters and Hormones

Monoamines

The central aminergic system has effects on feeding, with noradrenaline stimulating, serotonin inhibiting, and dopamine having region-specific stimulatory or inhibitory effects. Aging may be associated with increased satiating effects of serotonin, without apparent effects on dopamine or noradrenaline.

Opioids

Endogenous opioids play a role in mediating the short-term sensory reward response to food. Exogenous administration of opioid agonists increases food intake in animals, and opioid antagonists decrease food intake in animals and adult humans (MacIntosh *et al.*, 2001a). There is evidence that aging is associated with a reduced opioid feeding drive (reviewed; (Horwitz *et al.*, 2002)). Elderly patients with idiopathic, senile anorexia have lower plasma and CSF ß-endorphin concentrations than normal weight, age-matched controls (Martinez *et al.*, 1993). Intraperitoneal (IP) morphine injection increases food intake in young but not old mice, while IP naloxone decreases food intake in young but not older rats. Healthy older men are less sensitive to the inhibitory effects of subcutaneous naloxone on fluid intake than young men (Silver and Morley, 1992), and in one small study of feeding in humans, the suppression of food intake by naloxone was nonsignificantly greater in the older than young adults (MacIntosh *et al.*, 2001a:16 vs 8%).

Overall, these results suggest that the stimulatory effect of endogenous opioids does decline somewhat with advancing age and may contribute to the anorexia of aging. Further work is required to clarify these changes.

Neuropeptide Y

NPY is synthesized in the peripheral nervous system and brain and strongly stimulates food intake. There is preliminary evidence from animal studies that aging may be associated with reduced NPY activity, perhaps more in males than females. Old rats have lower levels of arcuate nucleus prepro NPY mRNA than young rats, and hypothalamic NPY levels decrease with aging in male, but not female rats. Studies in humans, however, suggest, if anything, *increased* NPY activity with increasing age. CSF NPY levels increase with healthy aging in women, and plasma and CSF levels are increased in elderly people with idiopathic anorexia (Martinez *et al.*, 1993). In rats, the feeding response to hypothalamic NPY injections diminishes with aging, whereas the stimulation of feeding by intracerebroventricular NPY administration in mice does not diminish with age. The effects of NPY administration in humans have not been reported. There is currently, therefore, no convincing evidence for an involvement of NPY in the human anorexia of aging.

Galanin

Galanin is a peptide hormone located in the brain and periphery, which stimulates food intake. Available animal evidence does not suggest a decline in galanin levels with aging, and circulating levels do not differ between young and older women (Baranowska *et al.*, 2000). Declining galanin levels are therefore unlikely to contribute to the anorexia of aging, but reduced sensitivity to galanin might. The effect of aging on stimulation of feeding by galanin has not been reported in humans, but older women (not men) display a reduced growth hormone secretory response to galanin compared to young adults (Giustina *et al.*, 1993).

Orexins (Hypocretins)

Orexin A and B (hypocretin-1 and -2) are neuropeptides synthesized in the hypothalamus and involved with feeding and sleep. Orexin deficiency causes narcolepsy in animals and humans and hypophagia and weight loss in animals (Matsumura *et al.*, 2002). Intracerebroventricular orexin injection dose-dependently increases food intake in rodents and orexin antibody reduces food intake (reviewed in Kirchgessner, 2002). Orexin A is the subtype mainly responsible for effects on feeding. The majority of evidence does not support declining orexin activity as a cause of the anorexia of aging. In a cross-sectional study of 82 healthy men and women aged 23–79 years, plasma orexin-A concentrations increased with age in both men and women (Matsumura *et al.*, 2002), which should, if anything, favor *increased* appetite and food intake. Studies in mice have found no changes or increases in total brain orexin levels and hypothalamic orexin-A receptors levels with increasing age, while a decrease in hypothalamic orexin gene expression in aging rats has been described (Kappeler *et al.*, 2003). In humans, the effects of normal aging on the levels of the orexin receptors and sensitivity to the effects of orexin are unknown.

Cocaine-amphetamine-regulated Transcript (CART)

Cocaine-amphetamine-regulated transcript (CART) is a peptide widely distributed in the brain including the hypothalamus. In animals, central CART administration reduces feeding and blocks NPY-induced feeding. Sohn *et al.* (2002) reported that arcuate nucleus CART mRNA levels were higher and NPY mRNA levels lower in healthy old than young, male rats, while testosterone treatment of castrated, older rats significantly lowered CART mRNA levels and increased NPY mRNA levels. This suggests that in males there is aging-related increased central activity of CART and reduced activity of NPY, both mediated by the normal age-related decline in testosterone. This is an intriguing possibility, but the effects of aging on CART in female animals have not been reported, nor have those in humans. The evidence that age-related increases in central CART levels may be a cause of the anorexia of aging is therefore currently derived from one study in male rodents.

"Peripheral" Hormones, Including Gut Peptides

Cholecystokinin (CCK)

CCK is present in the hypothalamus, cortex, and midbrain and is released from the lumen of the intestine in response to nutrients, particularly fat and protein, in the gut. CCK causes contraction of the gallbladder and relaxation of the sphincter of Oddi. Exogenous CCK administration decreases food intake in animals and humans. CCK is probably a physiological satiety hormone as its suppressive effect on food intake occurs with the administration of doses producing plasma CCK concentrations within the physiological range, and administration of CCK antagonists increases food intake in animals and young adult humans (Beglinger *et al.*, 2001). CCK also slows gastric emptying.

The satiating effects of CCK appear to increase with age. Most studies in humans have shown plasma CCK concentrations to be higher in healthy older than young adults (MacIntosh *et al.*, 1999, 2001b). Elderly people with idiopathic anorexia have significantly higher plasma levels and nonsignificantly higher CSF levels of CCK than healthy age-matched controls (Martinez *et al.*, 1993). IP CCK suppresses food intake more in old than young rats and mice. Intravenous CCK-8 administration has been found to acutely suppress food intake twice as much (31% vs 15%, $P = 0.02$) in older versus young adult healthy, human subjects (MacIntosh *et al.*, 2001b). The combination of increased circulating CCK

concentrations and enhanced sensitivity to CCK suggests that CCK may be a cause of the anorexia of aging, and raises the possibility of using CCK antagonists to increase energy intake in undernourished older people.

Glucagon-like Peptide-1 (GLP-1)

GLP-1 is released by the lining of the intestine in response to nutrient ingestion, particularly carbohydrates. It stimulates insulin secretion and, together with gastric inhibitory peptide (GIP), is one of the incretin hormones. It also slows gastric emptying. Administration of GLP-1 to humans increases feelings of fullness and reduces food intake (Flint *et al.*, 1998). Studies on the effects of aging on plasma GLP-1 concentrations have found either no effect or increased levels in older people (MacIntosh *et al.*, 1999). Further studies are needed to determine if increased GLP-1 activity is a cause of the anorexia of aging.

Peptide YY (PYY)

PYY is a peptide hormone present in the brain and released from the bowels in response to presence of fat and carbohydrate in the small intestine. PYY is involved in physiological processes such as memory, pain, blood pressure regulation, appetite, and anxiety (Pedersen-Bjergaard *et al.*, 1996). In rodents, feeding is increased by central PYY administration, but decreased by peripheral administration. Intravenous infusion of PYY to normal weight and obese humans aged less than 50 years, in doses that produce postprandial blood levels, reduces short-term food intake by approximately 30% (Batterham *et al.*, 2003). This suppression may be mediated by the associated suppression of ghrelin levels, whereas leptin, insulin, and GLP-1 are unaltered.

There is currently no evidence favoring alterations in PYY activity as a cause of the anorexia of aging and no difference in plasma PYY concentrations, fasting, and in response to intraduodenal nutrient infusions, between young and older subjects. Because there is a strong negative correlation between fasting plasma PYY levels and BMI in healthy, nonelderly subjects, studies involving accurate body composition analysis are needed to determine the true effect of healthy aging on PYY. The effects of aging on sensitivity to the appetite-suppressant effects of PYY have not been reported.

Leptin

Leptin is produced predominantly in adipose tissue and circulates in amounts directly related to the size of fat stores. It suppresses appetite and food intake. Congenital leptin deficiency in humans is a very rare cause of morbid obesity associated with hyperphagia, and leptin treatment produces substantial weight loss in these people. Most obese people, however, have elevated circulating leptin concentrations consistent with their increased fat mass. Leptin resistance is probably a feature of most human obesity, and leptin administration to obese people has resulted in only minor weight loss.

Although adipose tissue leptin mRNA expression increases with age in mice and rats, studies in rats and pigs have not found an increase in serum leptin with aging. Plasma leptin concentrations in humans often increase with aging, to a large extent because of the increased fat mass that also accompanies aging. Most studies show that adjustment for fat mass removes this effect (Baumgartner *et al.*, 1999). This is certainly so in women, but in men, some but not all studies have shown aging to be associated with an increase in circulating leptin levels, even allowing for fat mass. This appears to be because of age-related decreases in circulating testosterone concentrations. After adjusting for fat mass, plasma leptin levels in men are inversely related to plasma testosterone, while testosterone therapy reduces, and inhibition of testosterone production increases, circulating leptin levels (Hislop *et al.*, 1999).

Little is known about the effects of aging on sensitivity to the effects of leptin. Circulating levels of the soluble leptin receptor do not change with age in humans. Resting energy expenditure and carbohydrate oxidation are predicted by fat-free mass and serum leptin concentration in middle-aged, premenopausal women, but the relationship between fat store size and plasma leptin is much weaker in older adults (Moller *et al.*, 1998). Fasting normally dramatically suppresses plasma leptin concentrations, thus stimulating hunger. Reduced suppression of leptin levels by fasting has been reported in aging rats. Conversely, food intake, fat mass, and insulin action are suppressed less by leptin administration in older than young rats. This suggests that aging may be accompanied by leptin resistance, which would tend to *increase* food intake. The impact of human aging on the effects of fasting on leptin levels, and of leptin administration, has not been reported.

Ghrelin

Ghrelin stimulates feeding and growth hormone release. It is present in the hypothalamus but the main site of production is the gastric mucosa. Circulating ghrelin concentrations increase with fasting and with diet-induced weight loss in obese subjects, and are elevated in underweight, undernourished young and older subjects. In contrast, circulating concentrations decrease after ingestion of food, particularly fat and carbohydrate, and are reduced in obese people. These changes are consistent with compensatory responses to, rather than causes of, these altered nutritional states. It therefore seems unlikely that reduced ghrelin activity contributes significantly to the anorexia and weight loss in markedly undernourished older subjects. Nevertheless, the effects of aging and undernutrition on sensitivity to ghrelin have not been reported, and ghrelin resistance may occur in these states. In support of this, older subjects are less sensitive to the (growth hormone) GH-releasing effects of intravenous ghrelin (iv ghrelin) than young adults (Broglio *et al.*, 2003).

The effect of healthy aging on circulating ghrelin concentrations has not yet been clarified. A possible rationale for a decline in ghrelin levels with age, particularly in men, is the positive association between circulating testosterone and ghrelin concentrations and the increase in plasma ghrelin concentrations that occurs in hypogonadal men in response to testosterone therapy (Pagotto *et al.*, 2003). As normal aging is accompanied by reductions in circulating androgen levels (see the following text), this might have the effect of reducing ghrelin concentrations and thus food intake. One study found a rise in plasma ghrelin concentrations with increasing age, but there was no relationship with age *per se* when a multivariate analysis was performed (Purnell *et al.*, 2003), and the study did not include subjects older than 64 years. Two small studies have reported circulating ghrelin concentrations 20% (Sturm *et al.*, 2003) and 35% (Rigamonti *et al.*, 2002) lower in healthy older (69–87 and 67–91 years respectively) than young adults, the latter reduction statistically significant. However, increasing body fat, as indicated by BMI, is associated with decreasing ghrelin concentrations, and the older subjects had higher BMIs as compared to the young subjects in both studies. Neither study included detailed body composition analysis, so the lower ghrelin levels in older subjects may have been because of differences in body composition. Studies involving body composition analysis are needed to assess the effects of aging *per se* on ghrelin.

Insulin

Human aging tends to be associated with increased fasting and postprandial circulating insulin concentrations (Fraze *et al.*, 1987). Increased insulin activity could, therefore, be a cause of reduced food intake in older people. The evidence for a satiating role of insulin is, however, limited. Suppression of food intake by insulin has only been demonstrated in animals and has required central insulin administration at high doses or high dose, prolonged peripheral administration. Short-term, peripheral, euglycemic insulin infusions have been shown not to affect appetite or food intake in humans (Chapman *et al.*, 1998). Moreover, age-associated increases in insulin concentrations are due mainly to insulin resistance resulting from increased adiposity, and only to a small extent to aging itself. It seems unlikely that insulin contributes substantially, if at all, to the anorexia of aging.

Testosterone and Other Androgens

Circulating androgen concentrations decline with aging. This may contribute to the development of sarcopenia and the decrease in functional status that occurs with aging. While androgen replacement therapy (ART) is advocated for men with marked androgen deficiency, there is no consensus for the use of ART in elderly men with less severe aging-related declines in androgen concentrations, or in elderly women.

Studies of androgen replacement have been performed in healthy, older men with androgen deficiency, but although benefits have been seen in muscle mass and, in some cases, strength, there is, as yet, no agreement that this leads to improvements in functional status (reviewed; (Morley, 2001)). Two small studies have reported functional benefits when testosterone is administered in supraphysiological doses to older, frail men. Amory *et al.* (2002) gave older men with a mean total testosterone within the normal range 600 mg IM testosterone weekly for 4 weeks before elective knee replacement surgery and found significant increases in the ability to stand postoperatively and trends to improvements in walking and stair climbing, compared to placebo-treated men. Bakhshi *et al.* (2000) gave older men in a rehabilitation program with low-normal testosterone levels 100 mg IM testosterone or placebo weekly and found significant increases in grip strength and the Function Independence Measure after testosterone but not placebo.

In women, serum concentrations of testosterone and the adrenal androgens gradually and progressively decline from the decade preceding menopause. Even if testosterone therapy does not increase food intake in older, undernourished people, it may provide functional benefits by treating the associated sarcopenia, and studies to examine this are under way.

Cytokines

Age-associated increases in the production and/or effect of satiating cytokines may contribute to the anorexia of aging (Yeh and Schuster, 1999). Cytokines are secreted in response to significant stress, often because of malignancy or infection. Circulating concentrations of the cytokines interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) are increased in cachectic patients with cancer or AIDS. They act to decrease food intake and reduce body weight via a number of central and peripheral pathways. Blockade of these cytokines, for example, of TNF in mice with TNF-producing sarcomas, significantly attenuates weight loss in high stress conditions associated with cachexia.

Aging itself may be a form of stress. It is associated with stress-like changes in circulating hormonal patterns; increased cortisol and catecholamines and decreased sex hormones and growth hormone. Increased cortisol and catecholamine levels, in turn, stimulate the release of IL-6 and TNF-α, whereas sex hormones inhibit IL-6. Interleukin 1 and IL-6 levels are elevated in older people with cachexia, while plasma IL-6 concentrations apparently increase as a function of normal aging and correlate inversely with levels of functional ability in elderly people. Increased cytokine levels, due to the "stress" of aging *per se*, or the amplified stressful effects of other pathologies, may thus provide an explanation for some of the decline in appetite and body weight that occurs in many older people.

DIAGNOSES AND TREATMENT OF UNDERNUTRITION IN OLDER PEOPLE

These are covered in **Chapter 24, Epidemiology of Nutrition and Aging** and **Chapter 27, Weight Loss in Older Adults**.

KEY POINTS

- On an average, food intake is about 30% lower in the elderly than young adults, because of a physiological decrease in appetite, the anorexia of aging. This predisposes to the development of protein-energy malnutrition, which is surprisingly common in the elderly.
- The physiological anorexia of aging predisposes to the development of pathological anorexia and undernutrition when factors that become more common with aging, such as depression, dementia, poor dentition, social isolation, medications and various illnesses, are superimposed.
- A number of hormones involved in the control of feeding have been discovered recently and knowledge of the hormonal control of feeding is expanding rapidly. Understanding of the anorexia of aging is in its infancy.
- Current evidence supports the following as causes of the anorexia of aging:
  ↑ activity CCK
  ↑ activity cytokines
  ↓ activity androgens (particularly in men)
  weaker evidence for ↓ activity ghrelin, ↑ leptin

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Weight Loss in Older Adults

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INTRODUCTION

Weight loss has devastating consequences in older adults. Weight loss is strongly associated with a 76% increase in mortality risk among home-bound older adults, along with male gender and age. This effect of weight loss persists after adjusting for initial body mass index (BMI, the weight in kilograms divided by height in meters squared), smoking, health status, and functional status (Payette *et al.*, 1999).

A BMI of less than 22 $kg\,m^{-2}$ has been associated with a higher 1-year mortality rate and with poorer functional status among older community-dwelling persons (Landi *et al.*, 1999). The higher mortality risk in men older than 65 years begins at a BMI of less than 22 and increases to a 20% higher risk in men older than 75 years with a BMI of less than 20.5. Similarly, the higher mortality risk in women begins at a BMI of less than 22 in women older than 65 years and increases to a 40% higher risk in women older than 75 years with a BMI of less than 18.5 (Calle *et al.*, 1999).

Involuntary weight loss greater than 4% of body weight is an independent predictor of increased mortality in older community-dwelling male veterans. Over a 2-year follow-up period, mortality rates were substantially higher in the 13% of the population with involuntary weight loss (28%) than in those who did not lose weight (11%). This effect was present after adjusting in baseline age, BMI, tobacco use, and other health status and laboratory measures (Wallace *et al.*, 1995).

Weight loss is also associated with a decline in functional status. Weight loss of more than 5% in community-dwelling women 60–74 years old is associated with a twofold increase in risk of disability over time, compared to women who did not lose weight, after adjustment for age, smoking, education, study duration, and health conditions (Launer *et al.*, 1994).

BMI is an important predictor of mortality among both young and old hospitalized patients. A BMI of less than 20 is a risk factor for in-hospital mortality (Thomas *et al.*, 2005). In hospitalized veterans, a weight loss of greater than 5% in the preceding 6 months was a predictor of life threatening in-hospital complications (Sullivan *et al.*, 2002). BMI less than the 15th percentile is an independent predictor of 180-day mortality following hospitalization after controlling for recent weight loss, serum albumin, severity of illness score, and patient demographics (Galanos *et al.*, 1997).

A 10% loss of body weight over a six-month interval strongly predicted mortality in the ensuing six months in nursing home residents (Murden and Ainslie, 1994). When compared to controls, the 16% of subjects who lost at least 5% of their body weight were 4.6 times more likely to die within 1 year (Ryan *et al.*, 1995). In another study of long-term care residents, a 10-fold increased risk for death was seen for persons who lost 5% of their body weight in any month compared with those who gained weight (Sullivan *et al.*, 2004). For this reason, the Long-Term Care Minimum Data Set defines a loss of greater than 10% of body weight within 180 days or 5% within 30 days as an important clinical threshold for triggering resident assessment protocols (Health Care Financing Administration, 1999). Body weight and BMI are easily obtained clinical measurements that can predict adverse outcomes in older persons.

POPULATION-BASED OBSERVATIONS OF LOW BODY WEIGHT AND MORTALITY

Several epidemiological studies have focused on the relationship of body weight and mortality in older persons. The characteristics of the study and the populations are given in Table 1. In the National Health and Nutrition Examination Survey Epidemiological Follow-Up Study (NHANES I) (Cornoni-Huntley *et al.*, 1991), both race and sex groups in the lowest 15% of the BMI distribution had a statistically significant excess risk of mortality after adjusting for smoking

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Table 1 Representative observational studies of body weight and mortality in older persons

Study	N	Age-group	Follow-up	Comorbidities
NHEFS	3339	65–74	Up to 20 years	Smoking, cholesterol, blood pressure, history of diabetes, cardiovascular disease, bronchitis, alcohol intake, and education
FHS	1723	65 at baseline	Mean 9.5 years	Smoking, cholesterol, blood pressure, and blood glucose
EPESE	6387	70 and older	3–6 years	Self-reported smoking, number of chronic diseases (diabetes, coronary heart disease, stroke, hip fracture, cancer, angina), previous hospitalizations, or nursing home admissions, and measures of disability, function, and mental status
CHS	5201	65 and older	5 years	Coronary heart disease and stroke
Cancer Prevention Study I	324 135	30–74	12 years	Never smoked, no history of heart disease, stroke, or cancer, no history recent unintentional weight loss
Cancer Prevention Study II	1 184 657	Mean 57	14 years	Healthy, never smoked

NHANES, National Health and Nutrition Examination Survey Epidemiological Follow-up Study; FHS, Framingham Heart Study Longitudinal Database; EPESE, Established Populations for Epidemiologic Studies of the Elderly; CHS, Cardiovascular Health Study. For references, see text.

history, and presence of disease. In the Established Populations for Epidemiologic Studies of the Elderly (EPESE) (Losonczy *et al.*, 1995), death rates were higher for those who weighed the least. A low BMI in old age was an additional risk factor, with persons in the lowest quintile having a 40% higher mortality rate in men and women relative to persons in the middle quintile of BMI. In the Cardiovascular Health Study (CHS) (Diehr *et al.*, 1998), women with a BMI of 20 or lower had higher mortality than others, but there was not a significant relationship of BMI and mortality for men or for women whose BMI was greater than 20. This was true with or without controlling for a large number of clinical covariates, including recent unintended weight loss (Diehr *et al.*, 1998).

In the Framingham Heart Study database (FHS) (Harris *et al.*, 1988), the relative risk of death was almost twice as high for those at the lower extreme of BMI. However, most of this increased risk occurred in the years immediately after age 65 compared to later follow-up, suggesting that the increased early death rate was due to disease that was already present.

These observational data demonstrate that a low body weight adjusted for height is clearly associated with higher mortality. However, the effect of coexisting disease and early mortality may confound these observations.

THE RELATIONSHIP OF HIGH BODY WEIGHT TO MORTALITY

Obesity is associated with greater morbidity and poorer health-related quality of life than smoking, problem alcohol drinking, or poverty (Sturm and Wells, 2001), and has been argued to be the number one health problem in the United States. A national campaign has been advocated to reduce body weight by dieting and exercise to reduce the mortality and morbidity. However, body weight increases with age in women, at least until their seventies, and aging is accompanied by body composition changes in both men and women (Thomas and Morley, 2001a). There is evidence to suggest that a higher BMI in older persons may not convey the excess risk observed in younger persons.

In general population studies, the relationship between mortality and BMI has been reported as a J-shaped curve, or a U-shaped curve (Weindruch and Sohal, 1997). Excess risk of death has been observed at both extremes of high and low weight. This relationship is clear in the young and middle-aged population, but becomes more controversial in the older population.

In the Cancer Prevention Study I (Stevens *et al.*, 1998), greater BMI was associated with higher mortality in men and women up to 75 years of age. However, the magnitude of the risk associated with greater BMI diminished with age, as shown in Table 2. For example, an increment of 1 in the body mass index in women was associated with an 8% increase in cardiovascular disease mortality risk in 30–44-year-old women, but only a 2% increase in risk for 65–74-year-old women. In the Cancer Prevention Study II (Calle *et al.*, 1999), a higher BMI was associated with a higher all-cause mortality in women in all age-groups, including those 75 years or older. Again, the relative risk also diminished with increasing age.

There is an increased mortality risk for both men and women at the highest extremes of BMI in the Framingham Heart Study, even when accounting for potential effects of excess weight on serum cholesterol level, blood glucose level, and systolic blood pressure. At the upper extreme, risk of death was twofold higher over the entire follow-up period for persons with BMIs above the 70th percentile at both 55 and 65 years of age.

Data from EPESE demonstrates that mortality risk was approximately 40% higher for persons in the heaviest quintile of BMI at age 50 compared with persons in the middle quintile. In the CHS data, a BMI greater than 34 was associated with an age-adjusted 8% mortality for women and an 18% mortality in men (BMI greater than 32). In the Nurses Health Study (Manson *et al.*, 1995), a 60% increase in relative risk for death began at a BMI of $27\,kg\,m^{-2}$ and continued to about twofold from a BMI greater than 29, using a reference BMI of 19.

Not all studies have shown an increased risk of mortality with higher BMI. A BMI of greater than $27\,kg\,m^{-2}$ has not been significantly related to risk of mortality (Landi

Table 2 Association of mortality and high body weight

Study	Characteristic	RR	95% CI
Cancer Prevention Study I	30–44-year-old men	1.10	1.04–1.16
	65–74-year-old men	1.03	1.02–1.05
	30–44-year-old women	1.08	1.05–1.11
	65–74-year-old women	1.02	1.02–1.03
Cancer Prevention Study II	65–74-year-old men, BMI 26.5–27.9	1.1	1.0–1.3
	>75-year-old men, BMI 26.5–27.9	1.1	0.97–1.2
	65–74-year-old women, BMI 26.5–27.9	1.04	0.9–1.2
	>75-year-old women BMI 26.5–27.9	1.07	1.0–1.2
	65–74-year-old men, BMI 30–31.9	1.4	1.2–1.7
	>75-year-old men, BMI 30–31.9	1.2	1.0–1.3
	65–74-year-old women, BMI 30–31.9	1.3	1.2–1.5
	>75-year-old women BMI 30–31.9	1.3	1.2–1.4
Nurses Health Study	BMI 29–31.9 versus BMI 19	2.1	
	BMI >32 versus BMI 19	2.2	
Framingham Heart Study	BMI >70th percentile	2.0	
EPESE	BMI highest quintile versus middle quintile		
	Men	1.33	1.13 – 1.57
	Women	1.31	1.12 – 1.53
Cardiovascular Health Study	BMI >20	None	
NHANES I	BMI >30 versus BMI 22 to 30	None	
Community study[a]	BMI>27	None	

[a]Landi F, Zuccala G, Gambassi G *et al.* Body mass index and mortality among older people living in the community. *Journal of the American Geriatrics Society* 1999; **47**:1072–1076.
NHANES, National Health and Nutrition Examination Survey Epidemiological Follow-up Study; EPESE, Established Populations for Epidemiologic Studies of the Elderly. See text for references.

et al., 1999; Dorn *et al.*, 1997). All-cause mortality among women 55–74 years with a BMI greater than 30 was not higher compared to women with a BMI range 22–30 in the NHANES I data. In older patients, only a slight elevation in mortality rates occurred at a BMI of greater than $35\,kg\,m^{-1}$ (Landi *et al.*, 2000; Diehr *et al.*, 1998). Overall, the data suggest that a BMI $>27\,kg\,m^{-2}$ does not convey the same degree of increased mortality risk in older adults (Thomas and Morley, 2001a).

Current standards have defined overweight for all ages as a BMI of 27.8 or more for men and 27.3 or more for women (Kuczmarski *et al.*, 1994). Andres *et al.* have suggested that a BMI of 24–30 is the desirable range for people aged 60–69 (Andres *et al.*, 1985). Although there is increased mortality at extremes of body weight, this data would seem to support using higher desirable weights for older adults.

THE RELATIONSHIP OF WEIGHT LOSS TO MORTALITY

Weight in the general population is not stable. Twenty-nine percent of men and 44% of women in the United States report that they are attempting to lose weight. Thirty-five percent of men and 34% of women report that they are attempting to maintain weight. The most common strategy among those attempting to lose weight was to consume less fat, but not fewer calories (34.9% of men and 40.0% of women). Only 21.5% of men and 19.4% of women reported using a combination of eating fewer calories and engaging in at least 150 minutes of leisure-time physical activity per week (Serdula *et al.*, 1999).

When observational data for persons with the lowest and highest BMI have been adjusted for weight loss, weight loss rather than current BMI becomes the salient factor (Table 3). The presence of preexisting illness may confound the association between weight loss and death, either because of earlier deaths from noncardiovascular disease or because weight loss serves as a marker for more severe cardiovascular disease. In the NHANES I dataset, risk of mortality was higher for both men and women who lost 10% or more of their maximum lifetime weight within the 10 years before the study, even when controlling for current weight. The effect of preexisting illness was adjusted for, by excluding deaths within the first 5 and first 8 years of the study. This adjustment weakened the association between weight loss and increased risk for death from noncardiovascular disease in women. There was a strong association between weight loss and increased risk for death from cardiovascular disease among men and women even with a maximum BMI between 26 and 29 (relative risks of up to 2.1 and 3.6, respectively) (Pamuk *et al.*, 1993).

In the EPESE, persons who lost 10% or more of body weight between age 50 and old age had a 60% increase of mortality compared with persons with stable weight. Exclusion of participants who lost 10% or more of their weight and adjustment for health status eliminated the higher risk of death associated with low weight. This inverse association of weight and mortality in old age appears to reflect illness-related weight loss from heavier weight in middle age.

In the CHS, the age-adjusted death rate for people who reported an unintended loss of 10 lb or more in the year before evaluation (16.2% for women and 33.0% for men) was much higher than the death rate for those who lost weight through diet or exercise (5% in women and 16.4% in men) or who maintained or gained weight (9.5% in women and 14%

Table 3 Association of weight loss and mortality

Study	Characteristics	Factors	Relative risk	95% CI
NHANES I	BMI 22–26, who lost >10% of maximum lifetime weight within the 10 years before the study	Men	2.1	
		Women	3.6	
EPESE	Lost 10% or more of body weight between age 50 and follow-up	Men	1.69	1.45–1.97
		Women	1.62	1.38–1.90
CHS	Involuntary weight loss of 10 lb or more in the year before baseline	Men (% mortality)	33.0%	
		Women (% mortality)	16.2%	
Community Study	288 frail elders	Weight loss at baseline	1.76	1.15–2.71
	78 ± 8 years, home support services; followed 3–5 years.	Male gender	2.71	1.73–4.24
		Age at baseline	1.40	1.06–1.86

NHANES, National Health and Nutrition Examination Survey Epidemiological Follow-up Study; EPESE, Established Populations for Epidemiologic Studies of the Elderly; CHS, Cardiovascular Health Study. See text for references.

in men). People who had lost 10% or more of their body weight since age 50 also exhibited a relatively higher death rate (15.9% in women and 30.3% in men). The relationship between BMI and mortality disappeared after excluding those who lost weight since age 50. Weight loss between age 50 and baseline was a critical risk factor for higher mortality, rather than being overweight.

From the NHANES I data, an increased risk in women with a lower BMI occurred only among those who had lost more than 8.5% of their reported lifetime maximum weight. Women who had lost weight had a higher risk than women with a low BMI. In fact, women with a low BMI but whose weight remained stable had the lowest risk of mortality. Thus, the effect of weight loss on mortality is more profound than current weight, even when accounting for factors associated with weight loss and increased mortality risk (Rumpel *et al.*, 1993).

A high BMI at both age 55 and age 65 was associated with the highest mortality in the Framingham study. In contrast, CHS found that those with a high BMI at both times had better survival than those with a high BMI at age 50 and a lower BMI at follow-up (Diehr *et al.*, 1998).

The Framingham study, EPESE, and CHS all found little relationship between BMI and mortality when subjects with long-term weight loss were excluded. All of the observational studies have found that weight loss is associated with increased rather than decreased risk for death (Andres *et al.*, 1993; Williamson and Pamuk, 1993; Blair *et al.*, 1993; Lissner *et al.*, 1991) Furthermore, for those persons who have not had a substantial weight change, body weight does not seem to be an important concern.

The data suggest that obesity in older adults may not be a significant clinical target for reducing mortality, and that a preferred public health emphasis for this age-group would be to increase awareness that substantial weight loss after age 50 and unintended weight loss are potential indicators for poor prognosis.

Lifestyle modifications may be more important than weight loss. In an observational study, overweight and obese persons who were at least 35 years of age and who had a body mass greater than $25\,kg\,m^{-2}$, self-reported their intention to lose weight and actual weight change during the past year. Those persons reporting an intentional weight loss had a 24% lower mortality rate, compared with persons not trying to lose weight and reporting no weight change. However, mortality rates were independent of actual weight change. The persons who reported trying to lose weight but who had no weight change experienced a 20% reduction in mortality risk. An unexpected finding was that a decreased mortality rate was also found among those who reported gaining weight but who were not trying to lose weight.

In this study, an attempt at weight loss was associated with lower all-cause mortality, independent of weight change. A higher mortality rate (31%) occurred only in those persons reporting unintentional weight loss. Self-reported intentional weight loss was associated with lower mortality rates, and weight loss was associated with higher mortality rates only if it was unintentional (Gregg *et al.*, 2003).

Prospective studies on the effect of voluntary weight loss have not been done in older populations. Paradoxically, a higher 2-year mortality was found in community living subjects who lost weight by dieting (36%) compared to those who had involuntary weight loss (28%). This data suggests that even voluntary weight loss by dieting may place older persons at risk (Wallace *et al.*, 1995).

The data from these observational studies suggest that weight loss is the chief predictor of higher mortality rates in older adults, rather than the current BMI. Surprisingly, this risk appears to be associated even with voluntary weight loss in older persons. The recommendation that older adults voluntarily reduce body weight cannot be supported by the literature and may be hazardous.

EFFECT OF WEIGHT LOSS ON COMORBID CONDITIONS

Only limited data support the notion that intentional weight loss reduces total mortality. However, mortality is only a small part of the substantial burden of disease caused by obesity-related conditions such as hypertension (Stamler *et al.*, 1978; Reeder *et al.*, 1997), diabetes mellitus (Colditz

et al., 1995; Manson *et al.*, 1992), coronary artery disease (Willett *et al.*, 1995; Hubert *et al.*, 1983; Rabkin *et al.*, 1977; Harris *et al.*, 1997), degenerative arthritis (Sahyoun *et al.*, 1999), and cancers of the breast (Paffenberger *et al.*, 1980; Lubin *et al.*, 1985), uterus (Kelsey *et al.*, 1982), and colon (Phillips and Snowdown, 1985). Short-term reductions in caloric intake (dieting) have favorable effects on blood pressure, cholesterol, and metabolic rate. These benefits require at least a 20% reduction in caloric intake (Velthuis-te Wierik *et al.*, 1994).

Weight loss has been shown to reduce disease-specific risks such as hypertension and type 2 diabetes (Diabetes Prevention Program Research Group, 2002). However, it should be noted that overweight/obesity-related comorbidities, particularly those associated with the insulin resistance syndrome (e.g. hypertension, dyslipidemias, and hyperinsulinemia) can be improved rather independently of weight loss (De Lorgeril *et al.*, 1994; Weintraub *et al.*, 1989). Blood pressure can be lowered in the absence of weight loss by dietary changes (Appel *et al.*, 1997). The effect on blood pressure by nonpharmacological interventions can be maintained for 3–5 years despite significant increases in body weight (Leserman *et al.*, 1989). Other trials in coronary artery disease have shown prevention effects to be independent of weight loss (Gaesser, 1999). The data suggest that improvement in comorbid conditions can be improved with lifestyle changes, but that the effect is independent of whether weight loss occurs or not.

CAUSES OF WEIGHT LOSS

Weight loss can occur from a variety of causes. Weight loss can be either voluntary (a conscious decision to reduce body weight by either restricting calories or increasing energy expenditure) or involuntary (absence of any intention to reduce weight). Voluntary weight loss in older persons may be an unrecognized health risk. Involuntary weight loss generally occurs in association with disease. In this setting, weight loss may occur in the terminal phase of illness, and the association of mortality and weight loss may reflect the underlying disease rather than the weight loss *per se*.

Involuntary weight loss is rarely due to occult disease. A physical cause of weight loss was clinically evident on the initial evaluation in 55 of 59 patients, and in 23 of 32 patients, weight loss was without a physical cause (Marton *et al.*, 1981). The primary cause of undernutrition was found to be treatable in nearly 90% of medical outpatients (Wilson *et al.*, 1998). An algorithm for the approach to the differential diagnosis and management of involuntary weight loss has been published by the Council for Nutrition in Long-term Care (LTC) (Thomas *et al.*, 2000).

INVOLUNTARY WEIGHT LOSS

Involuntary weight loss may result from several conditions. Decreases in appetite (anorexia), ingestion of inadequate calories (starvation), disuse atrophy or hormonal deficiencies (sarcopenia), or the effects of disease (cachexia), or a combination of factors may result in weight loss.

Starvation

Simple starvation is caused by pure protein-energy deficiency. Starvation can be short-term (fasting) or long-term (chronic protein-energy undernutrition). Worldwide, starvation is most often caused by lack of food. In developed countries, starvation is usually associated with disease. Starvation occurring in the presence of adequate food results from inability to swallow, a nonfunctioning gastrointestinal tract, or failure of appetite (anorexia).

Older persons ingest less calories than younger adults. On average, persons over the age of 70 years consume one-third less calories compared to younger persons (McGandy *et al.*, 1966). Sixteen percent to 18% of community-dwelling elderly persons consume less than 1000 Kcal daily (Abraham *et al.*, 1977). Weight loss and undernutrition are related to functional decline (Zuliani *et al.*, 2001).

The decline in energy intakes that accompany aging has been the subject of intensive investigation (Morley and Thomas, 1999). Total energy expenditure (TEE) declines with aging, chiefly due to changes in resting energy expenditure (REE). REE decreases 10–20% with age, primarily due to a decrease in muscle mass (Kendrick *et al.*, 1994; Lipson and Bray, 1986). REE is higher in active older adults compared to sedentary older adults (Poehlman *et al.*, 1990), but a decline in muscle mass occurs in both sedentary and active aging adults (Aniansson *et al.*, 1983; Davies *et al.*, 1985; Larron *et al.*, 1979). A decrease in physical activity largely explains the decline in TEE with age (Westerterp and Meijer, 2001). Surprisingly, there is little correlation between physical activity and fat mass in older persons. Higher physical activity is not associated with a lower body fat mass in subjects older than 60 years (Westerterp, 1998).

Strategies for involuntarily increasing the intake of nutrients include enteral or parenteral feeding. Increasing voluntary consumption of nutrients is more problematic.

Anorexia

Appetite regulation is affected by illness, drugs, dementia, or mood disorders (Chapman and Nelson, 1994; Weinsier *et al.*, 1979; Wright, 1994). Anorexia may be a physiological response to aging, resulting from changes in the physiological regulation of appetite and satiety (Morley and Thomas, 1999). Acute illness is characterized by a spontaneous decrease in food intake despite an increased need for energy and nutrients (Plata-Salaman, 1996). Although seemingly paradoxical, the voluntary suppression of food intake during illness is common to most species (Hedlund *et al.*, 1995). The relationship between hedonic qualities of food, gastrointestinal and central satiation drives, and hormonal relationships may explain this observed difference

(Morley, 2001). The importance of understanding this relationship lies in the hope that pharmacological (Thomas and Morley, 2001b) or dietary interventions (Mathey *et al.*, 2001) may reverse this anorexia of aging.

The reduction in food intake accompanying acute illness occurs both before and during hospitalization. In a prospective study of elderly people, 65% of the males and 69% of the females had an insufficient energy intake in the month before hospitalization (Mowe *et al.*, 1994). This reduction in nutrient and energy intake beginning with acute illness predisposes to a risk for worsening undernutrition during hospitalization.

Inadequate intake of nutrients continues during hospitalization. In 286 general medical subjects, 27% became malnourished after hospital admission (defined as a reduction in mid-arm circumference of 3.6% during admission). These subjects were more likely to consume less than 40% of prescribed food, and were more likely to have lower Mini-Mental Status Examination scores, functional impairment, lower total lymphocyte counts, and lower serum albumin levels (Incalzi *et al.*, 1996).

Cachexia

Cachexia is the cytokine-associated wasting of protein and energy stores due to the effects of disease. Systemic inflammation mediated through cell injury or activation of the immune system triggers an acute inflammatory response. This response is the most common cause of anorexia observed in the acute-care setting (Rote, 1998).

Cytokine-mediated cachexia is almost always associated with anorexia. Cytokines are related to a number of disease conditions, including cancer, end-stage renal disease, chronic pulmonary disease, congestive heart failure, rheumatoid arthritis, and AIDS (Thomas, 2002). In subjects with pneumonia, the admission concentrations of α-1-antitrypsin and α-1-acid glycoprotein are better predictors of hospital morbidity than albumin and C-reactive protein levels (Hedlund *et al.*, 1995). In subjects with end-stage renal disease on hemodialysis followed for 3 years, increased IL-1, TNF-alpha, IL-6, and IL-13 levels were significantly associated with increased relative mortality risk, while higher levels of IL-2, IL-4, IL-5, IL-12, T-cell number and function, and CH50 were associated with improved survival (Kimmel *et al.*, 1998). Although the cancer anorexia–cachexia syndrome is present in 50% of advanced cancer patients and in 80% of terminally ill cancer patients, serum levels of cytokines are not always directly associated with the onset of cancer anorexia–cachexia syndrome (Maltoni *et al.*, 1997).

Cytokines directly result in feeding suppression and lower intake of nutrients and cachexia is nearly always accompanied by anorexia. IL-1 beta and TNF act on the glucose-sensitive neurons in the ventromedial hypothalamic nucleus (a "satiety" site) and the lateral hypothalamic area (a "hunger" site) (Espat *et al.*, 1995). The data suggest that cytokine levels are commonly associated with disease conditions characterized by cachexia, and may play a role in mortality, weight loss, and appetite suppression. In contrast to starvation, cachexia is remarkably resistant to hypercaloric feeding.

Nutritional Interventions

The first response of caregivers to clinical signs of undernutrition, whether due to starvation or cachexia, is to increase nutrient intake. A number of nutritional interventions have been directed toward improving intake. Yet, despite demonstrating an increase in nutrient delivery, clinical trials have shown disappointing results in improving clinical outcome (Atkinson *et al.*, 1998). The poor response of these subjects to hypercaloric feeding suggests that a different mechanism may be operative.

A 20% decline in lean body mass has been shown in critically ill patients, despite aggressive caloric support (Plank *et al.*, 1998). Malnourished or high-risk surgical patients have not had postoperative complications reduced to that of well-nourished patients undergoing similar procedures by enteral or parenteral support (Campos and Meguid, 1992).

Interventions to voluntarily consume adequate calories in the face of anorexia have been marginally effective. In a meta-analysis of 24 randomized, controlled clinical trials of dietary advice with or without nutritional supplements, no difference in mortality was observed. The nutritionally supplemented group, but not the group receiving dietary advice alone, had a small gain in weight at 3 months but no difference was seen at 6 months (Baldwin *et al.*, 2005).

In a trial of nutritional supplementation, 87 consecutive patients were randomized into a trial of a glucose drink containing vitamin A, B1, B2, B3, and B6 supplements or placebo. Compliance with the supplement was poor, with only one-third of subjects consuming more than 50% of the offered drink. Even when the analysis was limited to compliant subjects, there was no beneficial effect observed (Hogarth *et al.*, 1996).

Survival does not appear to be affected by enteral feeding. In 1386 nursing home residents older than 65 years with recent progression to severe cognitive impairment, 9.7% of patients had a feeding tube placed. Survival for a period of 24 months was not different compared to residents who were and who were not tube fed (Mitchell *et al.*, 1997).

The provision of additional calories and protein alone has not been shown to be efficacious in patients with cancer cachexia (Fearon *et al.*, 2001).

Pharmacological Interventions

Various appetite stimulants, shown in Table 4, have been studied. Corticosteroids in randomized, placebo-controlled trials have improved appetite, but have not demonstrated body weight gain (Moertel *et al.*, 1974; Willox *et al.*, 1984;

Table 4 Pharmacological agents for unintentional weight loss

Agent	Condition	Improved appetite	Weight gain
Corticosteroids	Cancer	Yes	No
Corticosteroids	AIDS	Yes	No
Cyproheptadine	Cancer	Yes	No
Cannabinoids (dronabinol, marinol, and nabilone)	Cancer	Yes	No
Cannabinoids (dronabinol)	AIDS	Yes	No
Cannabinoids (dronabinol)	Weight loss in LTC	–	Yes
Thalidomide	AIDS	–	Yes
Recombinant human growth factor	AIDS	–	Yes
Recombinant human growth factor	Weight loss in LTC	–	Yes
Oxymetholone	AIDS	–	Yes
Oxymetholone	Cancer	–	No
Hydrazine sulfate	Cancer	No	No
Megestrol acetate	Cancer	Yes	Yes
Megestrol acetate	Cancer	Yes	No
Megestrol acetate versus dexamethasone versus fluoxymesterone	Cancer	–	Yes
Megestrol acetate & prednisolone	Cancer	Yes	Yes
Megestrol acetate	AIDS	–	Yes
Megestrol acetate	Dialysis	Yes	Yes
Megestrol acetate	Weight loss in LTC	Yes	Yes
Megestrol acetate (noncontrolled)	Weight loss in LTC	Yes	Yes

LTC, Long-Term Care. See text for references.

Bruera *et al.*, 1985; Robusteli Della Cuna *et al.*, 1989; Popiela *et al.*, 1989). Cyproheptadine has been shown to increase appetite in cancer patients without weight gain (Kardinal *et al.*, 1990). Cannabinoids (dronabinol, marinol, and nabilone) have shown promise in improving mood and appetite in cancer patients (Plassee *et al.*, 1991; Nelson *et al.*, 1994) and in AIDS cachexia (Beal *et al.*, 1995), but body weight gain was not seen. Thalidomide, a tumor necrosis factor inhibitor, has produced body weight gain in a small number of patients with human immunodeficiency virus-associated wasting syndrome (Reyes-Teran *et al.*, 1996). Recombinant human growth factors have produced weight gain (mean 1.6 kg vs. 0.1 kg in the placebo group) in patients with AIDS, but at substantially higher than physiological doses (Schambelan *et al.*, 1996).

Sex steroids have shown promise in producing weight gain in ill subjects. The male anabolic hormone, testosterone, declines with age (Morley *et al.*, 1997). This decline is associated with a loss of muscle mass and strength (Baumgartner *et al.*, 1999). Testosterone levels are even lower in ill and malnourished persons (Morley *et al.*, 1979; Rudman *et al.*, 1988). Testosterone replacement leads to an increase in muscle mass (Snyder *et al.*, 2000), and muscle strength (Morley *et al.*, 1993; Sih *et al.*, 1997). Testosterone has been shown to improve function in a rehabilitation center (Bakhshi *et al.*, 2000). For these reasons, testosterone may be an ideal drug to use for malnourished males. The combination of testosterone and megestrol acetate may be particularly useful in the anorectic, sarcopenic older person.

An anabolic-androgenic steroid, oxymetholone, has produced body weight gain in advanced HIV-1 infection (Hengge *et al.*, 1996), but not in cachectic cancer patients (Pengelly, 1973). The weight gain has usually occurred only in patients who were hypogonadal. Medroxyprogesterone acetate has been observed to produce body weight gain when used as a chemotherapeutic agent, independent of tumor response (Work group. Federation of the French Cancer Centres (FNCLCC), 2000).

Dronabinol may be useful not only for treatment of anorexia but also to improve disturbed behavior in patients with Alzheimer's disease. Body weight of study subjects increased more during the dronabinol treatment than during the placebo periods (Volicer *et al.*, 1997).

Of the pharmacological agents demonstrated to produce weight gain in patients with anorexia and cachexia, megestrol acetate has shown the most promise and has been the most widely studied agent used in cachexia (Tchekmedyian *et al.*, 1987; Cruz *et al.*, 1990). An increase in body weight has been shown in 54% (seven of 13) clinical trials (Bruera *et al.*, 1990; Loprinzi *et al.*, 1990; Schmoll *et al.*, 1991; Heckmayr and Gatzenneier, 1992; Feliu *et al.*, 1992; Azona *et al.*, 1996; Mantovani *et al.*, 1995). Other trials with megestrol acetate have shown improvement in appetite, but not shown an increase in body weight (Tchekmedyian *et al.*, 1992; Beller *et al.*, 1997; Bruera *et al.*, 1996; Fietkau *et al.*, 1997; McMillan *et al.*, 1999; Gebbia *et al.*, 1996). When megestrol acetate was directly compared to dexamethasone and fluoxymesterone in patients with cancer cachexia, fluoxymesterone was clearly inferior in producing weight gain. Megestrol and dexamethasone produced an equal nonfluid weight gain, but the rate of discontinuation due to toxicity was higher in the dexamethasone group (Loprinzi *et al.*, 1999).

In a meta-analysis of 26 trials, megestrol acetate was found to increase appetite, produce weight gain, and improve health-related quality of life in oncology patients, compared to placebo. In AIDS patients, increased weight was demonstrated. A significant benefit over dronabinol in improving appetite was apparent, but no statistically significant advantages over other drugs for treating cachexia were observed.

Only edema was significant as an adverse event (Pascual *et al.*, 2004).

Although body weight gain has been shown with growth hormone, thalidomide, oxandrolone, and megestrol in cancer cachexia and AIDS cachexia, very little data is available on whether this effect occurs in geriatric anorexia and cachexia syndromes not associated with cancer or immunodeficiency syndrome.

Megestrol acetate has been evaluated in three long-term care settings. In a prospective trial, 69 patients in a veterans nursing home were randomized to receive 800 mg of megestrol acetate or placebo for 12 weeks. Forty-four patients completed a 25-week evaluation. Weight gain occurred in 68% of treated subjects. The treatment group gained 1.1 kg compared to 0.9 kg in the control group at 12 weeks. By 25 weeks, the treatment group continued to gain weight (3.0 kg) compared to a weight loss (0.5 kg) in the control group (Yeh *et al.*, 2000).

In another study of 13 elderly nursing home residents who were losing weight and refused enteral feeding, megestrol acetate was prescribed. All residents showed improvement in food intake, BMI, and serum albumin. One patient had an exacerbation of congestive heart failure (Karcic *et al.*, 2002). In an unpublished observational trial comparing megestrol acetate with cypoheptadine, weight gain occurred in the megestrol treated group (Diabetes Prevention Program Research Group, 2002). The data are suggestive that megestrol may have some effect in producing weight gain in nursing home residents.

CONCLUSIONS

In older persons, a low BMI is associated with a higher mortality risk. When the observational studies are adjusted for weight loss, nearly all of the higher mortality risk is due to weight loss. The effect of a higher BMI is weakened or disappears when an adjustment for weight loss is made, suggesting that weight loss in older persons is a profound risk factor despite initial body weight. Involuntary weight loss has an intensified effect of mortality risk, and is usually associated with clinical illness. There is some data to suggest that even voluntary weight loss in older person may carry a higher mortality risk. Body weight is an easily obtained clinical measurement and weight loss is a profound marker for adverse outcome. A careful differential diagnostic approach is mandatory, combined with nutritional and often pharmacological interventions.

KEY POINTS

- Body weight and body mass index are easily obtained clinical measurements that are profound markers for adverse outcome.
- In older adults, nearly all of the higher mortality risk is due to weight loss, independent of initial body weight.
- Involuntary weight loss may result from decreases in appetite (anorexia), ingestion of inadequate calories (starvation), disuse atrophy or hormonal deficiencies (sarcopenia), or the effects of disease (cachexia), or a combination of these factors.
- There is some data to suggest that even voluntary weight loss in older persons may carry a higher mortality risk.
- A careful differential diagnostic approach is mandatory, combined with nutritional and often pharmacological interventions.

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28

Dehydration

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"Drink and be thankful to the host! What seems insignificant when you have it, is important when you need it."

Franz Grillparzer (1791–1872)

INTRODUCTION

Dehydration is the most common fluid and electrolyte disorder in older adults. Approximately 1.5% of community-dwelling elderly will be hospitalized with dehydration each year. Additionally, over 5% of octogenarians admitted to hospital have significant hypernatremic dehydration compared to younger patients. In the United States, direct health-care costs of dehydration among persons older than 65 years exceeds 1.2 billion dollars annually.

Dehydration is associated with significant morbidity and is often the presenting illness in patients with underlying diseases such as malignancy, diabetes, or stroke (Warren *et al.*, 1996). Approximately two-thirds of older adults with dehydration will have a coexisting infection such as pneumonia, urinary tract infection, or gastroenteritis. Available date indicates that the mortality rate observed during hospitalization among dehydrated patients ranges from 33 to 72%. Untreated dehydration is associated with mortality rates exceeding 50% (Long *et al.*, 1991; Molaschi *et al.*, 1997). Notably, age is one of two major risk factors – advanced age and hypernatremia – associated with exceedingly high mortality rates in dehydrated patients.

Multiple physiological and pathophysiological factors increase the risk of dehydration in older adults. Aging is associated with a disproportionate reduction in the proportion of total body water. In addition, water handling ability is compromised in older adults because of impaired renal tubular concentrating ability and blunted sensitivity to antidiuretic hormone (Kenney and Chiu, 2001; Ritz, 2001). Aging is also associated with physiological hypodipsia that may be further exacerbated by superimposed illness. Hydration status may also be compromised by medications such as diuretics or laxatives, psychosocial factors, and environmental barriers (Morley, 2000).

From the practical perspective, the ultimate goal of all dehydration intervention and prevention strategies is increased fluid intake. Thus, maintaining the integrity of mechanisms underlying thirst and dipsogenesis (thirst provocation) is pivotal to combating dehydration in older adults.

THIRST AND AGING

Contrary to popular opinion, thirst is not the primary driving force behind fluid consumption. In the healthy and nonstressed adult, behavioral and nonregulatory psychosocial factors are the major determinants of fluid ingestion. However, under physiologically stressful or threatening conditions, homeostatic mechanisms are triggered that motivate an active search for fluids and encourage drinking. Thus, under normal circumstances, fluid intake is primarily voluntary and subject to appetitive control. In contrast, the maintenance of fluid balance under physiological or pathological stress is primarily a homeostatic function (Kenney and Chiu, 2001; Rolls, 1998). Thirst mechanisms may therefore be classified as either homeostatic or nonhomeostatic (Table 1).

Homeostatic Thirst Mechanisms

Neural control mechanisms of thirst are highly complex and involve multiple neural interconnecting pathways. Plasma tonicity and intravascular volume are the major homeostatic dipsogenic factors. Osmoreceptor cells are present in the hypothalamus within the *organum vasculosum* and the subfornical region of the *lamina terminalis*. These cells function as tonicity sensors in response to alterations in plasma osmolality. Following stimulation of these osmoreceptors, afferent

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Table 1 Thirst regulation in older adults: homeostatic and nonhomeostatic factors

Homeostatic
Plasma osmolarity
Intravascular volume
Plasma rennin activity
Peripheral and central vasopressin levels
Oropharyngeal metering
Nonhomeostatic
Hedonic qualities of fluid
Palatability of drink
Taste preferences
Access and availability
Psychosocial factors
Lifestyle habits
Social isolation
Functional ability

signals travel within the nucleus *tractus solitarius* and converge on the supraoptic and paraventricular nuclei. Axonal projections from both nuclei traverse the median eminence and terminate in the posterior pituitary gland. This pathway modulates vasopressin release. An alternate dipsogenic pathway comprises fibers from the nucleus *tractus solitarius* that terminate in the lateral preoptic region of the hypothalamus (Schoorlemmer *et al.*, 2000; Stricker and Verbalis, 1998).

Afferent fibers arising from peripheral baroreceptors located in the carotid sinus, aortic arch, and left atrium also terminate in the *nucleus tractus solitarius*. Decreased intravascular volume stimulates these fibers, resulting in increased plasma renin activity and elevated serum angiotensin and aldosterone levels. Increased plasma renin activity induces dipsogenesis by increasing circulating angiotensin II levels (Stachenfield *et al.*, 1997; Kenney and Chiu, 2001).

Angiotensin II is a very strong stimulus of thirst. Intraventricular injection of angiotensin II induces an immediate and highly motivated search for water that results in the rapid ingestion of large volumes of water far in excess of the animal's daily needs. Elevated circulating angiotensin II has similar, though less marked effects on drinking.

Angiotensinergic nerve endings and angiotensin receptors have been identified in the median preoptic nucleus, *organum vasculosum*, and *lamina terminalis* in the periventricular and subfornical areas. Efferent impulses arising from thirst regulatory centers located in the latter areas allow circulating angiotensin II to exert an effect on other regions of the hypothalamus and brain stem involved in sodium appetite and blood pressure control. Animal studies have shown that Angiotensin II induces vasopressin release when administered intraventricularly. Plasma hypertonicity and intravascular volume depletion both stimulate vasopressin release, thereby inducing a dipsogenesis. Although the precise mechanism is unknown, available data indicates the existence of a separate central renin-angiotensin axis that independently modulates thirst and vasopressin release (Fitzsimons, 1998; McKinley and Johnson, 2004).

Short-term regulation of fluid intake is largely predicated on the act of swallowing and an additional thirst regulatory mechanism described as oropharyngeal metering. Deglutition appears to trigger the afferent arm of a conceptual pathway that determines the appropriate amount of drinking that occurs in response to dipsogenic stimuli. Oropharyngeal metering is most likely responsible for the rapid perception of relief from thirst during drinking, even prior to sensing of restored homeostasis by the osmoreceptors and baroreceptors. Oropharyngeal metering may also play a role in the suppression of vasopressin secretion that occurs during drinking. Although the precise physiology underlying oropharyngeal metering has not been identified, this mechanism prevents excessive ingestion of water in response to thirst and subsequent wide fluctuations in intravascular volume or plasma tonicity (Figaro and Mack, 1997). The effect of aging on oropharyngeal metering is unknown. However, it is plausible that age-related xerostomia, esophageal dysmotility, and blunting of oral chemosensory perception may compromise oropharyngeal metering. Further research is needed in this area.

In the nonstressed person, dipsogenesis is triggered and drinking occurs even in the presence of adequate amounts of total body water. Similarly, in the presence of adequate food and drink, fluid ingestion exceeds the amount strictly required to maintain physiological fluid balance (Kenney and Chiu, 2001). Clearly, drinking is a multifactorial phenomenon that occurs in response to a variety of dipsogenic (thirst provoking) factors. Such factors may be physiological or pathological. Behavioral, psychosocial, cultural, and hedonic cues have all been implicated as triggers.

Overall, available data implicates elaborate and highly coordinated cortical and subcortical neural dipsogenic pathways that are yet to be precisely defined. In older adults, the overlay of age-related changes renders these elaborate mechanisms even more tenuous (Horani and Morley, 1998).

Dipsogenesis

Experimental fluid deprivation observations have yielded useful information on the response of older adults to fluid deprivation under controlled conditions. Compared to younger subjects, older adults exhibit lower thirst ratings and decreased fluid consumption for comparable degrees of thirst. Hypertonic intravenous saline infusion results in relatively higher serum vasopressin levels in older adults compared to younger adults, suggesting heightened sensitivity of central vasopressin osmoreceptors with aging. Aging also results in the loss of the normal circadian rhythm of vasopressin secretion expressed as nocturnal peaking (Phillips *et al.*, 1993; Mack *et al.*, 1994). Thus, quantitative and qualitative changes in circulating vasopressin levels may partially account for age-related attenuation of the thirst response.

Evidence also indicates that aging osmoreceptors may have a higher osmolarity threshold and are less sensitive to changes in osmolarity. Observational studies of older adults undergoing prolonged exercise in relatively high ambient temperatures suggest impaired compensatory fluid balance mechanisms. Results from such studies show that older

subjects fail to drink enough fluid to restore euvolemia. However, fluid loading and thirst suppression studies indicate less suppression of thirst in older adults compared to younger adults following ingestion of equal amounts of fluid. Thus, although older adults are more susceptible to dehydration following water deprivation, there is a paradoxical increase in the risk of fluid overload due to compromised ability to appropriately limit the quantity of fluid ingested in response to dipsogenic stimuli (Mack *et al.*, 1994; Kenney and Chiu, 2001).

Several other hormones have been implicated in the etiology of age-related hypodipsia. Atrial natriuretic peptide (ANP) is a 28-amino acid peptide produced by atrial myocytes in response to volume overload and distension. Angiotensin II induces increased synthesis and release of ANP. Increased circulating ANP exerts a negative feedback effect on renin release, thereby decreasing and regulating angiotensin levels.

ANP is the foremost hormonal mechanism that prevents volume overload. Elevated circulating levels of ANP occur in response to hypervolemic states and induce increased diuresis and natriuresis, thereby reducing intravascular volume. ANP receptors are also located in the atria, hypothalamus, and areas of the brain stem involved in the regulation of intravascular volume and blood pressure. Within the brain, ANP receptors also receive afferent activating impulses from baroreceptors. Angiotensin II antagonizes the effects of ANP. ANP inhibits renin release, thereby decreasing angiotensin II levels (Levin *et al.*, 1998; Kamoi *et al.*, 1991; McKinley and Johnson, 2004).

Norepinephrine (NE) has also been implicated in thirst regulation. Animal studies indicating an antidipsogenic effect of NE suggest a possible role for NE in the pathogenesis of age-related hypodipsia (Izumi, 1991; Racotta *et al.*, 1995).

Adrenomedullin (AM) is a 52-amino acid peptide that has been shown to reduce thirst in fluid deprived rats. AM is similar in structure to calcitonin gene-related peptide (C-GRP) Although the main source of AM is the vascular endothelium, AM is also found in high concentrations in the adrenal glands, hypothalamus, anterior pituitary, kidneys, lungs, gastrointestinal tract, pancreas, heart, skin, salivary, and sweat glands. AM release is enhanced by proinflammatory cytokines. Additionally, both nitric oxide (NO)-dependent and NO-independent pathways have been implicated in the release of AM during inflammation (Bunton, 2004). Little is known about the exact role of AM in human thirst regulation.

Naloxone, an opioid receptor antagonist, has been shown to suppress fluid intake after overnight water deprivation in younger subjects. However, the antidipsogenic effect of naloxone is far less pronounced in older adults possibly because of age-related blunting of opioid receptor sensitivity (Silver and Morley, 1992; Fregoneze *et al.*, 1999).

Nonhomeostatic Regulation of Hydration

Age-related changes in functional status and quality of life threaten independence and socialization. Compromised access to utilities and limited recreational activity invariably affect domains such as nutrition and hydration that are vulnerable to environmental and sociocultural influences. In the young and healthy adult, fluid balance is rarely significantly threatened in the absence of restricted access to fluids or disease. In contrast, older adults are not only subject to adverse pathophysiological events but may also develop dehydration as a result of compromised nonhomeostatic dipsogenic influences.

Observations of ad-lib fluid intake in free-living individuals of all ages highlight the importance of nonphysiological factors in regulation of fluid balance. When a fluid is freely accessible, drinking consistently results in sufficient fluid intake to forestall the development of hypovolemic or hypertonic deficits. Psychosocial and cultural influences are major determinants of the volume and type of fluid ingested (Rolls, 1998). Thus, hedonic factors such as taste preferences, palatability, and culinary presentation affect drinking. Social, cultural, and environmental factors may also trigger dipsogenesis. In older adults, age-related changes in chemosensory perception may detract from the pleasantness of specific drinks and thereby discourage drinking. Health awareness and lifestyle habits also affect the type and quantity of fluid consumed. Health conscious adults are more likely to make an active effort to consume relatively large volumes of fluid. In contrast, elders who participate in religious practices or sociocultural rituals that involve fasting or fluid restriction are more vulnerable to dehydration.

CLINICAL DEHYDRATION AND AGING

Risk Factors for Dehydration in the Older Adult

Common causes of dehydration are preventable and easily treatable. However, early diagnosis and intervention is critical. Prompt clinical detection is facilitated by an increased awareness of the risk of dehydration in geriatric patients. Available data identifies a positive correlation between the amount of food consumed and fluid ingested. Thus, a direct consequence of anorexia of aging from either physiological or pathological causes will be a reduction in fluid intake and an increased risk of dehydration.

Specific pathological syndromes in the aging adult may further threaten hydration status (Table 2). Frailty, depression, impaired cognition, and social isolation may diminish or motivate or compromise the drinking ability. Likewise, functional disability, neurological deficits, and impaired mobility may bar access to adequate amounts of fluid. Neurological diseases such as cerebrovascular disease, Parkinson's disease, and Alzheimer's disease may restrict access to fluids either by compromising the patient's ability to overcome environmental barriers or by disrupting pharyngeal and neuromuscular mechanisms that control drinking. Iatrogenesis is another important cause of dehydration. Polypharmacy in older adults increases the risk of drug-related adverse events. Diuretics, nephrotoxic drugs, and laxatives can compromise

Table 2 Common risk factors for dehydration in the elderly

Neurological
Focal motor deficit
Cognitive impairment: dementia, delirium
Tremors
Movement disorders
Poor vision
Altered chemosensory perception
Psychiatric
Depression
BPSD
Paranoid delusions
Obsessive compulsive disorders
Chronic schizophrenia
Anxiety/panic attacks
Cardiopulmonary
Poor exercise tolerance
Persistent dyspnea
Diuretic therapy
Gastrointestinal
Dysphagia
Anorexia
Persistent vomiting
Chronic diarrhea
Incontinence
Endocrine/metabolic
Hypercalcemia
Diabetes mellitus
Diabetes insipidus (central and neurogenic)
Miscellaneous geriatric syndromes
Frailty
Gait abnormality
Multiple comorbidity
Polypharmacy
Pain
Arthritis
Institutionalization

hydration and fluid balance. Inappropriate use of nonprescription medications such as calcium supplements may result in dehydration from hypercalcemia-induced polyuria. Institutionalized elders dependent on staff for feeding assistance are also vulnerable to dehydration. Inadequate staffing levels may result in the failure to identify patients at high risk for dehydration. Physical restraints are a recognized cause of dehydration as they increase the dependency of the patient on staff for hydration. Similarly, chemical restraints may result in oversedation or amotivational states that result in reduced fluid intake (Warren *et al.*, 1996; Horani and Morley, 1998; Wilson, 1998).

Clinical Assessment and Diagnosis of Dehydration

Clinical diagnosis of dehydration is unreliable. Symptoms are usually nonspecific such as lethargy, muscle weakness, dizziness, and confusion. Furthermore, patients with hypertonic dehydration may remain asymptomatic until serum sodium levels exceed 160 mmol l^{-1}, at which point they may present with delirium, seizures, or other neurological symptoms. Physical examination may also be unreliable. Reduced skin turgor from dehydration is not easily distinguished from age-related cutaneous atrophy (Adrogue and Madias, 2000; Pals *et al.*, 1995; Weinberg and Minaker, 1995). Axillary moisture assessment has been shown to be a fairly specific, though poorly sensitive, index of hydration in younger adults. However, in older adults, evidence shows that axillary sweating is a reproducible and reliable sign of hydration in ill elderly patients with a high negative predictive value and moderate positive predictive value (Eaton *et al.*, 1994). Dry oral mucous membranes in older patients are not necessarily indicative of systemic dehydration. Similar changes occur with chronic mouth breathing, supplemental oxygen use, pathological xerostomia, or adverse effects of anticholinergic medication.

Cardiovascular responses to dehydration may also be impaired in older adults. Blunted age-related chronotropic responsiveness to intravascular volume depletion confounds early detection of significant fluid deficits, prior to the development of hypotension. Reliability of orthostatic hypotension as an index of dehydration in older adults is also suspect. Confounding factors include medications, age-related vascular changes, and prolonged bed rest, all of which may result in autonomic dysfunction and orthostasis (Gross *et al.*, 1992; Weinberg and Minaker, 1995).

Weight loss is a valuable sign of dehydration. Generally, rapid and acute weight loss in excess of 3% of baseline body weight is most likely due to reduced total body water from dehydration (Weinberg and Minaker, 1995). Dehydration may also masquerade as a variety of nonlocalizing geriatric syndromes due to increased vulnerability of aging organs to stress. Reduced skin integrity due to subcutaneous dehydration may result in xerosis, pruritus, recurrent skin infections, and pressure ulcers in the immobile patient. Cystitis and urinary tract infections may result from the irritant effect of highly concentrated urine on the vesical mucosa. Inspissated oral and gastrointestinal secretions can lead to constipation, impaction, xerostomia, periodontal sepsis, and mouth ulcers. Neurological dysfunction in dehydrated older adults may present as delirium, dizziness, recurrent falls, and subsequent complications such as hip fractures or traumatic brain injury.

Overall, the detection of dehydration is largely dependent on a high threshold of suspicion. Laboratory indices are often relied on to support the diagnosis of dehydration, assess severity, and guide intervention. Serum osmolarity >300, blood urea nitrogen (BUN) >20, or BUN: Creatinine ratio >20 are useful indices of dehydration. However, data shows that biochemical indices, though frequently used as indices of dehydration lack specificity (Wakefield *et al.*, 2002).

Dehydration may be classified as isotonic, hypertonic, or hypotonic. Isotonic dehydration is the more common type of dehydration and reflects loss of water and electrolytes in relatively equal proportions. Serum osmolarity and electrolytes are often normal. Restricted oral intake or diseases manifesting with both diarrhea and vomiting are likely to result in isotonic dehydration. Hypertonic dehydration is most often observed in patients with compromised ability to replace

ongoing free water losses. Thus, functionally disabled or cognitively impaired patients with restricted excess to water are more likely to be affected. Serum sodium and serum osmolarity exceeds 145 mmol l^{-1} and 300 mmol l^{-1} respectively. A general rule of thumb is that hypernatremia in older adults indicates hypertonic dehydration. In hypotonic dehydration, serum sodium is below 135 mmol l^{-1} and serum osmolarity is less than 280 mmol kg^{-1}. Excessive natriuresis, such as may occur with excessive diuretic use or renal tubular disorders, causes a disproportionately excessive loss of sodium compared with free water. Affected patients may present with hyponatremic dehydration.

Available evidence examining urine osmolarity indicates poor correlation between serum and urine parameters. Several bedside tools have been developed to screen urine for dehydration, some of which use colorimetric devices. However, most of these tools are yet to be validated. Biochemical measurements are still regarded as the best laboratory benchmark for the assessment of dehydration.

Fluid balance charts documenting input and output are helpful in determining the risk and characterizing the severity of dehydration. However, charting is often rendered inaccurate because of a variety of factors such as staff errors in documentation, poor patient history, and urinary incontinence (Weinberg and Minaker, 1995; Kim and Berlowitz, 1994).

Management of Dehydration

Ultimately, identification of patients at risk for dehydration and institution of appropriate preventive measures are the most cost-effective strategies to ensure adequate hydration in the older adult. Unlike the pediatric population where fluid requirements are more clearly defined, precise recommendations are not available for older adults. Arbitrary guidelines recommend consumption of at least 2 l (68 oz glasses) of fluid daily. This estimate assumes relatively cool ambient temperature, average body weight of approximately 70 kg, and moderately intense physical exercise of about 20 minutes daily. Nevertheless, available evidence-based data supports the benefits of ingestion of at least 1.5 l of fluid daily. There is no data to show that the consumption of fluid in excess of this amount is of added benefit. Paradoxically, age-related defects in cardiac and renal tubular water handling increase the risk of fluid overload and dilutional hyponatremia with excessive fluid consumption. Providers should therefore ensure that patients are provided with specific hydration recommendations to guide intake (Lindemann *et al.*, 2000).

As a rule of thumb, hemodynamically stable hospitalized patients require at least 30–35 ml kg^{-1} day^{-1}. However, requirements will differ widely in older adults, depending on the underlying illness. Fluid intake may need to be restricted in patients with liver cirrhosis, chronic kidney disease, or cardiac failure. Insensible loss occurs through the skin, respiratory surfaces, and fecal loss. Therefore, during the warmer months and in warm climates, increased ambient temperature should prompt careful attention to fluid intake.

In addition, patients with fevers, extensive burns, persistent vomiting, diarrhea, or draining fistulas may need additional fluid. Similarly, patients with chronic lung disease, decubitus ulcers, excessive tremors, or movement disorders are likely to have increased amounts of insensible fluid loss. Increased daily fluid intake may also be necessary in patients with poorly controlled diabetes mellitus and patients on chronic diuretic or laxative therapy.

Hedonic influences are important, as taste preferences and palatability are an important determinant of fluid intake. Providers often emphasize water intake; however, patients should be made aware that preferred fluid beverages may be substituted for water. Preventive strategies, particularly in institutionalized patients, should include ensuring easy access to fluid. Water fountains should be located at convenient intervals and esthetically pleasing locations. Circulating water or juice carts are other methods by which fluid consumption can be encouraged.

Drinking assistance must be readily available for dependent elders. Cognitively impaired elders need to be frequently reminded to drink. In addition, offering fluid at very frequent intervals (1.5–2 hours) has been found to improve hydration among dependent institutionalized elders. Data indicates that the major proportion of fluid ingestion occurs with medication rounds. Encouraging fluid intake at medication rounds may help maintain adequate hydration (Morley, 2000; Wilson, 1998).

Although the suspicion of impaired hydration status may be notably strengthened by laboratory testing and ancillary data, therapy should not be unduly delayed. Fluid replacement therapy can very often be started empirically. Effective treatment of dehydration mandates due attention to restoration of normal plasma tonicity and replacement of the fluid deficit and ongoing losses. Calculation of the free water and sodium deficit are helpful guides to fluid therapy prescription in younger adults (Table 3). Although the same formulas are used in older patients, aggressive and rapid replacement should be avoided in older persons, unless absolutely necessary, because of the increased risk of fluid overload. Additionally, rapid correction of hypernatremia in patients with hypertonic dehydration may result in neurological complications. This is due to severe cerebral edema arising from the reabsorption of large volumes of fluid due to the osmotic gradient created by the intracellular neuronal accumulation of organic osmolytes during the hyperosmolar period (Adrogue and Madias, 2000; Lien *et al.*, 1990; Gullans and Verbalis, 1993).

Table 3 Helpful formulae for fluid prescription

Free water deficit (l)
(Total body water = [0.6 × body weight (kg)]) × (Sodium/140 − 1)
Na deficit (mEqiv)
(135 − [Na^+]) × (total body water = [0.6 × body weight (kg)])
Plasma osmolality (mOsm kg^{-1})
2[a][mEqiv $l^{-1}Na^+$] + (mg dl^{-1}glucose)/18 + (mg dl^{-1} BUN)/2.8

[a]Do not replace more than 1/2 of fluid deficit in the first 24 hours. Recommended Na^+ reduction rate should not exceed 0.5 mmol l^{-1} $hour^{-1}$.

In patients with a functioning gut, oral ingestion or enteral tube administration are the safest routes for fluid replacement. Although in acutely hospitalized elders the intravenous route is frequently utilized for fluid replacement, complications are not uncommon. These include difficulty with peripheral access, subcutaneous fluid infiltration, local infection, air embolism, bacteremia, and septicemia. Direct intravenous infusion also increases the likelihood of hemodynamic overload with rapid fluid infusions. Peripheral venous cannulation access is much safer than central venous line placement. However, in patients with emergent and life threatening diseases, central access may be unavoidable. Intravenous fluid infusion is a highly effective delivery system in patients who require resuscitation, as this method facilitates delivery of precise amounts of fluid and rapid restoration of intravascular volume.

Hypodermoclysis is an underutilized parenteral hydration method that delivers fluid into the subcutaneous tissue. Hypodermoclysis has been shown to be effective in restoring hydration, especially in mild to moderately dehydrated older adults. This infusion method is often advocated in frail, institutionalized persons. However, this is also a convenient technique that can be used in all geriatric health-care settings, including subacute care and home care. Family members, lay caregivers, and nurses are easily trained to administer hypodermoclysis. Technically, hypodermoclysis is a relatively safe procedure suitable for use in many hospital and home-care situations regardless of the patient's age and is simpler to perform than intravenous cannulation. Emerging research clearly favors hypodermoclysis as an alternative infusion method (Sasson and Shvartzman, 2001; Lipschitz *et al.*, 1991; Hussain and Warshaw, 1996; Ferry *et al.*, 1999).

KEY POINTS

- Dehydration is the most common fluid and electrolyte disorder in older adults. Multiple risk factors for dehydration coexist in the elderly. These include age-related physiological hypodipsia, frailty, polypharmacy, acute and chronic illnesses, and iatrogenic factors.
- Recommended daily intake of fluids in older adults is unclear, but should not be less than 1500 mL/24 hours in order to ensure adequate hydration. Fluid intake and hydration status should be monitored closely, especially in dependent elders.
- Clinical diagnosis of dehydration is unreliable. Thus, multiple assessment modalities should be used to assess hydration status and define therapeutic intervention.
- Aggressive and rapid fluid and electrolyte replacement in older adults may lead to fluid overload and neurological complications.
- Oral and enteral routes are safest for fluid replacement therapy. In patients requiring intravenous infusion, cautious administration is required. Hypodermoclysis is a safe and effective subcutaneous infusion technique that can be used in all health-care settings.

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Vitamins and Minerals in the Elderly

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INTRODUCTION

Poor nutritional status is a primary concern for the elderly. Nutritionally inadequate diets can contribute to or exacerbate chronic and acute diseases and hasten the development of degenerative diseases associated with aging (Weimer, 1998).

Undernutrition is one of the most common and devastating conditions in the older population. Thirty percent to 40% of men and women over the age of 75 are at least 10% underweight. Full-blown undernutrition occurs in 5 to 12% of community-dwelling older persons, in 11% of medical outpatients, and in 20% of higher risk community-dwelling populations. In hospitalized older adults, protein-calorie undernutrition reaches epidemic proportions, with a reported frequency of 32 to 50%. In institutionalized, long-term care settings, an even higher prevalence of undernutrition (23–85%) has been reported. The devastating consequences of undernutrition include a higher mortality, greater functional decline, more frequent infections, and higher rates of adverse complications in all settings (Thomas, 2002).

As people age, activity levels and energy requirements tend to decrease. Concomitant decreases in food consumption may cause protein and micronutrient intake to fall below desirable levels. It is well documented that many older persons develop physiological anorexia associated with aging. Additional factors that increase the risk of undernutrition include physiological changes that affect digestion, absorption and metabolism of nutrients, social isolation, chronic diseases, oral problems, sensory impairment, cognitive impairment, depression, multiple and chronic medication use, poverty, and inappropriate food intake (Tripp, 1997; Thomas *et al.*, 2000; Morley, 1998; The Nutrition Screening Initiative, 1991).

The specific requirements for micronutrients in the elderly have not been studied until quite recently. Vitamin and mineral requirements do not stay static over the adult life span. There are several micronutrients for which there is strong evidence that requirements are in fact increased in the elderly compared to younger people such as: vitamins D, B6, and B12 (Russell, 1992; Johnson, 2002a). It is clear that individuals change physiologically during aging and that aging is often associated with the development of chronic degenerative diseases. The roles that various supplements play in these changes appear to be less defined. There is overall lack of evidence on the nutritional needs of the elderly, with particular lack of data from clinical trials. Additionally, there is a critical need for the development of valid and reliable methods to detect undernutrition and the generation of data to determine the dietary reference intakes (DRIs) of individuals 51 to 70 years and >70 years old (*Nutrition Reviews*, 2004).

Vitamin disorders in the elderly usually present atypically or are masked by coexisting diseases or a general failure to thrive (Larry, 1995). Vitamin preparations are consumed on a daily basis by 20–60% of elderly. These supplements are consumed for various reasons including the following: to increase energy, improve health, improve appetite, and to prevent and treat diseases. Older persons may consume potentially toxic amounts of vitamins and minerals by supplementation (Hartz *et al.*, 1988; Subar and Block, 1990; Kim *et al.*, 1993; Kellet *et al.*, 1984; Schneider and Nordlund, 1983; Hale *et al.*, 1982; Read and Graney, 1982). Drug–nutrient interactions are common in the elderly because of the high incidence of polypharmacy, many of which may occur unrecognized (Roe, 1992). Table 1 summarizes drugs with potential for interaction with various vitamins and minerals.

PREVALENCE/SCOPE OF THE PROBLEM

There have been few studies concentrating on the prevalence of vitamin and mineral deficiencies, most studies have concentrated on protein energy malnutrition (*Vitamin*

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Table 1 Potential micronutrient–drug interaction (Larry, 1995; Warber *et al.*, 2002)

Micronutrient	Drugs
Calcium	Vitamin D, lysine
Chromium	Vitamin C
Copper	Zinc, iron
Folic Acid	Methotrexate, cotrimazole, phenytoin, sulfasalazine, triamterene, zinc, alcohol
Magnesium	B6, calcium
Manganese	Calcium, iron, zinc, copper
Selenium	Vitamin E
Vitamin A	Iron, vitamin E, tetracycline, cholestyramine
Vitamin B1 (Thiamine)	Vitamin B2, vitamin B3
Vitamin B2 (Riboflavin)	Ouabain, theophylline, penicillin, boric acid, probenecid, chlorpromazine, phenothiazines, barbiturates, streptomycin, and oral contraceptives, antidepressants, or probenecid, tobacco, alcohol
Vitamin B3 (Niacin)	Vitamin B1, vitamin B2, anticonvulsants, aspirin, clonidine, hydroxymethylglutaryl (HMG) Coenzyme A reductase inhibitors
Vitamin B6 (Pyridoxine)	Magnesium, anticonvulsants
Vitamin C	Copper, iron, vitamin
Vitamin D	Aluminum hydroxide, corticosteroids, diuretics, rifampin, phenytoin.
Vitamin E	Antacids, cholestyramine, colestipol, mineral oil, sucralfate, iron, vitamin A, tobacco, alcohol, coumarins, anticoagulants or indandiones
Vitamin K	Calcium, anticoagulants
Zinc	Diuretics, copper, *N*-acetyl cysteine, iron, calcium, magnesium

Deficiency, 2004). The prevalence of vitamin deficiency in usual western diets is higher than generally believed, especially in the elderly (Fletcher and Fairfield, 2005). Various studies reveal that up to 20% of community-dwelling ambulatory adults, 37% of home-bound elderly, 30–60% of hospitalized patients and 17–85% of institutionalized patients are malnourished (Morley and Silver, 1995; Abbasi, 1995; Abbasi and Rudman, 1993; Ritchie *et al.*, 1997; Keller, 1993; Guigoz *et al.*, 1996).

According to the National Health and Nutrition Examination Survey (NHANES), up to 16% of Americans over the age of 65 consume less than 1000 calories a day. The reduced caloric intake is incompatible with maintaining adequate vitamin and mineral intakes. Studies on vitamin deficiencies in older individuals reveal that vitamin deficiencies vary from 2.6 to 6.8% for vitamin D in the general population to 35% in the institutionalized patients, while vitamin A deficiency is seen in 1% or less of the older adults. The prevalence for vitamin B deficiency shows marked heterogeneity. The prevalence for vitamin B1 varies from <5% in the nursing home patients to as high as 43% in independent older persons; B12 deficiency is seen in up to 43% of independent older adults and up to 29% of nursing home patients (*Vitamin Deficiency*, 2004; Drinka and Goodwin, 1991; Vir and Love, 1979; Baker *et al.*, 1979; Garry *et al.*, 1984). Table 2 gives the prevalence of vitamin deficiencies. Information on prevalence of trace mineral deficiencies comes from the developing world; zinc deficiency is widely recognized to be a common association with malnutrition. Geographic surveys show trends for selenium deficiency in individuals living in areas with low soil content of selenium (Jacobs and Wood, 2003a,b).

Table 2 Prevalence of vitamin deficiencies in the elderly

Vitamin	Independent	Hospitalized	Nursing Home
Vitamin A	1%	Unknown	Unknown
Vitamin B1 (thiamine)	13–43%	40%	2–5%
Vitamin B2 (riboflavin)	3–42%	12%	1–34%
Vitamin B6 (pyridoxine)	5–56%	19%	21–93%
Folate	2.5–34%	24%	4–24%
Vitamin B12 (cobalamin)	4–43%	Unknown	4–29%
Vitamin C (ascorbic acid)	Unknown	Unknown	0–5%
Vitamin D	2–5%	22%	35%

DIETARY REFERENCE INTAKES

The goal of the Recommended Dietary Allowances (RDA) was to estimate nutritional requirements for preventing basic deficiency diseases. The recommendations were also meant to be applied as general guidelines for groups, not as a gold standard for individuals. Research, led by the American Heart Association in the 1960s, demonstrated the links between diet and disease. It was already known that deficiency in certain nutrients results in disease. Studies went on to show clearly that increased intake of certain nutrients actually helps prevent some chronic illnesses. Because of this research and because the RDAs were being used for purposes other than those for which they were created, new recommendations were in order.

The new guidelines are called *Dietary Reference Intakes* or *DRIs*. They were developed by the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences, and published in 1998. These were designed to reflect the latest understanding of nutrient requirements based on optimizing health in individuals. For the first time, the group included data for individuals 70 years and older. They are being developed with individuals in mind. They are also concerned about the prevention of chronic degenerative diseases, such as macular degeneration, heart disease, and osteoporosis. The DRIs are based on several factors. These include the level of a nutrient needed to meet the needs of a healthy individual and the level at which a nutrient will produce harmful side effects. The DRIs also consider the source of the nutrient, for example, the body is often better able to use nutrients supplied in food than by supplements. The new DRIs take age and gender into consideration as well (*Vitamin Deficiency*, 2004; www.nap.edu, 2005; Institute of Medicine, 2000, 2001).

The committee described four categories of reference values:

1. Estimated average requirement (EAR): represents the amount of nutrient intake that meets the requirements of

Table 3 Dietary reference intake for micronutrients (National Policy and Resource Center on Nutrition and Aging, 2004)

	RDA/AI*				TUL			
	51–70 years		>70 years		51–70 years		>70 years	
Micronutrient	Male	Female	Male	Female	Male	Female	Male	Female
Vitamin A (μg)	900	700	900	700	3000	3000	3000	3000
Vitamin C (mg)	90	75	90	75	2000	2000	2000	2000
Vitamin D (ug)	10*	10*	15*	15*	50	50	50	50
Vitamin E (mg)	15	15	15	15	1000	1000	1000	1000
Vitamin K (ug)	120*	90*	120*	90*	ND	ND	ND	ND
Thiamine (mg)	1.2	1.1	1.2	1.1	ND	ND	ND	ND
Riboflavin (mg)	1.3	1.1	1.3	1.1	ND	ND	ND	ND
Niacin (mg)	16	14	16	14	35	35	35	35
Vitamin B6 (mg)	1.7	1.5	1.7	1.5	100	100	100	100
Folate (ug)	400	400	400	400	1000	1000	1000	1000
Vitamin B12 (ug)	2.4	2.4	2.4	2.4	ND	ND	ND	ND
Calcium (mg)	1200*	1200*	1200*	1200*	2500	2500	2500	2500
Chromium (ug)	30*	20*	30*	20*	ND	ND	ND	ND
Copper (ug)	900	900	900	900	1000	1000	1000	1000
Fluoride (mg)	4	3	4	3	10	10	10	10
Iron (mg)	8	8	8	8	45	45	45	45
Selenium (ug)	55	55	55	55	400	400	400	400
Zinc (mg)	11	8	11	8	40	40	40	40

TUL, Tolerable Upper Intake Levels; RDA, Recommended Dietary Allowance; AI, Adequate Intakes; ND, not determined. AI are in ordinary type followed by an asterisk.

50% of the individuals in that group. The EAR serves as the basis for developing the recommended dietary allowance.

2. Recommended dietary allowance (RDA): the daily nutrient intake that meets the nutrient needs of 97–98% of healthy individuals in that group. It is set at 2 standard deviations above the EAR.
3. Adequate intakes (AI): the average observed or experimentally derived intake by a defined population or subgroup that appears to sustain a defined nutritional state, such as normal circulating nutrient values, growth, or other functional indicators of health.
4. Tolerable upper intake level (TUL): represents the maximum nutrient intake by an individual that is unlikely to pose risks of adverse health effects in 97–98% of individuals. It is not intended to be a recommended level of intake.

Table 3 gives the DRIs for vitamins and minerals for individuals aged 51–70 and over 70 years.

FACTORS AFFECTING NUTRIENT INTAKE IN THE ELDERLY

Total energy intake decreases substantially with age; this results in concomitant declines in most nutrient intakes including vitamins and minerals. Despite the common occurrence of protein energy undernutrition in older persons, its presence is rarely recognized. Factors implicated in the decreased nutrient intake in the elderly can be divided into the following categories (Thomas, 2004; Morley, 1995a):

- Social
- Psychological
- Medical
- Age-related

Factors affecting the nutrient intake are summarized in Table 4.

THE ANTIOXIDANTS

One of the leading theories proposed for cellular and organism aging is that damage to cellular mechanisms and tissues occurs because of chronic damage resulting from oxidative stress caused by free oxygen radicals. Endogenous oxidative damage to proteins, lipids, and DNA is thought to be an important etiologic factor in aging and development of chronic diseases such as cancer, atherosclerosis, and cataract formation. The developing recognition that many disease states are caused by oxidative damage and that certain antioxidant compounds may scavenge these damaging free oxygen radicals has resulted in an increased interest in vitamins and minerals as antioxidants. Vitamins A, C, E, and β-carotene, referred to as *antioxidant vitamins* have been suggested to limit oxidative damage in humans. Riboflavin (vitamin B2) and selenium, a trace metal, are also suggested to have antioxidant capabilities (Thomas, 2004; Larry, 1995; Morley, 1992; Christensen, 1993; Sies *et al.*, 1992).

A large body of epidemiological evidence suggests that eating a diet rich in sources of vitamins has a protective effect on development of disease. The strong association of dietary intake of vitamins and disease in epidemiological studies has not been borne out in clinical trials (Larry, 1995). Caution

Table 4 Factors affecting nutrient intake in the elderly

Social
1. Poverty
2. Social isolation
3. Ignorance
4. Problems with meal preparation
5. Inability to shop
6. Lack of recognition of ethnic or other food preferences in institutional settings
7. Monotony of institutionalized food

Psychological
1. Depression
2. Bereavement
3. Alcoholism
4. Dementia
5. Late-life paranoia
6. Late-life mania
7. Anorexia Tardive
8. Sociopathy
9. Overwhelming burden of life

Medical
1. Increased metabolism
   - Hyperthyroidism, phaechromocytoma
   - Movement disorders: Parkinsonism and Tardive dyskinesia
   - COPD.
   - Severe cardiac disease
2. Anorexia
   - Drugs: Digoxin, psychotrophic drugs, theophylline, cimetidine, ranitidine, l-thyroxine.
   - Gallstones, chronic and recurrent infections
   - Malignancy
   - Physiologic anorexia of aging
3. Swallowing problems
   - Esophageal candidiasis
   - Teeth and denture problems
   - Severe tremors and strokes
4. Malabsorption
   - Late onset gluten enteropathy
   - Lactose deficiency
5. Feeding problems
   - Severe tremor
   - Strokes
   - Dementia

Age related
1. Anorexia of aging
2. Decreased olfaction
3. Decreased taste

must be used in interpreting the results of observational studies, as the association of diets rich in fruits and vegetables with reduced risk of cancer and cardiovascular disease may be due to the vitamins themselves, other compounds in fruits and vegetables, or the substitution of dietary meat and fat with fruits and vegetables (Jha *et al.*, 1995).

Vitamin A and β-carotene

Vitamin A consists of preformed vitamin A (retinol) and the carotenoids such as β-carotene. The carotenoids are a diverse group of more than 600 naturally occurring pigments. Natural sources include yellow, orange, and red plant compounds, such as carrots and green leafy vegetables. Humans cannot synthesize carotenoids and depend on dietary intake exclusively for these micronutrients. β-carotene can act as an antioxidant by quenching the unpaired electrons of free radicals and divert free-radical damage toward itself. Vitamin A refers to preformed retinol and the carotenoids that are converted to retinol. Preformed vitamin A is found only in animal products, including organ meats, fish, egg yolks, and fortified milk. More than 1500 synthetic retinoids, analogs of vitamin A, have been developed. Vitamin A intake decreases with age; however, hypovitaminosis A is uncommon even in the very old. The current RDI for vitamin A is $1500\,\mu g\,l^{-1}$ (5000 IU). Except at the extreme ranges, retinol levels correlate poorly with vitamin A status and are affected by many nonnutritional diseases. Hepatic levels of vitamin A appear unchanged in adults. About 50–85% of the total body retinol is stored in the liver. It is also found in many other tissues in much smaller concentrations. (Thomas, 2004; Larry, 1995; Ross, 2000; Harrison, 1993).

Dietary proteins undergo proteolysis to release retinyl esters in the stomach. They then join lipids and bile salts to form micelles for absorption through the intestinal mucosa. Preformed vitamin A is absorbed by the intestinal cell by a carrier-mediated mechanism, however; carotenoids are passively absorbed by the intestinal epithelium. Vitamin A is then transported to the liver via the lymphatics. By means of a receptor-mediated endocytosis on the surface of the hepatocytes, the retinol esters are released and stored as retinyl ester. These are further metabolized to eventually combine with retinol binding proteins (RBP) before storage in vitamin A–containing lipid globules within the hepatic stellate cells. In order for vitamin A to reach its target organs, it binds to RBP molecules for release into plasma as a Retinol-RBP complex (Larry, 1995; Ross, 2000; Harrison, 1993; Pazirandeh and Burns, 2005a).

Vitamin A has a number of biologic actions. In the eye, it is required for prevention of xerophthalmia and phototransduction. Vitamin A is crucial to cellular differentiation and integrity (Pazirandeh and Burns, 2005a; Jacobs and Wood, 2003c).

Vitamin A deficiency is rarely seen in the United States and other industrialized countries. However, it is still the third most common nutritional deficiency in the world. In the elderly, diminished physical activity reduces intake and concentrations may drop, but there is little evidence to support the need for supplementation, and, indeed, toxicity is manifested more readily with age (Ross, 2000; Pazirandeh and Burns, 2005a; Higdon, 2002; Cantorna *et al.*, 1995, 1996). Deficiency can result in

- night blindness, complete blindness, and xerophthalmia;
- Bitot's spots (areas of abnormal squamous cell proliferation and keratinization of the conjunctiva), which can be seen in young children;
- corneal perforation, keratomalacia, and punctate keratopathy, which have been observed in early childhood development;
- nonspecific dermatological problems, such as hyperkeratosis, phrynoderma (follicular hyperkeratosis), and the

destruction of hair follicles and their replacement with mucous-secreting glands;
- impairment of the humoral and cell-mediated immune system via direct and indirect effects on the phagocytes and T cells.

In a majority of cases, vitamin A toxicity occurs because of the ingestion of large amounts of synthetic vitamin A, about 10 times higher than the Daily Value, or about 50 000 IU. In the elderly, diminished physical activity reduces intake and concentrations may drop, but there is little evidence to support the need for supplementation, and indeed, toxicity is manifested more readily with age. Hypervitaminosis can occur both acutely and after chronic ingestion. Symptoms of toxicity include dry skin, nausea, headache, fatigue, irritability, ataxia, alopecia, hyperlipidemia, hepatotoxicity, bone and muscle pain, and visual impairments (Larry, 1995; Pazirandeh and Burns, 2005a; Jacobs and Wood, 2003c; Biesalski, 1989).

Epidemiologic studies of dietary vitamin A on possible cancer chemoprevention appear to primarily represent the effect of β-carotene. Studies of relationships between cancer and vitamin A and carotenoids have provided mixed results. Observational data and clinical trial data have not been consistent.

Two large, randomized, placebo-controlled trials assessed the risk of lung cancer among male smokers or asbestos workers receiving β-carotene supplements. The risk of lung cancer was significantly increased among men receiving supplements. In the α-Tocopherol, β-Carotene (ATBC) Cancer Prevention Study, there was an increase in both prostate cancer incidence and mortality among subjects randomized to β-carotene. The excess risk appears to resolve over time once supplements are stopped (The α-Tocopherol, β-Carotene Cancer Prevention Study Group, 1994; Omenn *et al.*, 1996; Virtamo *et al.*, 2003).

There have been no clinical trials of vitamin A intake and breast cancer. However, observational studies of vitamin A intake and breast cancer have yielded varying results. In a study by Kushi *et al.*, no association between dietary vitamin A and breast cancer was observed (Kushi *et al.*, 1996). In contrast, recent data from the Nurses' Health Study suggest that premenopausal women, particularly those with a positive family history, have significant reductions in breast cancer risk with increasing dietary α-carotene and β-carotene, lutein /zeaxanthin, and total vitamin A (Hunter *et al.*, 1993; Zhang *et al.*, 1999a) Data from the Polyp Prevention Study Group did not show a reduction in adenoma risk in patients randomized to receive either β-carotene, vitamin C and E or both β-carotene and vitamins C and E (Greenberg *et al.*, 1994).

Vitamin A and β-carotene supplements have shown no benefit for primary or secondary prevention of coronary heart disease (CHD) in randomized trials and have been associated with potential harm (Vivekananthan *et al.*, 2003). There is consistent evidence from observational studies that vitamin A intake within the range taken by many people in western societies, is a risk factor for osteopenia and fractures. The Physicians Health Study found that 12 years of β-carotene supplements had no effect overall on the risk of cataract formation, but appeared to significantly decrease the risk among current smokers (Melhus *et al.*, 1998; Feskanich *et al.*, 2002; Michaelsson *et al.*, 2003; Christen *et al.*, 2003).

On the basis of current clinical data and the lack of clinical efficacy with respect to cancer prevention, along with its possible adverse effects, the use of vitamin A and β-carotene supplement use should be discouraged.

Vitamin E

Vitamin E occurs in eight natural forms as tocopherols (α, β, γ, and δ) and tocotrienols (α, β, γ, and δ), all of which possess potent antioxidant properties. Vitamin E was originally found to affect reproduction in rats and was given the name tocopherol derived from the Greek word of *toc* (child) and *phero* (to bring forth) to describe its role as an essential dietary substance in normal fetal and childhood development (Machlin, 1991; Mason, 1980).

Vitamin E absorption depends upon the breakdown of fatty acids and their uptake via enterocytes to the enterohepatic circulation. The synthesis of chylomicrons are required for transport of vitamin E via the lymphatic system to the liver. Within hepatocytes chylomicron, remnants are broken down by lysosomes, and RRR-α-tocopherol is preferentially secreted into the bloodstream, packaged within very low density lipoproteins (VLDL) molecules. The transport protein for α-tocopherol is named *α-tocopherol transfer protein* (α-TTP) (Traber *et al.*, 1990; Cohn *et al.*, 1988a,b).

Vitamin E works as a free-radical scavenger and antioxidant. α-tocopherol is the biologically active form of vitamin E. It protects polyunsaturated fatty acids (PUFA), a major structural component of the cell membranes, from peroxidation. Primary sources of vitamin E are vegetable oil, wheat germ, leafy vegetables, egg yolk, margarine, and legumes (Olson, 1998; Burton *et al.*, 1983). Vitamin E deficiency can be measured by examining serum or tissue α-tocopherol levels (Reuben *et al.*, 1995).

Deficiency of vitamin E is uncommon in humans except in unusual circumstances. In the elderly, conditions resulting in fat malabsorption can cause vitamin E deficiency. The effects of deficiency are widespread throughout the body and include the following (Pazirandeh and Burns, 2005a; Perrig *et al.*, 1997; Johnson, 2002b):

- Neuronal degeneration resulting in spinocerebellar ataxia, decreased deep tendon reflexes or areflexia, peripheral neuropathy, and posterior column destruction with impairment of proprioception and vibratory sense. This can result in gait disturbance, which is a basic manifestation of vitamin E deficiency.
- Degenerative myopathy.
- Ocular impairment such as retinopathy and extraocular muscle paresis.
- Brown bowel syndrome, a result of lipofuscin deposition and oxidative damage.
- Red blood cell life span reduction.

The effects of long-term supplementation of vitamin E are unclear. Some studies caution against the use of vitamin E in patients with an increased propensity to bleeding or those taking oral anticoagulants. Impaired absorption of fat-soluble vitamins A and K with large vitamin E supplements have been seen in animal models. Necrotizing enterocolitis is seen in infants supplemented with high doses of vitamin E. It may impair the hematologic response to iron in children with iron-deficiency anemia (Pazirandeh and Burns, 2005a; Hathcock, 1997; Finer *et al.*, 1984).

There have been several studies examining the role of vitamin E in cancer prevention. The ATBC Cancer Prevention Study observed a 32% decrease in prostate cancer incidence and 41% decrease in prostate cancer mortality among men receiving α-tocopherol compared with placebo (Hennekens *et al.*, 1996) In contrast, observational data from the Health Professionals Follow-up Study showed no association between vitamin E supplement use and all prostate cancers. However, it showed a decrease in risk of metastatic or fatal prostate cancer among smokers who consumed at least 100 IU of supplemental vitamin E daily (Chan *et al.*, 1999). A second report from the ATBC study showed a significant 19% reduction in lung cancer risk associated with higher serum vitamin E levels. The reduction in risk was greatest among men younger than 60 years and among patients with fewer years of cumulative smoking exposure (Woodson *et al.*, 1999).

Vitamin E supplementation has shown no benefit in both primary and secondary prevention of CHD (Vivekananthan *et al.*, 2003). In the ATBC study, daily supplementation with vitamin E had no overall effect on stroke risk. However, a subgroup analysis suggested that vitamin E may increase the risk for subarachnoid hemorrhage and decrease the risk for ischemic stroke, particularly in men with hypertension (Leppala *et al.*, 2000). In the Heart Outcomes Prevention Evaluation (HOPE) trial, daily supplementation with vitamin E had no effect on progression of carotid intimal medial thickness (Lonn *et al.*, 2001). The HOPE-TOO trial (ongoing outcomes) showed that vitamin E at 400 IU was associated with an increase in heart failure (Lonn *et al.*, 2005). The Health Professionals Follow-up Study showed no association between supplemental vitamin E and stroke risk (Ascherio *et al.*, 1999)

Data from observational studies have suggested that increased dietary intake of vitamin E may have a protective effect against the development of Alzheimer's disease. A longitudinal cohort study found that both vitamin E and C supplementation protected against the development of vascular dementia and improved cognitive function late in life (Masaki *et al.*, 2000; Morris *et al.*, 2002; Engelhart *et al.*, 2002). In a randomized trial of selegiline, vitamin E, both, or placebo among patients with Alzheimer's disease showed that both selegiline and vitamin E were independently associated with significant reductions in several outcomes, including functional decline (Sano *et al.*, 1997)

There have been several studies reporting that vitamin E supplementation improves the immune response. However, randomized, placebo-controlled studies have found no reduction in the incidence of respiratory infections in institutionalized or noninstitutionalized elderly patients receiving daily vitamin E supplements (Meydani *et al.*, 1997; Serafini, 2000; Girodon *et al.*, 1999; Meydani *et al.*, 2004; Graat *et al.*, 2002).

A meta-analysis of vitamin E supplementation that did not stratify trials by dose of vitamin E found no significant effect of supplementation on all-cause mortality (Vivekananthan *et al.*, 2003) However, a recent meta-analysis that examined the dose–response relationship between vitamin E and overall mortality in a total of 19 randomized clinical trials found that vitamin E supplementation with a dose $\geq$400 IU/day was associated with a significantly increased risk of all-cause mortality (Miller *et al.*, 2005).

Current evidence for vitamin E supplementation is inconclusive. Data at present suggest that high-dose vitamin E ($\geq$400 IU/day) increases all-cause mortality. Also, individuals taking anticoagulants should be particularly advised against high doses of vitamin E because of the synergistic action of vitamin E with these drugs.

Selenium

Selenium, a trace element, is a component of several enzymes. These include glutathione peroxidase and superoxide dismutase. Both these enzymes are important in the prevention of oxidative and free-radical damage of various cell structures. Evidence suggests that the antioxidant protection conveyed by selenium operates in conjunction with vitamin E because deficiency of one seems to enhance damage induced by a deficiency of the other (Mason, 2004). Selenium is incorporated as selenocysteine at the active sites of multiple selenoproteins. Selenoproteins are also important for thyroid function, muscle metabolism, and sperm function, as well as immune function (McClain, 2002).

Dietary sources include vegetables, grains, brazil nuts, seafoods, and organ meats. The amount of Se in plant food is determined by the amount present in the soil. The mechanism of absorption of Se from the gut is unknown. Dietary Se has a high bioavailability and its absorption from the gut is unregulated (Massey, 2002; Pazirandeh and Burns, 2005b).

The risk of Se deficiency seems to increase in proportion to age. Also, low levels have been documented in type II diabetes (McClain, 2002; Savarino *et al.*, 2001). In China, Keshan disease is seen in areas where the soil is poor in selenium. It is an endemic cardiomyopathy which improves with selenium supplementation. Se deficiency has been reported in individuals on chronic total parenteral nutrition (TPN) (van Rij *et al.*, 1979). Severe deficiency of Se manifests as

- cardiomyopathy
- myopathy

Toxicity can result from excessive intake. The most common manifestations are hair and nail loss. Other manifestations include nausea, emesis, tooth lesions, mental status

changes and peripheral neuropathy (Yang *et al.*, 1983; *Morbidity and Mortality Weekly Report*, 1984).

The potential protective effect of selenium status on the risk of developing cancer has been examined in animal and epidemiologic studies. Low levels of dietary selenium are associated with a greater risk of prostate, esophageal, colon, and antral gastric cancers (Massey, 2002; Clark *et al.*, 1991; Mark *et al.*, 1999; Schulman *et al.*, 2000). There have been studies evaluating the effect of selenium on cancer related chemotherapy. A study assessing the *in vitro* effects of Se on chemotherapy revealed that the addition of selenium enhanced drug-mediated cancer cell death. In another study, the addition of dietary selenium at the beginning of chemotherapy prevented the development of resistance to cisplatin (Vadgamma *et al.*, 2000; Caffrey and Frenkel, 2000).

The antioxidant properties of selenium have been linked to a lower incidence of cardiovascular disease in humans. However, the therapeutic benefit of selenium administration in the prevention and treatment of cardiovascular diseases still remains controversial (Salvini *et al.*, 1995; Neve, 1996).

Se deficiency has been associated with impaired cell-mediated immunity and enhanced activity of natural killer cells (Spallholz *et al.*, 1990; Kiremidjian-Schumacher *et al.*, 1994). Studies done on the coxsackievirus and influenza virus by Beck *et al.* (1994, 2001) have shown that selenium prevented the genomic conversion of a nonvirulent strain into a virulent strain that occurred in the presence of selenium deficiency in mice. These effects of Se may have considerable implications on the elderly population, especially in the institutional setting.

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin widely found in citrus fruits, raw leafy vegetables, strawberries, melons, tomatoes, broccoli, and peppers. Humans cannot synthesize vitamin C, and a deficiency results in scurvy. The amount in food consumed, however, depends on the season of the year, the transportation time to the store, the shelf time before purchase, the form of storage, and the method of cooking. Boiling can cause a 50–80% loss of vitamin C. Cooking with minimal water or microwaving food reduces losses (Thomas, 2004; Johnson, 2002b).

Vitamin C is absorbed in the distal small intestine through an energy dependent process. Blood concentrations of ascorbic acid are regulated by renal excretion. The greatest concentrations of ascorbic acid are found in the pituitary, adrenal, brain, leukocytes, and the eye. Its absorption does not seem to be affected by age. The bioavailability of vitamin C is inversely related to the amount ingested as well as the form. Sustained release tablets allow higher absorption than standard pills. It is a reversible biologic reductant, and provides reducing equivalents for a number of biochemical reactions involving iron and copper. It therefore functions as a cofactor, enzyme complement, cosubstrate, or a strong antioxidant in a variety of reactions and metabolic processes (Larry, 1995; Jacob, 2000; Schorah, 1992; Kallner *et al.*, 1985; Garry *et al.*, 1987).

Vitamin C has multiple functions. It is an antioxidant and reduces harmful free radicals. It is purported to be an immune enhancer and is known to be crucial to collagen synthesis and to norepinephrine synthesis. The conversion of iron from the ferric (+3) to the ferrous (+2) form requires vitamin C. Without this conversion, methemoglobin could not be converted to hemoglobin, and iron could not be absorbed in the duodenum. Vitamin C is also involved in the reduction of nitrates, a function that possibly is involved in stomach cancer. Vitamin C has a role in prostaglandin and prostacyclin metabolism. It may be capable of attenuating the inflammatory response or even sepsis syndrome (Johnson, 2002b; Willett and Stampfer, 2001; Levine *et al.*, 1999; Pazirandeh *et al.*, 2005).

Vitamin C deficiency is common in many frail elderly populations. Because vitamin C is supplied only by diet, deficiency is caused by insufficient dietary intake (Larry, 1995; Morgan, 1987; Mandal and Ray 1987; McClean *et al.*, 1976). Deficiency primarily affects the musculoskeletal and hematopoietic systems. Deficiency results in the following (Johnson, 2002b):

- Reduced collagen cross-linking and therefore decreased collagen tensile strength, leading to impaired wound healing, and to weakened blood vessels.
- Hemostasis abnormalities occur, producing painful subperiosteal hemorrhages, hemarthrosis, hemorrhagic perifolliculitis, gingival bleeding, ecchymoses, petechiae, and nail bed splinter hemorrhages. Some of these manifestations are common in elderly persons and are usually attributed to age-related physiologic changes and not to vitamin deficiency.
- Structurally abnormal collagen that produces structurally abnormal osteoid, which produces structurally abnormal bone;
- Scurvy: Scurvy is the clinical syndrome produced with deficiency and develops after intake of less than 10 mg/day for 3 to 6 months. Scurvy includes the previously mentioned physical findings plus the development of corkscrew hairs, glossitis, gingival hyperplasia and bleeding, and poor dentition caused by periodontitis and loss of teeth. Iron-deficiency anemia can also occur. Terminal features include icteris, edema, hypotension, and convulsions.

There have been some reports of excessive use of vitamin C as risk factor for calcium oxalate nephrolithiasis. However, a prospective epidemiologic study demonstrated that consumption of high doses of vitamin C lowered the relative risk of calcium oxalate stones compared to 250 mg or less of vitamin C per day. Ingestion of large quantities of vitamin C has been rarely associated with fatal cardiac arrhythmias in patients with iron overload, presumably due to oxidative injury. Vitamin C toxicity has been associated with diarrhea and abdominal bloating. High doses are also associated with false negative guaiac tests and they also alter the results of

glucose measurements (Pazirandeh *et al.*, 2005; Urivetzky *et al.*, 1992; McLaran *et al.*, 1982; Block, 1991).

A large, randomized trial of vitamin C for secondary prevention of CHD found no benefit of supplementation with vitamin C. The Health Professionals Follow-up Study showed no association between supplemental vitamin C and stroke risk. Prospective data from the Nurses' Health Study showed a 45% reduction in the risk of cataract requiring extraction in women using vitamin C supplements for at least 10 years. In contrast, a randomized, placebo-controlled study of high-dose supplementation with vitamins C and E and β-carotene found no reduction in the 7-year risk of development or progression of age-related lens opacities with vitamin C supplementation (Vivekananthan *et al.*, 2003; Ascherio *et al.*, 1999; Hankinson *et al.*, 1992; Age-Related Eye Disease Study Research Group, 2001).

Riboflavin

Riboflavin or vitamin B2 is an important component of the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). It is involved in an array of biochemical reactions. It is important for oxidative phosphorylation, ATP production, and the production of reduced glutathione, which is an antioxidant. Vitamin B2 has been implicated in a signal transduction role for programed cell death and regulation of a number of other important intracellular pathways. Dietary sources include dairy products, green leafy vegetables, whole and enriched grains, meats, liver, poultry, and fish. It is not destroyed by heat, oxidation, or acid but is susceptible to ultraviolet light and alkalis (Johnson, 2002b; Jacobs and Wood, 2003d).

Riboflavin is released by proteolysis from the ingested food and undergoes passive absorption from the intestinal lumen. It then enters the hepatic cells and undergoes conversion to FAD and FMN. Like other B vitamins in this class, stores are minimal, and regulated replacement is necessary through food or supplements.

Vitamin B2 deficiency is regarded as the most common vitamin deficiency in the United States, it is usually seen in conjunction with other vitamin B deficiencies. There is some evidence that the requirements for riboflavin may increase with aging and that the glutathione reductase activity declines with aging. Plasma riboflavin concentrations tend to reflect recent dietary intake. Erythrocyte glutathione reductase assay is a better test for riboflavin deficiency; it is however not valid in individuals with glucose 6-phosphate dehydrogenase deficiency (*Vitamin Deficiency*, 2004; Jacobs and Wood, 2003d; Mason, 2004).

Deficiency may be secondary to inadequate dietary intake or a result of chronic diarrhea, alcoholism, or liver disease. Deficiency may manifest as (Johnson, 2002b; Jacobs and Wood, 2003d; Mason, 2004)

- Cheilosis
- Magenta-colored glossitis
- Inflammation of the oral mucosa
- Seborrheic dermatitis
- Normocytic normochromic anemia
- Corneal revascularization.

Vitamin B2 supplementation helps only in the prevention of deficiency. A small randomized control trial has shown some benefit of supplementation with a very large dose in the prevention of migraine (Johnson, 2002b; Schoenen *et al.*, 1998).

VITAMIN D

Vitamin D, or calciferol, is a generic term, and refers to a group of lipid soluble compounds with a four-ringed cholesterol backbone. Vitamin D is not a true vitamin, because humans are able to synthesize it with adequate sunlight exposure. By photoconversion, 7-dehydrocholesterol becomes previtamin D3, which is metabolized in the liver to 25-hydroxyvitamin D3, the major circulating form of vitamin D. In the kidneys, this is converted to two metabolites, the more active one being 1,25-dihydroxyvitamin D3. It is derived primarily via synthesis in the skin. Dietary sources include fortified milk, milk products, oily fish, egg yolks, and fortified foods (Thomas, 2004; Pazirandeh and Burns, 2005a; Johnson, 2002b).

Vitamin D is absorbed in the form of micelles by the intestinal epithelium to form chylomicrons. Chylomicrons enter the liver via the portal circulation where vitamin D undergoes a hydroxylation process by 25-vitamin-D hydroxylase to form 25-hydroxy-vitamin-D (calcidiol). Further hydroxylation of 25-hydroxy-vitamin-D to 1,25-dihydroxy-vitamin D (1,25(OH)2-vitamin D or calcitriol) occurs in the mitochondria of the proximal tubules of the kidney. Vitamin D from any source and in either form is absorbed into circulation and bound to vitamin D-binding protein. Calcitriol, the biologically active form, has a short half-life of 4–6 hours and thus does not accurately reflect body stores, whereas 25OHD (calcidiol) has a longer half-life of 3 weeks. Thus, 25OHD is more widely used to measure vitamin D status. Laboratory measurements reflect both vitamin D2 and vitamin D3 status. Deficiency is defined as a 25OHD level below 15 mg dl^{-1} (Pazirandeh and Burns, 2005a; Johnson, 2002b; Gloth and Tobin, 1995; Thomas *et al.*, 1998; Gloth *et al.*, 1995).

Increased age is a risk factor for vitamin D deficiency. Several studies have shown that the levels of 1,25dihydroxyvitamin D are lower in older people (Dandona *et al.*, 1986; Russell, 1992). 25-hydroxyvitamin D has been shown to decline with age in a longitudinal study by Perry *et al.* (1999). Factors resulting in low circulating levels in the elderly include:

- inadequate intake of vitamin D due to decreased intake of dairy products in their diets;
- decreased ability to form previtamin D3 in the skin upon ultraviolet light exposure secondary to decreased amounts

of 7-dehydrocholesterol levels in the skin with advancing age;
- decreased synthesis of 1,25-dihydroxyvitamin D by the kidney;
- medications interfering with vitamin D metabolism.

Deficiency of vitamin D can result in the following biochemical and physical manifestations (Johnson, 2002b):

- low calcium and low phosphorus levels and elevated alkaline phosphatase levels;
- secondary hyperparathyroidism;
- osteomalacia;
- fractures;
- neuromuscular irritability;
- proximal myopathy, deep proximal musculoskeletal pain, neuropathy, and hyperesthesia.

Vitamin D excess is associated with hypercalcemia, hypercalciuria, confusion, polyuria, polydipsia, anorexia, vomiting, muscle weakness, and bone demineralization with pain (Pazirandeh and Burns, 2005a).

Vitamin D supplementation results in a decreased bone loss and fracture rate in older men and women. In a study done by Dawson-Hughes *et al.*, vitamin D supplementation in healthy postmenopausal women was associated with a net gain in bone mineral density during the summer-fall period with a significantly lower spinal loss compared to the placebo group during the winter-spring period. In a randomized, controlled trial vitamin D supplementation with calcium, reduced bone loss in several sites and decreased the incidence of nonvertebral fractures by one-half after 3 years. In another study, vitamin D supplementation decreased the risk of falls in the elderly, possibly secondary to improvements in muscle strength (Gloth and Tobin, 1995; Gloth *et al.*, 1995; Dawson-Hughes *et al.*, 1997; Bischoff-Ferrari *et al.*, 2004; Dawson-Hughes *et al.*, 1991). Vitamin D improves muscle strength only in persons with low circulating levels.

The daily intake of vitamin D in older adults should be at least 800 IU with at least 1200 mg of elemental calcium in the diet or as a supplement (Pazirandeh and Burns, 2005a). This is particularly important in the elderly individuals who are unable to expose themselves to sunlight since a large part of the daily requirements are met by skin synthesis.

VITAMIN K

Vitamin K occurs in two naturally occurring forms, phylloquinone found in plants and menaquinones synthesized by the GI flora. Vitamin K produced by the gut flora is thought to provide upto 50% of the requirement in humans. Vitamin K is found in various food sources which include green leafy vegetables, vegetable oils, and liver (Johnson, 2002b; Jacobs and Wood, 2004).

Vitamin K is a fat-soluble vitamin absorbed by the intestinal epithelium in the form of micelles. It is then incorporated in chylomicrons and enters the liver via the portal circulation. Within the body, the stores are relatively small. They are mostly hepatic; however, the trabecular and cortical bone also contain substantial concentrations (Pazirandeh and Burns, 2005a; Jacobs and Wood, 2004).

Vitamin K is an important cofactor for the endoplasmic enzyme γ-glutamylcarboxylase. This enzyme acts as a catalyst for the carboxylation of glutamate to γ-carboxyglutamate. This is an important step for the activation of several coagulation factors within the hepatic cells. It thus plays a central role in blood coagulation, by activating factors II, VII, IX, and X. It is also needed for the activity of the natural anticoagulants proteins C and S (Pazirandeh and Burns, 2005a; Johnson, 2002b; Jacobs and Wood, 2004).

Deficiency of vitamin K in healthy adults is uncommon because of the widespread distribution of the vitamin in nature, its recycling within the cells and its synthesis by the GI flora. Deficiency can be seen in the following conditions (Pazirandeh and Burns, 2005a; Johnson, 2002b; Jacobs and Wood, 2004; Shearer *et al.*, 1988):

- prolonged antibiotic therapy, which disrupts the GI flora;
- parenteral nutrition;
- disorders associated with fat malabsorption;
- medications such as anticonvulsants, high doses of vitamins A and E, warfarin;
- starvation.

Deficiency results in prolongation of the prothrombin time and partial thromboplastin time, signs and symptoms of bleeding such as easy bruisability, splinter hemorrhages, mucosal bleeding, melena, and hematuria (Pazirandeh and Burns, 2005a; Olson, 1998; Johnson, 2002b; Jacobs and Wood, 2004; Shearer *et al.*, 1988). Studies have shown an increase in the incidence of hip fractures in the elderly. There have been studies showing a decrease in bone mineral density in hemiplegic limbs of vitamin D deficit stroke patients (Sato *et al.*, 1999; Booth *et al.*, 2000).

Toxicity associated with excess doses is rare, it can however cause hemolytic anemia and jaundice in infants. Doses greater than 150 μg/day from food supplements can interfere with anticoagulation in patients on warfarin.

FOLATE

Folates represent a group of related pterin compounds. More than 35 forms of the vitamin are found naturally. The term folic acid is derived from the latin word *folium* which means leaf. The pharmacologic form is folic acid; it is more bioavailable and does not exist in nature in this form. The various dietary sources include green leafy vegetables, fresh fruits, yeast, liver, and other organ meats. Folate in foods is destroyed by excessive cooking, as much as 95% may be destroyed (Larry, 1995; Johnson, 2002b; Stabler and Allen, 2004).

Folate is required for the transfer of single carbon groups; it is essential in the *de novo* synthesis of nucleotides and metabolism of several amino acids. It is an important component for the regeneration of the "universal" methyl donor, *S*-adenosylmethionine. In the body, homocysteine is remethylated into methionine. The process of remethylation requires folate and cobalamin (vitamin B12). In the presence of folate deficiency, homocysteine levels are elevated (Johnson, 2002b; Stabler and Allen, 2004).

The luminal enzymes convert the polyglutamate forms of folate present in the dietary sources to the monoglutamate and diglutamate forms. Folate is then absorbed from the lumen of the small intestine by both active and passive absorption. In the plasma, folate is present as 5-methyltetrahydrofolate, it is bound loosely to albumin, from which it is readily taken up by the high-affinity folate receptors present on cells throughout the body. Folates undergo enterohepatic circulation and are thus reabsorbed from the gut; they also undergo urinary excretion (Johnson, 2002b; Stabler and Allen, 2004).

Studies reveal that folate deficiency may range from 2.5–34% among the elderly persons. Folate deficiency occurs within a few days of insufficient intake, however, clinical signs of deficiency develop after approximately 4 months of decreased intake. Folate deficiency can be determined on the basis of decreased serum folate levels; however, red cell folate levels may be better indicators if there has been a recent dietary change. Factors responsible for deficiency in the elderly include (*Vitamin Deficiency*, 2004; Larry, 1995; Johnson, 2002b; Stabler and Allen, 2004):

- inflammatory diseases of the GI tract;
- atrophic gastritis;
- part of generalized malnutrition;
- poor oral intake;
- excessive alcohol intake;
- smoking;
- medications such as cotrimazole, methotrexate, triamterene, phenobarbital, and phenytoin.

Folate deficiency can result in megaloblastic anemia, leukopenia, thrombocytopenia, anorexia, fatigue, delirium, diarrhea, glossitis, and hyperhomocysteinemia.

Current evidence suggests that high dietary intake of folate is associated with a decreased risk of developing colorectal cancer in both men and women. Data from the Nurses' Health Study reveal a protective effect of high dietary intake of folate on the development of breast cancer. There was a normalization in the risk of breast cancer associated with concurrent alcohol use (Zhang *et al.*, 1999b; Giovannucci *et al.*, 1998, 1993).

Folate deficiency is associated with hyperhomocysteinemia. Homocysteine is prothrombotic and atherogenic. It causes vascular injury characterized by thickened vascular intima, disruption of the elastic lamina, smooth muscle hypertrophy, platelet aggregation, and the formation of platelet-rich occlusive thrombi (Harker *et al.*, 1974; Tsai *et al.*, 1994). In a multicenter case-control study done by Robinson *et al.* (1998), lower levels of folate and vitamin B6 conferred an increased risk of atherosclerosis. The increased risk was explained partly by an elevated homocysteine level. In the Health Professional Follow-up Study, increased folate intake was associated with a decreased risk of ischemic stroke in men (He *et al.*, 2004). In another study, an inverse association between a high-folate diet and coronary heart disease was found to be strongest among women who consumed up to one alcoholic beverage per day (Rimm *et al.*, 1998).

Data also suggest that there may be a correlation of high homocysteine levels with osteoporotic fractures and dementia (Seshadri *et al.*, 2002; Kalmijn *et al.*, 1999; van Meurs *et al.*, 2004).

VITAMIN B12

Vitamin B12 is a group of cobalamin compounds that have a corrin ring with a cobalt atom at the center. The corrin ring is connected through an aminopropanol bridge to a ribonucleotide. Dietary sources of vitamin B12 include meat and dairy products. It is an important cofactor for the enzymes, methionine synthase, and methylmalonyl-coenzyme A (CoA) mutase. It is essential for the synthesis of succinyl coenzyme A (CoA) from methylmalonyl-CoA. Vitamin B12 serves as a cofactor in the conversion of 5-methylene THF (tetrahydrofolate) to THF (the active form of folate); during this reaction, the methyl group is donated to cobalamin, forming methylcobalamin. Methylcobalamin then donates its methyl group to homocysteine to form methionine. The synthesis of methionine is essential for purine and pyrimidine synthesis, methylation reactions, and the intracellular retention of folates. A deficiency of cobalamin leads to an increase in homocysteine and methylmalonic acid (Stabler and Allen, 2004; Snow, 1999).

Cobalamin is released from the food by the gastric enzymes and bound to R-binding proteins. Further, enzymatic degradation occurs in the small intestine and it then gets bound to the intrinsic factor (IF). The B12-IF complex is then absorbed in the ileum and stored in the liver. It is transported through the body attached to the protein transcobalamin II. Vitamin B12 undergoes enterohepatic circulation and most of it gets reabsorbed from the bile (Larry, 1995).

The prevalence of B12 deficiency ranges from 4 to 43%. The levels of vitamin B12 have been found to decline at the rate of $3.4\,\text{pmol}\,l^{-1}$ annually. Vitamin B12 deficiency may be seen in the elderly population as documented by elevated methylmalonic acid with or without elevated total homocysteine concentrations in combination with low or low-normal vitamin B12 concentrations. Owing to the long half-life and hepatic stores of vitamin B12, deficiency secondary to inadequate intakes takes 2–6 years to develop. Deficiency is seen in individuals with atrophic gastritis, total gastrectomy, pernicious anemia (may be seen in upto 5% of those aged 80 and above in some populations), terminal ileal resection, bacterial overgrowth of the bowel, drugs use such as prolonged use of H-2 antagonists, colchicines

and aminosalicylic acid, and practice of strict vegetarianism (*Vitamin Deficiency*, 2004; Larry, 1995; Johnson, 2002b).

Deficiency can result in (Johnson, 2002b; Stabler and Allen, 2004):

- increased homocysteine levels;
- increased methylmalonic acid levels;
- megaloblastic anemia;
- neurologic syndrome manifested as

1. peripheral neuropathy with paresthesias and decreased vibratory sensation, which may progress to ataxia, weakness, and an inability to walk. It affects both the dorsal and lateral spinal cord columns and is termed *subacute combined degeneration*;
2. impaired mentation, memory loss, and depression. This syndrome may occur without evidence of anemia and may not be associated with macrocytic erythrocytes.

Current evidence suggests an increased risk of cardiovascular disease associated with elevated homocysteine levels. Vitamins B12, folate, and vitamin B6 are needed for homocysteine metabolism and deficiency results in elevated levels of homocysteine. Although studies have shown a decreased risk of cardiovascular disease with high levels of folate and vitamin B6, this has not been shown with B12 supplementation (Thomas, 2004; Eikelbloom *et al.*, 1999).

In a study by Lindenbaum *et al.*, neuropsychiatric disorders due to cobalamin deficiency were seen in the absence of anemia or an elevated mean cell volume. They recommend measuring of serum methylmalonic acid and total homocysteine, both before and after treatment for diagnosis in these patients (Lindenbaum *et al.*, 1988).

Vitamin B12 supplementation should be considered in the elderly and at-risk individuals.

VITAMIN B6

Vitamin B6 comprises of the various derivatives of pyridine, which include pyridoxine, pyridoxal, and pyridoxamine. As a coenzyme, B6 is involved in many transamination reactions. It is required for the synthesis of niacin from tryptophan. Vitamin B6 is involved in the synthesis of several neurotransmitters (γ-aminobututyric acid (GABA), serotonin, and norepinephrine), and δ-aminolevulinic acid (and therefore in heme synthesis). Dietary sources include meats, whole grains, vegetables, and nuts (Johnson, 2002b; Mason, 2004; Jacobs and Wood, 2003e).

Pyridoxine-5′-β-D-glucoside is the major, naturally occurring form of vitamin B6. It undergoes hydrolysis in the intestine and is absorbed by diffusion from the lumen of the small intestine. Vitamin B6 is not stored, and cannot be synthesized. Dietary intake thus provides the metabolic requirements (Jacobs and Wood, 2003e).

Dietary deficiency is rare; however, there is evidence that the requirements are increased in the elderly. Deficiency may result from alcoholism, malabsorption, and high-energy states such as dialysis. Medications such as isoniazid, hydralazine, cycloserine, penicillamine, ethanol, and theophylline act as pyridoxine antagonists (Russell, 1992; Johnson, 2002b).

Vitamin B6 deficiency usually occurs in association with deficiencies of other water-soluble vitamins. Deficiency can be diagnosed by assessing plasma or erythrocyte pyridoxal-5-phosphate (PLP) levels. Manifestations of deficiency include (Johnson, 2002b; Mason, 2004; Jacobs and Wood, 2003e)

- stomatitis, angular cheilosis, glossitis;
- irritability, depression, and confusion, occurring in moderate to severe depletion;
- normochromic, normocytic anemia that has been reported in severe deficiency;
- abnormal electroencephalograms, convulsions, and peripheral neuropathy.

Long-term use with doses exceeding 200 mg/day (in adults) may cause peripheral neuropathies and photosensitivity (Mason, 2004).

Elevated homocysteine levels are associated with an increased risk of cardiovascular disease. Vitamin B6 deficiency is associated with elevated homocysteine levels; low levels of vitamin B6 may be independently associated with CHD (9; Eikelbloom *et al.*, 1999; Folsom *et al.*, 1998). In a case-control study, lower levels of folate and vitamin B6 were associated with an increased risk of atherosclerosis (Robinson *et al.*, 1998). The Nurses' Health Study found an inverse association between higher dietary intakes of folate and vitamin B6 and CHD (Rimm *et al.*, 1998) There is evidence of a lower risk of breast cancer in women with higher plasma levels of vitamin B6 (Zhang *et al.*, 2003). In another study, vitamin B6 supplementation in the elderly resulted in improvement of long-term memory by improving storage of information (Deijen *et al.*, 1992).

ZINC

Zinc is a bivalent trace metal that plays a critical role in protein synthesis. It also serves as a cofactor, catalyst or a part of several enzymes. It is involved in the synthesis of nucleic acids and gene regulation. Zinc is required for the maintenance of genetic stability and gene expression and for controlling differentiation, proliferation, maturation, and programed cell death. It is essential for the maintenance of plasma membrane integrity. It may have antioxidant and antiatherogenic properties (Jacobs and Wood, 2003a; Powell, 2000; Hennig *et al.*, 1996).

Dietary sources of zinc are red meat, seafood, fresh fruit, vegetables, and dairy products. During the process of digestion, zinc is released from these dietary sources. It is primarily absorbed in the jejunum. Its absorption is inhibited by phytates present in many staple foods. Metallothionein, present in the gut enterocyte is responsible for the homeostatic control of zinc absorption. Ninety percent of the total

body zinc stores are in bone and skeletal muscle. It undergoes enterohepatic circulation. Excretion is mainly fecal, with small amounts being excreted in the urine (McClain, 2002; Pazirandeh and Burns, 2005b; Jacobs and Wood, 2003a).

Data at present are insufficient to determine the frequency of zinc deficiency in the elderly. Deficiency may be seen with poor dietary intake, inflammatory processes, malabsorption, chronic diarrhea, sickle-cell anemia, diabetes, cirrhosis of the liver, thiazide diuretics, lung cancer, following thermal injury, in drug addiction, and renal injury (Hennig *et al.*, 1996; Sandstead *et al.*, 1982). Low zinc levels seen in inflammatory conditions result from redistribution of zinc; an action mediated by cytokines. Serum and plasma levels of zinc do not correlate with tissue levels and are not reliable indicators (McClain, 2002; Pazirandeh and Burns, 2005b; Jacobs and Wood, 2003a; Hennig *et al.*, 1996; Sandstead *et al.*, 1982). Manifestations of deficiency in the elderly may be subtle; these include the following:

- Impaired immune response. Aging is associated with an altered T-cell response. Zinc has been identified as a potent T-lymphocyte mitogen. Studies have revealed a beneficial effect of zinc supplementation of immune function (Bogden *et al.*, 1987; Fraker *et al.*, 2000; High, 2001; Williams and Loer, 1973; Duchateau *et al.*, 1981).
- Anorexia resulting from impaired taste and smell. Several mechanisms have been hypothesized to result in anorexia; however, the relationship of zinc status to anorexia still remains unclear (Shay and Mangian, 2000).
- Confusion, irritability, and restlessness. Acrodermatitis enteropathica (AE) is an autosomal recessive inherited disease. The manifestations of AE are thought to occur secondary to zinc deficiency. Confusion and apathy in these children responds to zinc supplementation. Also, zinc deficiency induced in humans may be associated with irritability or apathy, which is reversed with zinc supplementation. However, data on the role of zinc deficiency on mental status in the elderly are limited (McClain, 2002; McClain *et al.*, 1985).
- Impaired wound healing. Studies have shown impaired wound healing of pilonidal sinuses and venous leg ulcers in patients with low serum zinc levels (Pories *et al.*, 1967; Hallbook and Lanner, 1972). Current data on zinc supplementation for pressure ulcers is controversial.
- Diarrhea has been reported in patients who develop severe zinc deficiency during total parenteral nutrition therapy. There are no randomized studies on zinc supplementation in the elderly with diarrhea (McClain, 2002; Latimer *et al.*, 1980).
- Impaired vision. In a study by Keeling *et al.* (1982), adaptation to darkness was impaired in cirrhotics with low neutrophil zinc concentrations.
- Epidermal abnormalities characterized by skin lesions around body orifices and the extremities as seen in AE. In a study of institutionalized patients with skin lesions and low zinc levels, there was no improvement in skin lesions following supplementation with zinc (Weismann *et al.*, 1978).
- Impaired spermatogenesis and testosterone steroidogenesis resulting in impaired testicular function. In one study, individuals on a zinc-deficient diet developed decreased libido, depressed serum testosterone levels, and marked reduction in sperm counts. Hydrochlorthiazide induced sexual dysfunction associated with low zinc levels may respond to zinc supplementation in some individuals (McClain, 2002; Abbasi *et al.*, 1980; Prasad, 1979).
- Disruption of vascular endothelium with possible implications for atherosclerosis (Hennig *et al.*, 1996)

Zinc toxicity is relatively unusual; however, high dietary intake may cause nausea, vomiting, epigastric pain, lethargy, and fatigue. Immune response may be impaired. It can cause hypocupremia, macrocytosis, or neutropenia (Jacobs and Wood, 2003a).

COPPER

Copper plays a significant role in several enzymatic pathways. Some of these enzymes include monoamine oxidase, dopamine-beta-hydroxylase, cytochrome-C oxidase, ferroxidase II, superoxide dismutase, and lysyl oxidase. Copper plays an important role in iron absorption and mobilization to sites of erythropoesis. Copper is essential for inactivation of catecholamines, synthesis and cross-linking of collagen, and the conversion of dopamine to norepinephrine (McClain, 2002; Morley, 1995b; Jacobs and Wood, 2003f).

The various dietary sources for humans are legumes, nuts and meats (Pazirandeh and Burns, 2005b). A study by Ma *et al.* revealed less-than-recommended intakes of copper by the elderly (Ma and Betts, 2000). Individuals at risk of copper deficiency include patients with chronic diarrhea, those on chronic TPN and chronic peritoneal dialysis (Pazirandeh and Burns, 2005b). Deficiency can be seen in individuals on high-dose oral zinc supplementation. Serum copper levels are used to assess copper status. These levels however are affected by inflammation and hormonal status. Ceruloplasmin, the copper binding protein is an acute phase reactant. Serum copper levels therefore increase during stress and inflammation (McClain, 2002). Serum copper levels increase with aging; however, there is no change in the leukocyte copper levels. Advancing age is also associated with an increase in ceruloplasmin (Morley, 1995b).

Dietary copper is absorbed from the upper gastrointestinal tract (from the stomach to the distal small bowel). Bioavailability is affected by dietary fiber and protein content and the ingestion of other minerals such as zinc. Copper undergoes enterohepatic circulation and only small amounts are excreted in the urine. Portal flow delivers histidine-bound and albumin-bound copper to hepatocytes. Release into systemic circulation is primarily via the specific transporter known as *ceruloplasmin* (McClain, 2002; Jacobs and Wood, 2003f).

The classic manifestations of copper deficiency can be seen in the congenital disorder, Menkes Syndrome. It is characterized by eating difficulties, hypothermia, seizure activity, and

"steel wool" hair, cerebellar ataxia, profound arteriopathy and early death. Copper deficiency may present as follows (Tamura *et al.*, 1994; Masugi *et al.*, 1994; Christen, 2000; Saari, 2000):

- Anemia, leukopenia, and neutropenia. Anemia is unresponsive to iron supplementation;
- hypopigmentation;
- immune dysfunction;
- skeletal abnormalities;
- increased cholesterol with atherosclerosis;
- neurologic problems such as AD.

Copper metabolism seems to be conserved with aging. Although older individuals ingest lower amounts than younger individuals, they are able to maintain a metabolic balance (Jacobs and Wood, 2003f).

Severe copper toxicity can result in hepatic necrosis, coma, oliguria, renal failure, hypotension, and even death. Mild gastrointestinal symptoms such as nausea, vomiting, and abdominal pain can occur in less acute and less serious toxic conditions (Pazirandeh and Burns, 2005b).

CHROMIUM

Chromium, an essential trace element, was first identified as the glucose tolerance factor which corrected hyperglycemia in rats (Schwarz and Mertz, 1957). Glucose Tolerance Factor is a combination of chromium and nicotinamide. Chromium functions as a coenzyme and is also a component of metalloenzymes (Mertz, 1993). Low chromium levels may be seen in some diabetic patients and it may have a role in glucose homeostasis (Anderson, 2000; Anderson *et al.*, 1991). Data suggest that chromium may augment the production and binding of insulin to the receptors (Vincent, 2000). Data suggest that chromium may have a role in elevating high-density lipoprotein (HDL) and lowering overall cholesterol levels (Railes and Albrink, 1981).

Dietary sources of chromium include brewer's yeast, cereals, fruits, vegetables, grains, and processed meats (Pazirandeh and Burns, 2005b; Morley, 1995b). Chromium is absorbed in the small intestine and its absorption is determined by the total body chromium concentration. Its

Table 5 Micronutrient functions and the effects of aging on these micronutrients

Micronutrient	Function	Effect of aging
Vitamin A	Prevention of xeropthalmia, phototransduction, cellular differentiation, and integrity	Intake decreases with aging, retinol levels correlate poorly with vitamin A status. Hepatic levels appear unchanged
Vitamin D	Calcium and phosphorus homeostasis	Decreased levels of 1,25-dihydroxyvitamin D
Vitamin E	Antioxidant and free-radical scavenger, stabilization of cell membranes	Unknown
Vitamin K	Central role in blood coagulation	Unknown
Vitamin B1 (thiamine)	Oxidative decarboxylation of alpha ketoacids and trans ketolase degradation	Decreased thiamine levels
Vitamin B2 (riboflavin)	It acts with its coenzymes Flavin mononucleotide and flavin adenine dinucleotide in oxidation–reduction reactions	Erythrocyte glutathione reductase activity declines with aging
Vitamin B3 (niacin)	Dehydrogenase reactions as a coenzyme for nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate	Probably decrease with aging
Vitamin B6 (pyridoxine)	Cofactor for intermediary metabolism	Pyridoxal phosphate levels decline
Folate	Single carbon atom transfer in intermediary metabolism	Unknown
Vitamin B12 (cobalamin)	Metabolism of fatty acids and methyl transfer	Levels decrease with aging
Vitamin C (ascorbic acid)	Antioxidant and reduces harmful free radicals. Important for collagen and norepinephrine synthesis	Levels decrease with aging
Arsenic	Urea cycle, myocardial muscle function and triglyceride synthesis	Unknown
Boron	Bone structure, mineral metabolism	Unknown
Chromium	Glucose homeostasis, lipid metabolism	Decrease
Cobalt	Erythropoesis and triglyceride synthesis	No change
Copper	Cholesterol metabolism, erythropoesis, collagen cross-linking, conversion of dopamine to norepinephrine, electron transport chain, coagulation factor V	Increase in serum, decrease in saliva, hair, and heart
Fluoride	Bone structure and tooth enamel	Increase up to age 60, then decline in skeleton
Iodine	Thyroid hormones	Increase in serum after age 45
Lead	Uncertain	Unknown
Lithium	Endocrine secretory functions	Unknown
Manganese	Protein and energy metabolism, mucopolysaccharides	No change in serum, reduced in the kidney and heart
Molybdenum	Uric acid production, oxidation of sulfite to sulfate	Unknown
Nickel	RNA and DNA structure, membrane stabilization, iron absorption and metabolism, pituitary function	Increase in lungs
Selenium	Constituent of glutathione peroxidase, T and B cell function, muscle metabolism	Decrease
Silicon	Bone and connective tissue structure	Decrease in aorta and skin
Tin	Induces hemoxygenase and carbon monoxide production	Increased in Alzheimer's Disease
Vanadium	Cholesterol synthesis, catalysis of oxidation–reduction reactions	Unknown

absorption is enhanced in the presence of zinc and iron deficiency (Pazirandeh and Burns, 2005b; Offenbacher *et al.*, 1997). Vitamin C also enhances its absorption. Nonsteroidal anti-inflammatory medications and antacids decrease its absorption (Jeejeebhoy *et al.*, 1977; Kamath *et al.*, 1997).

Chromium deficiency is seen in individuals on total parenteral nutrition. Tissue chromium levels decline with age and urinary excretion increases (Pazirandeh and Burns, 2005b; Morley, 1995b). Chromium deficiency has been associated with (McClain, 2002)

- glucose intolerance with peripheral insulin resistance;
- altered lipid metabolism;
- neuropathy;
- encephalopathy.

Chromium toxicity has been described in a patient on chromium supplements who presented with renal insufficiency, elevated liver enzymes, anemia, and thrombocytopenia. Discontinuation of the supplement and supportive measures resulted in normalization of all laboratory values within a year. Attention to the use of over the counter (OTC) nutritional supplements is important, especially in the elderly (Cerulli *et al.*, 1998).

Table 5 summarizes the functions of various vitamins and trace metals and the effects of aging on these micronutrients.

CONCLUSION

It is important to maintain adequate intake of micronutrients to maintain health. Data suggest that vitamin and mineral deficiencies exist in the elderly; these are exacerbated during hospitalization, hypermetabolic states, alcohol use, liver disease, diuretic use, and laxative abuse. Observational data suggest a link between dietary micronutrient intake and health outcomes. However, randomized control trials have not supported the use of vitamin and mineral supplements among well-nourished individuals. Food still remains the best vehicle for nutrient consumption. The elderly are at great risk of toxicity with a greater potential for drug–nutrient interaction. Other concerns in the elderly include cost and convenience of administration. The use of vitamin and mineral supplements as antiaging treatments or as treatments for specific diseases in the elderly is not supported by the currently available scientific data. Education and counseling is important in this age-group in order to maintain adequate nutrient intake via methods that are both convenient and affordable (Tripp, 1997; Dangour, 2004).

KEY POINTS

- The elderly are at increased risk of undernutrition as a result of multiple factors such as physiologic anorexia of aging, physiological changes affecting digestion, absorption, and metabolism of nutrients, social isolation, chronic diseases, sensory impairment, cognitive impairment, depression, and polypharmacy.
- There is overall lack of evidence on the nutritional needs of the elderly, with particular lack of data from clinical trials.
- Vitamin disorders present atypically or are masked by coexisting diseases or a general failure to thrive.
- Vitamin preparations are consumed on a daily basis by 20–60% of the elderly and drug–nutrient interactions are common in this population because of the high incidence of polypharmacy.
- The use of vitamin and mineral supplements as antiaging treatments or as treatments for specific diseases in the elderly is not supported by the currently available scientific data.

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Obesity in the Elderly

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AGE-RELATED CHANGES IN BODY COMPOSITION

Body weight increases until approximately the age of 60–65 years, and decreases in over 60% of the population thereafter. Muscle mass peaks between the third and fourth decades, followed by a decline of about 1.2 kg/decade in men and 0.1 kg/decade in women. Muscle mass and strength decrease by approximately 15% and 30%, respectively, between the second and seventh decades (Hughes *et al.*, 2002). Factors which may be responsible for, or are at least associated, with these changes include decreased physical activity, inadequate nutrition, vascular disease, increased activity of the cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF α), and decreased levels of the anabolic hormones testosterone, dehydroepiandrosterone (DHEA), growth hormone (GH), and insulin-like growth factor-1 (IGF-1) (Morley *et al.*, 2001).

The contribution of fat mass to the weight loss that occurs in the elderly is small, and occurs predominantly in women over the age of 70 years (Mott *et al.*, 1999; Perry *et al.*, 1997). Fat mass has also been reported to increase with increasing age in both genders (Hughes *et al.*, 2002). More importantly, adipose tissue tends to be redistributed toward the abdomen, particularly viscerally (Beaufrere *et al.*, 2000).

There are a number of longitudinal studies that have examined the changes in body composition that occur with increasing age. The SENECA study included elderly Europeans aged between 65–70 years at baseline and 80–85 years at follow-up. Stature decreased by 1.5–2.0 cm. Mean weight decreased by 2.6–4.2 kg in three towns. Overall, body weight increased by 5 kg in 13% of men and women, but decreased by 5 kg in 23% of men and 27% women. Waist circumference increased by 3.0–4.0 cm (de Groot *et al.*, 2002). Gallagher *et al.* (2000) studied a group of men and women, aged over 60 years, in 1986 and, again, in 1994. Although there was no significant change in the overall body weight of men, fat mass increased by approximately 1.2 kg and total appendicular skeletal muscle mass decreased by approximately 0.8 kg. In women, both body weight and fat mass were reduced by about 0.8 kg, while appendicular skeletal muscle mass decreased by about 0.4 kg (Gallagher *et al.* 2000). Malnutrition may also be a significant problem as it was present in 5% of both genders (Perissinotto *et al.*, 2002). There is also data suggesting that visceral redistribution in old age predominantly affects females (Perissinotto *et al.*, 2002).

ASSESSMENT OF OBESITY WITH INCREASING AGE

At different ages, the same levels of body mass index (BMI), calculated as $kg\,m^{-2}$, correspond to different amounts of fat and fat-free mass. BMI is a poor indicator of obesity after it has peaked at about the fifth decade, as some elderly individuals with low BMI have been shown to carry as much fat as those with high BMI (Seidell and Visscher, 2000). The prevalence of overweight and obesity, with its attendant risks for chronic disease, may be underestimated using BMI (Baumgartner *et al.*, 1995) in the elderly. Increased (abdominal) fatness is better reflected by increased waist circumference which, in turn, relates better to obesity-related disease risk (Seidell and Visscher, 2000; Baumgartner *et al.*, 1995). Low lean body mass is better reflected by low BMI. The accurate identification of sarcopenic obesity requires precise simultaneous methods of measuring fat and lean components, such as dual-energy X-ray absorptiometry (Baumgartner *et al.*, 1995). The value of bioelectrical impedance analysis (BIA) has been questioned because the prediction errors are larger as compared to young and middle-aged subjects (Visser *et al.*, 1995). However, BIA models with increased accuracy and precision for predicting extracellular water and total body water have now been derived in healthy elderly subjects (Vache *et al.*, 1998).

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PREVALENCE OF OBESITY IN THE ELDERLY

Studies of the prevalence of obesity in the elderly are all based on standard BMI criteria. The prevalence of obesity has been reported to be 28% and 16% in elderly Italian women and men, respectively (Perissinotto *et al.*, 2002). In a representative sample of elderly Mexicans from five southwestern states in the United States, 23% of men and 35% of women were obese (Ostir *et al.*, 2000). In elderly Taiwanese subjects, 27.3% of men and 34.9% of women were overweight, while obesity was present in 3.2% of men and 6.4% of women (Chiu *et al.*, 2000). A Dutch nutrition survey of 539 healthy, independently living elderly persons, aged 65–79 years, found an overall prevalence of obesity of 13% (Lowik *et al.*, 1990). In urban Mexican women with a mean age of 71.6 years, the proportion of overweight and obese women was 60.7%, 36.2%, and 76.5% in urban, rural, and marginal areas, respectively (Gutierrez *et al.*, 2001).

Among residents aged over 50 years in a defined area in Jerusalem, the prevalence of obesity, standardized by age and sex, was 21% in 1970 and 25% in 1986, although the increase was statistically significant only in men (Gofin *et al.*, 1996). In elderly Italians aged 65–95 years, the prevalence of obesity in 1985 was 28% in women and 13% in men; this increased to 16% in men in a little over a decade, while remaining unchanged in the women (Perissinotto *et al.*, 2002). Analysis of data from the Longitudinal Study of Aging and the Assets and Health Dynamics of the Oldest Old Survey showed that the prevalence of obesity, over time, increased among those aged 70 years and older (Himes, 2000). Data from male participants of the Normative Aging Study showed that new cases of obesity, defined on the basis of BMI, increased over time while the numbers of subjects classified as lean and intermediate decreased. Among the oldest subjects, both the lean and obese had slight but significant decreases in mean BMI. Amongst the lean subjects, only the young showed consistent increments (Grinker *et al.*, 1996).

MECHANISMS OF OBESITY OF THE ELDERLY (TABLE 1)

Table 1 Mechanisms of obesity in older persons

1. *Reduced energy expenditure*
   - Reduced physical activity
   - Reduced resting metabolic rate
   - Poorer health status
2. *Lesser degree of fall in energy intake compared to fall in energy expenditure*
3. *Dysfunctional hormonal regulation*
   - Leptin resistance
   - Lack of ghrelin suppression after food intake
4. *Others*
   - Increased fat accumulation
   - Reduced fat oxidation

Energy Expenditure

Energy expenditure decreases by around 165 kcal/decade in men, and 103 kcal/decade in women, primarily due to changes in voluntary physical activity and, to a lesser extent, a decrease in resting metabolic rate (RMR) (Elia, 2001). In a population-based cohort of 33 466 men aged 45–79 years in central Sweden, total daily physical activity was found to decrease by approximately 4% by age 50 as compared to age 15. Physical activity was 2.6% lower in obese men compared to those with normal weight. Men with self-rated poor health had 11.3% lower levels of physical activity than those reporting very good health (Norman *et al.*, 2002; Norman *et al.*, 2003). A progressive decline in RMR is seen with increasing age. This is explained by both a loss of fat-free mass and a decrease in physical activity. RMR is around 6% higher in physically active older men than in untrained older men, independent of differences in fat-free mass (Poehlman, 1992).

Energy Intake

Food intake is regulated by a complex system involving orexigenic (appetite-stimulating) and anorexigenic (appetite-inhibiting) hormones that link hypothalamic satiety centers with gastrointestinal function and energy stores (Figure 1). Ghrelin, which is produced in and secreted from the gastric mucosa, increased by fasting and low protein diets, and inhibited by somatostatin, growth hormone, and high fat diet, is responsible for the main orexigenic signal that stimulates neuropeptide Y (NPY) and agouti-related peptide (AgRP) in the hypothalamus (Inui *et al.*, 2004). NPY and AgRP, which are capable of orexigenic stimuli themselves while simultaneously antagonizing anorexigenic melanocortin pathways, increase appetite, gastric motility, and triglyceride stores in adipocytes, but reduces energy expenditure, resulting in net body weight gain (Inui *et al.*, 2004). Cerebrospinal fluid levels of NPY increase with age in women, but not men (Morley, 1997). Conversely, the actions of NPY and AgRP are inhibited by the anorexigenic stimulus of leptin, produced from adipose tissue, especially after a meal. Leptin levels are higher in women as compared to men and this does not appear to change with age (Mann *et al.*, 2003). Other gastrointestinal peptides, such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), pancreatic polypeptide (PP) and peptide YY (PYY) 3–36, act in synergy with leptin to reduce gastric emptying, resulting in increased gastric distension, which has been identified as a satiety signal to inhibit food intake (Inui *et al.*, 2004). Ghrelin and leptin are, thus, complementary, but antagonistic, in their actions on hypothalamic satiety and gastrointestinal functions.

Obesity in humans is characterized by low ghrelin and weight loss leads to an increase in ghrelin levels, indicating that ghrelin plays an important role in the long-term maintenance of body weight despite its low levels (Hansen *et al.*, 2002). The sustained suppression of ghrelin levels in patients who have lost weight through gastric bypass surgery further

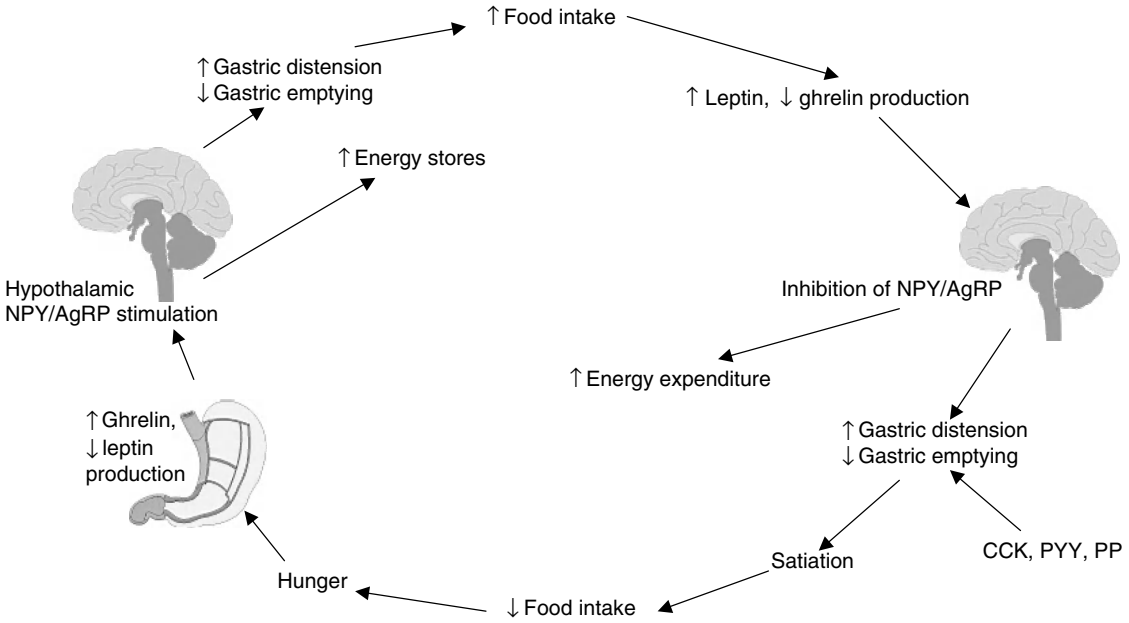

Figure 1 Hormonal regulation of energy homeostasis

supports this view (Hasler, 2003). The lack of ghrelin suppression after a meal in obese persons may also result in persistent food intake (English *et al.*, 2002). Ghrelin and CCK appear to be similarly regulated in older subjects as compared to younger ones (Sturm *et al.*, 2003). There is also no evidence that PYY regulation changes with aging.

The higher circulating levels of free (bioactive) leptin in obese persons suggest the presence of leptin resistance, as they do not result in reduced caloric intake (Mann *et al.*, 2003). In addition, leptin has been found to correlate strongly with body weight and fat mass, but not age or waist-hip ratio, in older subjects, suggesting that the accumulation of adipose tissue directly supports greater leptin production (Maugeri *et al.*, 2002).

While there is no data suggesting that significant changes in either the neural circuits or gut peptides regulating food intake changes with age, energy intake decreases with advancing age, but probably to a lesser extent than energy expenditure (Poehlman, 1992). In a cross-sectional study of 15 266 healthy men aged 55–79 years, total energy and energy from fat, but not from other nutrients, increased linearly with increasing BMI, which increased by 0.53 kg m^{-2} and 0.14 kg m^{-2} for every 500 kcal of fat and total energy consumed, respectively (Satia-Abouta *et al.*, 2002). Specific nutrient deficiency is also a problem in the elderly; up to 30% community dwelling older persons have diets deficient in at least one major nutrient (Morley, 1986).

Nutrient Utilization

Other changes that occur with aging that increase the propensity to the accumulation of fat include: a decrease in whole body fat oxidation (0.5 g year^{-1} from age 30–70 years) associated with the decrease in fat-free mass (Poehlman *et al.*, 1995), a diminished ability to use fat as a fuel during exercise (Blaak, 2000), reduced adipose tissue lipoprotein lipase activity (Berman *et al.*, 1999), catecholamine (Blaak, 2000) and leptin (Berman *et al.*, 1999) resistance.

THE CONSEQUENCES OF OBESITY IN THE ELDERLY (TABLE 2)

Overall Mortality

The relative contribution of increased fat mass to mortality is, on the whole, less pronounced in the elderly. Although there is some variability between studies, it is clear that higher BMI values are associated with a smaller relative mortality risk in elderly persons compared with young and middle-aged populations (Heiat *et al.*, 2001). For example, older men and women (BMI range of 25 kg m^{-2} to less than 32 kg m^{-2}) have been shown to have no excess mortality (Bender *et al.*, 1999). In another study, the BMI range of 25–27 kg m^{-2} was reported not to be a risk factor for all-cause and cardiovascular mortality among elderly persons, whereas a BMI $\geq$ 27 kg m^{-2} was a significant prognostic factor for all-cause

Table 2 Consequences of obesity in older persons

- ↑ In mortality those with sarcopenic obesity
- ↑ Physical disability
- ↑ Glucose intolerance
- ↑ Blood pressure
- ↑ Hepatic steatosis
- ↓ Lung capacity
- ↑ Relative hypogonadism (men)

and cardiovascular mortality among 65 to 74 year olds. The same study found a significant positive association between overweight and all-cause mortality among those aged 75 years or older (Heiat *et al.*, 2001). In 2032 subjects (999 men, 1033 women) with a mean age of 80 years, recruited by random sampling of the Old Age and Disability Allowance Schemes in Hong Kong, stratified by sex and 5-year-age groups from 70 years onwards, overall mortality was negatively associated with BMI and participation in physical activity, after adjusting for age and sex (Woo *et al.*, 1998). Overall, the evidence suggests that the standardized mortality rate increases with increasing BMI but, within each BMI group, the standardized mortality rate decreases with age.

The elderly at greatest risk are those who are simultaneously sarcopenic and obese (Morley *et al.*, 2001). Low BMI and weight loss in the elderly are both strong and independent predictors of subsequent mortality, and low BMI better predicts mortality than low waist circumference (Seidell and Visscher, 2000). Prior weight history has also been shown to be important in predicting risk. Older heavier people who had gained more than 10% of midlife body weight, or thinner older people who had lost 10% or more of body weight, are at higher risk compared with thinner people whose weight had remained stable (Harris *et al.*, 1997).

A high waist circumference (in nonsmoking men) may be a better predictor of all-cause mortality than high BMI (Seidell and Visscher, 2000). In a prospective cohort study of 31 702 healthy Iowa women aged 55–69 years, waist-hip ratio was the best anthropometric predictor of total mortality (Folsom *et al.*, 2001). In men and women aged 67–78 years, waist circumference and supine sagittal abdominal diameter were closely related to cardiovascular disease (CVD) risk factors (Turcato *et al.*, 2000).

DISEASE-SPECIFIC RISKS

Mobility Related Disability

Among 2714 women and 2095 men aged 65–100 years, there was a positive association between fat mass and disability at baseline. Moreover, fat mass was predictive of disability 3 years later independently of low fat–free mass, age, physical activity, or chronic disease (Visser *et al.*, 1998). Data from the First USA National Health and Nutrition Examination Survey (NHANES I, 1971 through 1987) showed that high BMI is a strong predictor of long-term risk for mobility disability in older women and that this risk persists even to very old age. On the other hand, weight loss is associated with an increased risk of disability in very elderly women (Launer *et al.*, 1994).

Impaired Glucose Tolerance and Type 2 Diabetes Mellitus

The prevalence of type 2 diabetes mellitus (T2DM) increases progressively with age, peaking at 16.5% in men and 12.8% in women at the age of 75–84 years. T2DM or glucose intolerance was present in 30–40% of Framingham Study subjects over 65 years of age (Wilson and Kannel, 2002). Age associated increase in total adiposity is a major contributor to impaired glucose tolerance in middle-aged and older men. A prospective relationship between abdominal adiposity and the risk of T2DM was found among 1972 male participants in the Department of Veterans Affairs Normative Aging Study cohort (Cassano *et al.*, 1992). Increased body fatness and increased abdominal obesity, rather than aging *per se*, are thought to be directly linked to the greatly increased incidence of T2DM among the elderly (Colman *et al.*, 1995). Nevertheless, there is evidence that insulin secretion decreases with age even after adjusting for differences in adiposity, fat distribution, and physical activity (Muller *et al.*, 1996).

Hypertension

Data from the Honolulu Heart Program showed that obesity and high blood pressure continued to be highly correlated even in old age (Masaki *et al.*, 1997). Furthermore, the Veterans Administration Normative Aging Study showed that abdominal accumulation of body fat, apart from overall level of adiposity, was associated with an increased risk of hypertension (Cassano *et al.*, 1990).

Fatty Liver

In the elderly, the prevalence of fatty liver has been reported to be 3.3% in male and 3.8% in female nonobese individuals, compared with 21.6% in male and 18.8% in female obese individuals, and was shown to be independently related to coronary risk factors (Akahoshi *et al.*, 2001).

Pulmonary Function

Among 1094 men and 540 women from the Baltimore Longitudinal Study of Aging, there was a strong inverse association of WHR with forced expiratory volume (FEV_1) and forced vital capacity (FVC) in men, but not women (Harik-Khan *et al.*, 2001). Weight loss has been shown to improve static lung volumes, but not dynamic pulmonary function, in moderately obese, sedentary men (Womack *et al.*, 2000).

Hypogonadism

Plasma total testosterone levels are significantly lower in men with visceral obesity compared to their lean counterparts, independently of age (Seidell *et al.*, 1990; Vermeulen *et al.*, 1999). While male hypogonadism had previously been thought to predispose toward the development of metabolic

syndrome and T2DM (Laaksonen *et al.*, 2003; Tibblin *et al.*, 1996; Stellato *et al.*, 2000), there is increasing evidence that it results from visceral adiposity (Niskanen *et al.*, 2004; Phillips *et al.*, 2003) and, thus, acts as a marker of poor metabolic status. Our analysis of data (unpublished) from the Australian Longitudinal Study of Aging, in men aged 70 years or greater, is consistent with the latter view. It remains unknown whether the hypogonadism is reversible with a reduction in fat mass, as seen in younger men (Niskanen *et al.*, 2004).

Plasma testosterone levels in men are also inversely associated with circulating leptin concentrations, even after adjusting for fast mass (Luukka *et al.*, 1998), and testosterone therapy reduces leptin levels (Hislop *et al.*, 1999). The long-term consequences of hypogonadism in elderly men have not been well established.

The Management of Obesity in the Elderly (Table 3)

Modifiable behavioral factors (physical activity, smoking, and obesity) and cardiovascular risk factors (T2DM, high density lipoprotein (HDL) cholesterol, and blood pressure) are associated with maintenance of good health in older adults (Burke *et al.*, 2001). Many obesity-related health conditions (e.g. hypertension, dyslipidemia, insulin resistance, glucose intolerance) can be ameliorated independently of weight loss (Gaesser, 1999). It is appropriate to advise a reduction in fat intake, to increase fiber and to ensure that the diet contains sufficient micronutrients.

Calorie Restriction

Thinness and weight loss (regardless of initial BMI) are associated with increased mortality rates in humans, independently of smoking or weight loss resulting from subclinical disease. For overweight individuals in good health, there is no good evidence to show that mortality rates are reduced with weight loss. Even among overweight persons with one or more obesity-related health conditions, specific weight loss recommendations may be unnecessary (Gaesser, 1999).

Table 3 Management of obesity in older persons

1. *Nonpharmacological*
   - ↓ Calorie intake
   - ↑ Physical activity:
   - Endurance training
   - Resistive training
2. *Pharmacological*
   - Treat hypertension
   - Treat hypercholesterolemia
   - TZDs?
3. *Others*
   - Bariatric surgery?

Physical Activity

Regular exercise is the best predictor of successful weight maintenance. An increase in physical activity leads to improved insulin sensitivity and glucose tolerance, with a corresponding reduction in all-cause and cardiovascular mortality (Gaesser, 1999). Endurance training increases fatty acid oxidation, leads to a reduction in visceral fat, and increases, or attenuates, the decline in RMR that otherwise occurs with aging (Poehlman *et al.*, 1995). Beginning moderately vigorous sports activity, quitting cigarette smoking, maintaining normal blood pressure, and avoiding obesity were separately associated with lower rates of death from all causes and from coronary heart disease among middle-aged and older men (Paffenbarger *et al.*, 1993). Resistive training has particular benefits and improves quality and function of skeletal muscle, decreases total and intra-abdominal fat, improves insulin action, and lowers blood pressure (Ryan *et al.*, 2001; Hurley and Roth, 2000). Improvements in fitness have been shown to attenuate age-related increases in adiposity. People who exercise regularly have a lower risk of cardiovascular disease (Paffenbarger *et al.*, 1986), and appear to accumulate less adipose tissue in upper, central body regions as they get older, potentially reducing the risk for the metabolic disorders associated with upper body obesity (Kohrt *et al.*, 1992).

Drugs and Surgery

While most clinical trials exclude older patients, and little is known about benefits of diets or drugs inducing weight loss in these age groups, drug treatment of hypercholesterolemia and hypertension, in older people has proven to be beneficial in the primary and secondary prevention of cardiovascular morbidity and mortality (Aronow 2003; Grant and Meigs, 2004). Aggressive lowering of low density lipoprotein (LDL)-cholesterol to levels below 1.81 mmol L^{-1} may be necessary in the elderly at high risk of coronary events (Aronow, 2004). The use of metformin or thiazolidinediones to delay or prevent the onset of T2DM in elderly populations remains uncertain (Grant and Meigs, 2004). Administration of leptin in humans led to some degree of weight loss in obese individuals (Heymsfield *et al.*, 1999); however, there is no available data on such treatment in older subjects. Bariatric surgery can be safely performed in patients above age 70 with the same benefits as for younger subjects (St Peter *et al.*, 2005).

KEY POINTS

- Body mass index (kg m^{-2}) is not a useful measure of obesity in the elderly. Waist circumference should be utilised instead.

- Those elderly individuals with excessive visceral fat and loss of muscle mass (sarcopenia) are at greatest risk of excess morbidity and mortality.
- Increased physical activity, particularly with a resistance component is the management strategy associated with the greatest benefit.
- Diet-induced weight loss is of uncertain benefit, but saturated fat should be limited and nutrient density should always be optimized.
- There is no data to support the use of pharmacotherapy for the of obesity in the elderly.

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PART III

Medicine in Old Age

Section 2

Gastro Disorders

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Changes in Gastrointestinal Motor and Sensory Function Associated with Aging

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INTRODUCTION

The purpose of this chapter is to review changes in gastrointestinal contractile and sensory function associated with healthy aging, and their clinical significance. Furthermore, illnesses with clinical manifestations in the gut that are common, or present management problems in older patients, are considered. Mucosal functions of secretion and absorption are not discussed here (*see* **Chapter 25, Absorption of Nutrients**), and the focus is on the esophagus, stomach, and small intestine, since the oropharynx (*see* **Chapter 73, Communication Disorders and Dysphagia**), gallbladder (*see* **Chapter 33, Liver and Gall Bladder**), and colon and anorectum (*see* **Chapter 34, Sphincter Function**, **Chapter 35, Constipation**) are dealt with elsewhere.

CONTROL OF GASTROINTESTINAL MOTILITY AND SENSATION

Patterns of motor activity, involving the circular and longitudinal layers of smooth muscle that extend throughout the length of the gut, are coordinated by plexuses of nerves within the gut wall known collectively as the *enteric nervous system*. Located in the submucosa (submucous plexus) and between the muscle layers (myenteric plexus), this network contains an equivalent number of neurons (about 100 million) to that present in the spinal cord (Goyal and Hirano, 1996). The intrinsic sensory neurons, interneurons, and motor neurons that comprise the enteric nervous system control basic contractile activity such as reflex responses to distension. However, these intrinsic patterns of gut motility are modulated by both extrinsic neural and humoral signals. Central modulation of gut motility occurs via extrinsic sympathetic and parasympathetic nerves, while gut sensation is conveyed to higher centers by both the vagus and spinal afferent nerves, with noxious signals transmitted predominantly via the latter. Descending pathways to the spinal cord modulate the transmission of sensory signals.

PATHOPHYSIOLOGY OF THE AGING GUT

In rodent models of aging, there is a substantial reduction in the number of neurons in the enteric nervous system, which becomes increasingly prominent and more distally in the gut (40% loss in the small intestine and 60% in the colon, in the myenteric plexus of rats) (Wade, 2002). Similar neuronal loss is reported in the esophagus in older humans, while in the human colon, the decline in neuron numbers begins as early as the fourth year, but is most marked between young adulthood and old age. Although a selective, rather than global, loss of enteric neurons might be expected on the basis of age-related changes observed in the central nervous system, there is comparatively little information as to which neurons are most susceptible. Preliminary data in rodents indicate preferential loss of sensory neurons, which could impair stimulus-evoked motor responses. Cholinergic neurons appear vulnerable, but these subserve a wide variety of functions; conversely, nitrergic neurons, which typically mediate inhibitory motor responses, seem protected (Wade and Cowen, 2004). Regarding the extrinsic nerve supply to the gut, the number of vagal fibers innervating the upper gastrointestinal tract does not appear to decline in aging rats. Limitations to our understanding include the relative lack of studies relating to the upper gut and the sphincters, and the paucity of human data.

The relatively good preservation of gastrointestinal motility in the healthy elderly may imply that the large number of neurons in the enteric nervous system provides a considerable functional reserve, but even this may be limited; transit

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of a radiolabeled meal through the upper gut occurs at a comparable rate in the healthy elderly and the young, but is slower through the colon in the elderly, where the loss of enteric neurons is greatest (Madsen and Graff, 2004). In the esophagus, selective loss of intrinsic sensory neurons could explain why contractile activity in response to distension (so-called "secondary peristalsis") occurs less frequently in the healthy elderly than the young.

In contrast to motor function, gut sensation is more consistently impaired with age, as reflected by decreased perception of balloon distension in the esophagus (Lasch *et al.*, 1997), stomach (Rayner *et al.*, 2000), and rectum (Lagier *et al.*, 1999) in comparison to young subjects. A selective loss of intrinsic sensory enteric neurons may be responsible. However, the amplitude of cortical evoked potentials recorded from scalp electrodes during repeated esophageal distension in older subjects is lower than in the young, raising the possibility that altered central processing of signals might also contribute to diminished sensation (Weusten *et al.*, 1994). In addition to mechanical stimuli, perception of chemical stimuli such as acid decreases with age, suggesting a generalized impairment of gut sensation.

ESOPHAGUS

Patients with disordered esophageal function can present with dysphagia or "heartburn", or less specific symptoms such as chest pain or chronic cough. Age-related changes in esophageal motility are extensively documented, but probably impact mainly on the very old. Classic esophageal motility disorders like achalasia, while uncommon, can present particular challenges in the elderly. Gastroesophageal reflux disease (GERD) is as prevalent as in the young, often presents atypically, and is more likely to be severe.

Changes in Esophageal Motor Function Related to Aging

The esophagus incorporates striated muscle in the upper portion and smooth muscle in the lower, with an upper esophageal sphincter (UES) and lower esophageal sphincter (LES) at either end. The term "primary peristalsis" refers to the coordinated sequence of contraction associated with swallowing, propagated from proximal to distal esophagus. The LES relaxes early in this sequence to allow the swallowed bolus to enter the stomach. "Secondary peristalsis" is triggered by reflux of gastric contents into the esophagus, or experimentally by balloon distension, and serves to clear the esophagus of acid and bile. "Tertiary contractions" represent spontaneous, uncoordinated esophageal motor activity. While both tonic contraction of the LES and its position within the diaphragmatic hiatus are important barriers against acid reflux, transient sphincter relaxations, particularly after a meal, are the most prevalent mechanism of acid reflux in most GERD patients. Defenses against reflux include neutralization of acid by saliva (which contains bicarbonate), together with acid clearance by primary and secondary peristalsis.

Esophageal motility may be evaluated by manometry. In this procedure, a catheter incorporating multiple lumens within a relatively small external diameter is passed through the nose or mouth, and perfused with water. Each lumen terminates in a sidehole at a different level of the esophagus, and when coupled to pressure transducers, and displayed as recordings of pressure over time, the assembly provides information about the amplitude, duration, and propagation of pressure waves (Figure 1). Incorporation of a sleeve sensor into the assembly, which records the maximum pressure at any point along the sleeve, is ideal for measurement of both the resting pressure and relaxation of the UES and LES. Solid-state transducers, mounted at intervals along a catheter, represent an alternative method of manometry to water perfused catheters. Multichannel intraluminal impedance, a technique that records electrical impedance between sequential pairs of electrodes, is emerging as a method of evaluating flow of liquid and air in the esophagus. While offering new insights into esophageal function, it has yet to be applied specifically to the elderly. Radiographic imaging of swallowed contrast can reveal abnormal esophageal wall movements (especially cineradiography), dilatation, or delayed esophageal transit. Transit can also be evaluated by the passage of a radiolabeled bolus, imaged by a gamma camera – a technique known as *scintigraphy*. While endoscopy is most useful in demonstrating mucosal lesions or strictures, it may also provide evidence of abnormal motor activity in disorders such as esophageal spasm or achalasia.

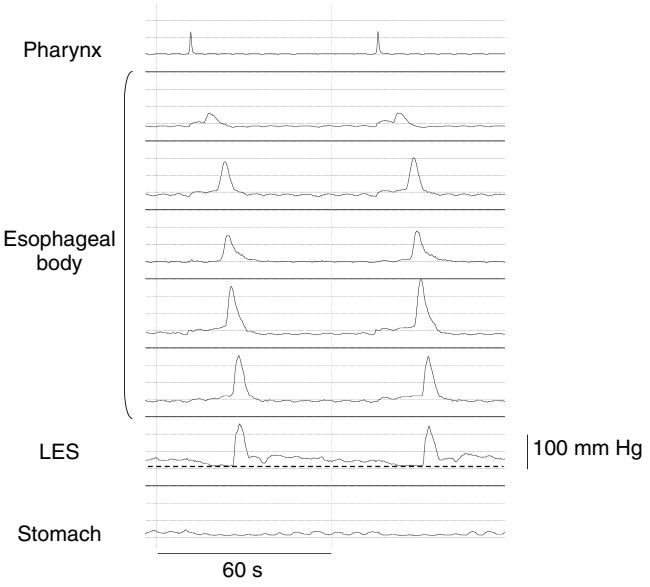

Figure 1 Normal esophageal manometry recording during water swallows, showing primary peristalsis. The pharyngeal pressure wave indicates the onset of swallowing, which is followed by an orderly sequence of waves from one channel to the next. Note the swallow-induced relaxations of the LES, whose pressure decreases to approximate intragastric pressure (dashed line)

The effects of aging have been studied more extensively in the esophagus than any other gastrointestinal region, reflecting both its accessibility and the importance of swallowing disorders in elderly. Soergel *et al.* coined the term "presbyesophagus" in 1964 when reporting radiological and manometric observations in a group of nonogenerians (Soergel *et al.*, 1964). Only two of 15 subjects had "normal" esophageal motility, and on barium examination there was a high prevalence of tertiary contractions, delayed clearance, and esophageal dilatation. Manometry showed nonperistaltic, multipeaked pressure waves. These subjects, however, could scarcely be described as healthy elderly, given the high prevalence of dementia and other chronic illnesses, including diabetes. Not surprisingly, more recent studies indicate that the prevalence and severity of esophageal motor dysfunction in healthy aging is less than suggested by early reports (Tack and Vantrappen, 1997). While there are other reports of esophageal dysmotility in the very old (Hollis and Castell, 1974), in subjects aged less than 80 years there appears to be little difference in primary peristalsis when compared to the young, though simultaneous contractions may occur more frequently. The impact of aging on the amplitude of esophageal pressure waves may vary by site; distal esophageal amplitudes increase with age, while a decrease is reported more proximally. Nevertheless, the magnitude of these changes is modest (Orr and Chen, 2002). Secondary peristalsis is elicited less consistently by distending stimuli in the healthy elderly when compared to the young (Ren *et al.*, 1995), and increasing esophageal stiffness, together with an increased threshold for perceiving distension, may contribute to this phenomenon (Rao *et al.*, 2003).

In the healthy elderly, while both the length of the UES high-pressure zone, and its resting pressure, are less than in young subjects, relaxation and opening of this sphincter are delayed (Shaw *et al.*, 1995). The result is a prolongation of the oropharyngeal phase of swallowing, and an increase in intrabolus pressure in the hypopharynx. While not clinically significant in the healthy elderly, these findings must be taken into account when evaluating swallowing studies in older patients with oropharyngeal dysphagia, where the use of reference ranges derived from the young would be inappropriate. Reflex responses of the UES to esophageal stimuli (increased pressure with esophageal balloon distension, and decreased pressure with air distension) appear to remain intact with healthy aging, but reflex UES contraction in response to laryngeal stimulation is impaired (Kawamura *et al.*, 2004); the latter could predispose to aspiration. Since only the frequency, and not the magnitude of the response, is diminished, the sensory side of the reflex arc appears to be impaired.

In contrast to the UES, both the length of the LES high-pressure zone, and its resting pressure, are comparable in older and younger subjects. However, in the elderly there is an increased prevalence of hiatus hernia (around 60% of those over 60 years) (Firth and Prather, 2002), and even in subjects without hiatus hernia apparent endoscopically, the respiratory inversion point (a marker of diaphragmatic position) tends to be located more distally in the high-pressure zone than is the case in young subjects. The implication is that, in general, the elderly have a less competent gastroesophageal junction than the young, predisposing them to GERD. Other predisposing factors include reduced flow of saliva, and impaired acid clearance. The frequency of transient LES relaxations, the major mechanism of acid reflux in most individuals, has not been specifically studied in the elderly; nor have mucosal repair mechanisms been compared with the young. The number of reflux episodes appears similar in both age-groups, but their duration appears to be more prolonged in the elderly (Smout *et al.*, 1989); this may relate to impaired clearance mechanisms. Nevertheless, reports relating to total acid exposure are inconsistent. The refluxate may be less acidic due to a higher prevalence of atrophic gastritis in the elderly, but it should be recognized that its bile content may be important in mucosal injury (e.g. Barrett's mucosa), and this has not been studied specifically in relation to age (Tack and Vantrappen, 1997).

Clinical Presentation of Disordered Esophageal Motility

Disordered esophageal motor function may present with symptoms of difficulty swallowing (dysphagia) or chest pain. In both nursing homes (50–60%) and general medical wards (10–30%), there is a high prevalence of dysphagia when patients are specifically questioned (Shaker and Staff, 2001), though less than half of elderly subjects who reported dysphagia in a population-based survey had consulted a physician about the problem. Potential consequences of dysphagia include aspiration, which contributes substantially to mortality, and inadequate intake of nutrition.

Swallowing disorders can be classified into those of oropharyngeal (difficulty initiating a swallow) or esophageal (impaired transport of swallowed material) origin, and these can usually be distinguished with a careful history and examination. The oropharyngeal component of swallowing comprises preparatory (chewing food, mixing with saliva, and bolus formation), oral (propulsion of the bolus by the tongue and palate to the pharynx), and pharyngeal (transport through the UES while protecting the airway) phases. A comprehensive discussion of dysphagia of oropharyngeal origin is included in the chapter on communication and swallowing disorders.

Potential causes of esophageal dysphagia are listed in Table 1. Key points in the history include whether dysphagia is for solids or liquids, is intermittent or progressive, and whether there are associated reflux symptoms like heartburn (Lock, 2001). Progressive difficulty in swallowing solids is suggestive of a structural lesion, while dysphagia for both liquids and solids is associated with motility disorders. Endoscopy provides a means to visualize and biopsy structural lesions, and may be therapeutic (e.g. dilatation of a peptic stricture). Endoscopy and biopsy are also likely to be helpful when odynophagia (painful swallowing) is the presenting complaint. Barium videofluoroscopy provides complimentary information regarding motor function as well

Table 1 Esophageal causes of dysphagia

Structural lesions
- Neoplasm
- Peptic stricture
- Rings and webs
- Vascular compression
- "Pill" esophagitis
- Reflux esophagitis
- Diverticula

Motility disorders
- Achalasia
- Diffuse spasm and "nutcracker" esophagus
- Nonspecific motility disorders
- Systemic disease (diabetes mellitus, progressive systemic sclerosis, Parkinson's disease)

as structural lesions, while manometry is of greatest use in confirming, or excluding, a diagnosis of achalasia.

Of the primary esophageal motility disorders, achalasia, diffuse spasm, and nutcracker esophagus are diagnosed over a wide age range. While the peak incidence of achalasia is in early to mid- adulthood, a second, smaller peak occurs in the elderly (Orr and Chen, 2002). Esophageal spasm is more commonly diagnosed over 50 years of age, while nonspecific motility disorders are particularly associated with an older population.

Achalasia

Achalasia is an esophageal motor disorder of unknown etiology, associated with incomplete or absent swallow-induced LES relaxation, and absence of peristalsis in the esophageal body. Occasionally, simultaneous esophageal pressure waves of high amplitude are observed (so-called "vigorous" achalasia). Inflammation of the myenteric plexus is an early histological finding, followed by ganglion loss and neural fibrosis. The condition typically presents with dysphagia for both liquids and solids, although weight loss, regurgitation, and aspiration may also be presenting symptoms, particularly in the elderly. Conversely, chest pain is reported less often than in young patients.

A barium swallow may show impaired peristalsis, delayed emptying, and dilatation of the esophageal body (the latter more characteristic in the elderly than the young), with "bird's beak" or "rat's tail" tapering at the LES (Figure 2). At manometry, the resting LES pressure may be high or within the normal range, but LES relaxation on swallowing is either absent or incomplete. In the esophageal body, pressure waves are simultaneous and of low amplitude, or absent altogether (Figure 3). Endoscopy (and sometimes endoluminal ultrasound, or computed tomography) must be performed to exclude "pseudo-achalasia", especially in the elderly; this entity presents with features of achalasia, but is due to carcinoma of the distal esophagus or cardia. A short history of symptoms and disproportionate weight loss are particularly suggestive of the diagnosis.

Pneumatic dilatation and surgical myotomy (now usually performed laparoscopically) represent the most efficacious

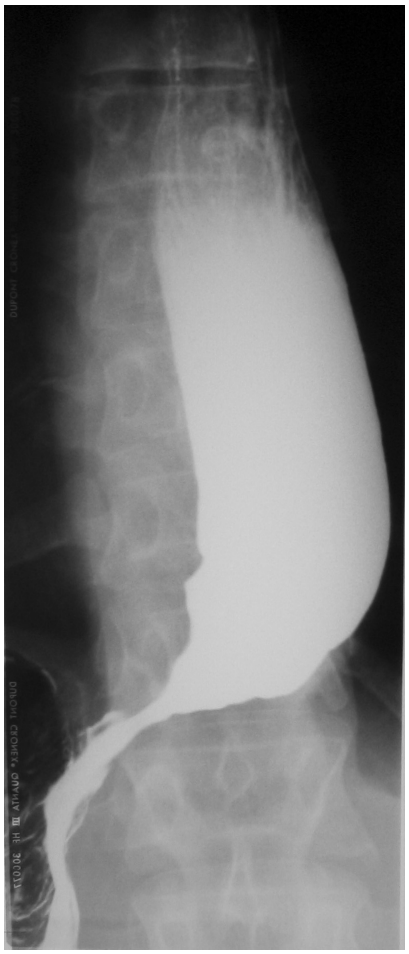

Figure 2 Barium swallow in a patient with achalasia, demonstrating a dilated esophagus with tapering at the distal end

treatments for achalasia. One large center has reported a symptomatic response of over 80% for each technique (Vela *et al.*, 2004), while the only randomized trial favored surgery (95% nearly completely relieved of symptoms, compared to 51% for dilatation (Spiess and Kahrilas, 1998). Esophageal emptying is improved in a smaller percentage, and neither therapy addresses aperistalsis of the esophageal body. Pneumatic dilatation produces controlled tearing of the LES, and is associated with a risk of esophageal perforation (about 3%) and induction of reflux symptoms (about 10%). Not infrequently, repeat dilatations are required. While myotomy may be associated with a greater risk of GERD, it can be combined with an antireflux procedure. The lower morbidity of dilatation may favor this procedure over surgery in older patients, with the caveat that a thoracotomy is required if perforation occurs. Pneumatic dilatation is more cost-effective than surgical myotomy.

Endoscopic injection of botulinum toxin into the LES represents an alternative and safe therapy, but adequate symptom relief may be achieved in fewer patients (around 60%) (Vela *et al.*, 2004), and the benefit lasts around 6 months, so that repeated treatments may be necessary.

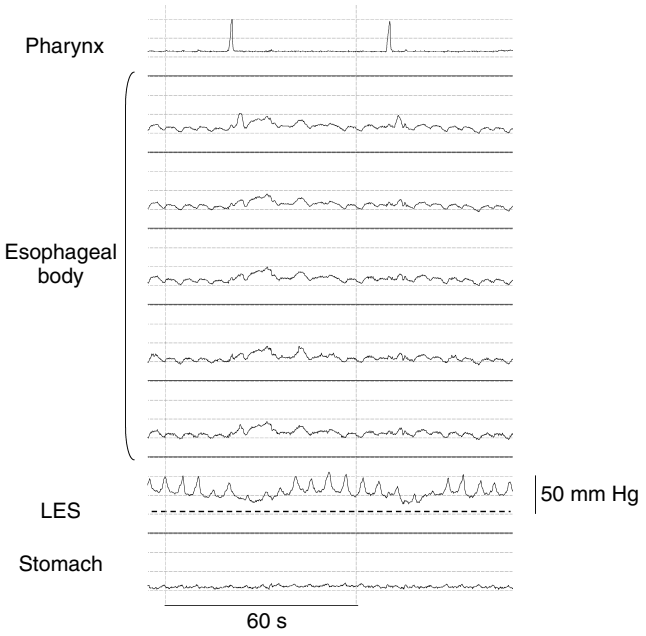

Figure 3 Esophageal manometry in achalasia. Note simultaneous, low amplitude pressure waves in the esophageal body, and minimal relaxation of the LES on swallowing

Therefore, this therapy is best reserved for patients in whom comorbidities represent contraindications to surgery or pneumatic dilatation; this group typically includes the frail elderly. This must be counterbalanced by evidence that the response to both pneumatic dilatation and botulinum toxin is better in older than younger patients. The cost of botulinum toxin injection is slightly greater than pneumatic dilatation, but substantially less than surgery.

Pharmacological therapy to reduce LES pressure (nitrates, calcium channel antagonists, or sildenafil) is of limited efficacy (possibly even less in the elderly than the young), requires frequent dosing, and is associated with side effects.

Patients with achalasia have an increased risk (estimated as 16-fold) of squamous cell carcinoma of the esophagus, but the absolute risk is small, and surveillance endoscopy has not been advocated (Spiess and Kahrilas, 1998). Occasional patients have persistent dysphagia despite therapy, together with a tortuous, dilated esophagus that empties poorly; in these circumstances, esophagectomy may be required.

Diffuse Esophageal Spasm and "Nutcracker Esophagus"

These disorders are diagnosed in a minority of patients with dysphagia or chest pain, and in many cases the relationship between symptoms and motor abnormalities is unclear. Criteria for the diagnosis of diffuse esophageal spasm are inconsistent; the presence of simultaneous esophageal pressure waves in more than 10%, but fewer than 100% of wet swallows, regardless of amplitude, is a reasonable definition (Dalton *et al.*, 1991) (Figure 4). The barium swallow may show segmentation of contrast by contractions, or a "corkscrew" appearance (Figure 5). Similar manometric abnormalities may occur in association with diabetes mellitus, alcohol abuse, amyloidosis, progressive systemic sclerosis, and GERD. "Nutcracker esophagus" is characterized by high amplitude esophageal pressure waves, but peristalsis is maintained. The management of both diffuse spasm and nutcracker esophagus is discussed below, in relation to noncardiac chest pain (NCCP).

Nonspecific Esophageal Motility Disorders

Many patients referred for investigation of symptoms such as dysphagia or chest pain have manometric features, which are outside the normal range, but do not meet formal criteria for the diagnosis of disorders such as achalasia and diffuse spasm. In cases where peristaltic waves are of abnormally low amplitude, absent, or fail to traverse the whole esophagus, often associated with a low LES pressure, a category of "ineffective esophageal motility" has been proposed (Spechler and Castell, 2001). Nonspecific abnormalities of esophageal motor function are evident in more than one-third of presentations with dysphagia in patients aged over 65, in contrast to the young, where a specific diagnosis can usually be made. It is important to recognize that a causal association cannot be assumed, since the presence of radiographic or manometric abnormalities of esophageal function correlates poorly with symptoms. Moreover, no specific therapy is available. Symptomatic management includes acid suppression when GERD is a feature, and optimizing nutrition.

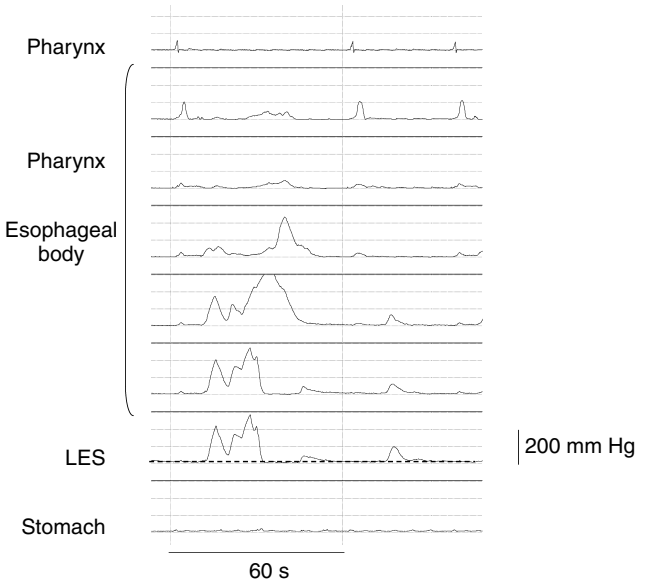

Figure 4 Manometry recording in diffuse esophageal spasm. Note simultaneous pressure waves after water swallows, including multipeaked and high amplitude waveforms

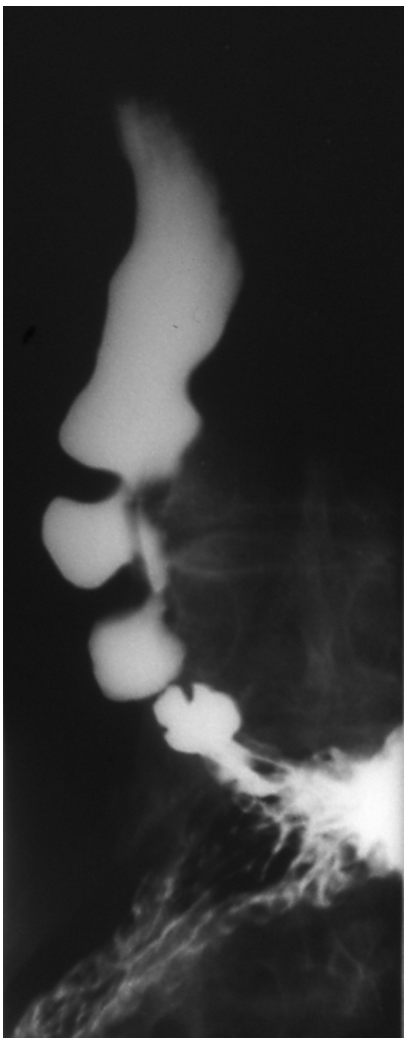

Figure 5 Barium swallow in a patient with diffuse esophageal spasm, demonstrating segmentation of the barium column by contractions, producing a "corkscrew" appearance

Pill Esophagitis

An important cause of dysphagia or odynophagia in older individuals is mucosal injury caused by impaction of medications in the esophagus, the incidence of which is likely to be increasing as the number of medications prescribed in this group escalates. Risk factors that are more prevalent in the elderly include less saliva, delayed esophageal transit, and immobility. Capsules may present a greater risk than tablets, owing to slower esophageal transit. The most frequent sites of hold-up are the upper and midesophagus, corresponding to extrinsic compression from left main bronchus, aortic arch, or enlarged left atrium, and also to a zone of low amplitude pressure waves between the proximal and distal esophagus. Numerous medications are associated with esophageal injury, including potassium chloride, tetracyclines, aspirin, nonsteroidal drugs, quinidine, theophylline, ferrous sulfate, and alendronate (Levine, 1999).

Symptoms usually resolve when the offending drug is withdrawn, but may sometimes be persistent, and related to stricture formation. Perforation and bleeding are other complications, associated particularly with potassium chloride, quinidine, and nonsteroidal drugs. The typical endoscopic or barium swallow appearance in pill esophagitis is of small superficial ulcers. There is anecdotal evidence that sucralfate is beneficial in severe or persistent disease. As a preventive measure, patients should be advised to take oral medications in the upright position, followed immediately by a full glass of water.

Noncardiac Chest Pain

Chest pain is a prevalent symptom in the community, and not infrequently presents a diagnostic difficulty, especially in older patients who are at greater risk of ischemic heart disease than the young. The esophagus is often implicated when cardiac causes have been excluded, but musculoskeletal, pulmonary, pericardial, gastric, and biliary pathology should also be considered, and an association with panic disorder has been reported (Eslick and Fass, 2003).

GERD may be responsible for NCCP, and a majority of NCCP patients (50–60%) have excessive esophageal acid exposure on pH studies. Many patients with excessive acid exposure do not have reflux esophagitis, which limits the value of endoscopic examination. Rather, a trial of double dose proton pump inhibitor (PPI) for between two and eight weeks (depending on symptom frequency) is a useful and cost-effective initial test in NCCP, with a sensitivity and specificity as high as 80% each for a diagnosis of GERD. If symptoms are relieved, the dose of medication can subsequently be titrated down to the minimum effective dose. If PPIs are ineffective, then esophageal manometry and ambulatory pH measurement (while remaining on the PPI) are indicated. Endoscopy should be performed whenever there are "alarm symptoms" such as dysphagia, anorexia, weight loss, hematemesis, or anemia. The threshold for endoscopy in older patients should be lower than in the young (age less than 40 years).

NCCP can be associated with esophageal motility disorders, including diffuse esophageal spasm, "nutcracker esophagus", hypertensive LES, and achalasia. A causal relationship between symptoms and abnormal motility can, however, be difficult to establish, even with 24-hour ambulatory manometry. A study from a large tertiary referral center indicates that esophageal dysmotility is evident in less than a third of patients with non-GERD-related NCCP (Katz *et al.*, 1987), a much lower prevalence than is assumed by many physicians. Sustained contraction of longitudinal, as opposed to circular, esophageal smooth muscle may account for some cases of esophageal chest pain, but detection of this phenomenon requires intraluminal ultrasound rather than manometry. Furthermore, medical therapy for esophageal motility disorders with smooth muscle relaxants such as nitrates, calcium channel antagonists, or sildenafil has limited efficacy, and assumes that excessive smooth muscle contraction is the

cause of pain. Surgical myotomy has had anecdotal success, but should only be considered in the presence of an intractable spastic motor disorder. Pain modifying agents such as tricyclic antidepressants or selective serotonin reuptake inhibitors, on the other hand, have been shown to be superior to placebo in non-GERD-related NCCP, regardless of whether a motility disorder is evident, but caution should be exercised in the elderly because of potential side effects, particularly when prescribing tricyclics.

Gastroesophageal Reflux Disease

GERD presents with more severe disease (erosive esophagitis, stricture, or Barrett's esophagus) than in the young (Fass *et al.*, 2000), perhaps related to the predisposing factors discussed earlier, or to a longer duration of disease (Firth and Prather, 2002). Conversely, symptoms are characteristically milder, or may be qualitatively different in the elderly, so that dysphagia, vomiting, respiratory difficulty, weight loss, or anemia are not uncommon presenting features, while "typical" reflux symptoms like heartburn occur less often than in the young – the latter perhaps as a result of diminished esophageal sensitivity. In the general population, symptoms of heartburn or regurgitation have a high sensitivity (about 70%) for a diagnosis of GERD, but a low specificity, when using 24-hour pH monitoring as the "gold standard"; corresponding data are not available for an aging population. The "alarm symptoms" mentioned for NCCP are indications for prompt endoscopic investigation.

Atypical or "extra-esophageal" manifestations of GERD include chronic cough and asthma, and may be mediated either directly by acid-pepsin reflux, or by esophageal acid exposure triggering vagal reflexes. The prevalence of excessive acid reflux in patients complaining of these symptoms is controversial, and as for NCCP, the most useful diagnostic test may be a therapeutic trial of intense acid suppression with double dose PPI, again for two to eight weeks, depending on symptom frequency.

There appear to be no significant differences in the capacity to heal esophagitis in older patients when compared to the young, and PPIs maintain their superiority over histamine receptor antagonists in this age-group. No dosage adjustment is needed in the elderly to compensate for age-related changes in renal or hepatic function, but downward titration of the dose according to symptoms may be less appropriate than in the young, especially when the original symptoms were mild, or in the setting of complicated GERD. Long-term acid suppression in individuals with *Helicobacter pylori* is associated with an increased prevalence of atrophic gastritis, which is thought to be a risk factor for gastric cancer. Therefore, *Helicobacter* eradication is generally recommended in patients on long-term PPI therapy, but this is unlikely to be of significance in the very old. Although impaired acid clearance may be an important contributor to GERD in the elderly, the role of prokinetic drugs in the treatment of reflux disease has not been specifically studied in this group, but is less of an issue since the withdrawal of cisapride in many countries. Maintenance therapy for GERD has not been specifically compared between elderly and young patients, but long-term medical therapy is likely to be more cost-effective than antireflux surgery in older patients, on the basis of the number of years of medical therapy likely to be needed. Nevertheless, the healthy elderly have outcomes from laparoscopic fundoplication that are comparable to the young (Firth and Prather, 2002). Endoscopic antireflux procedures have not been sufficiently evaluated to be widely recommended.

STOMACH AND DUODENUM

While only a modest delay in gastric emptying is observed with healthy aging, both the perception of gastric distension, and humoral responses to duodenal nutrient exposure, differ markedly from the young, and could contribute to the "anorexia of aging". Recent studies indicate that postprandial hypotension, a common cause of falls and syncope in the elderly, can be regarded as a gastrointestinal disorder, and can be related to both the rate of gastric emptying and the small intestinal response to ingested nutrient.

Changes in Gastric Motor Function Related to Aging

The stomach is responsible for the accommodation of ingested food and fluids, their mixing with digestive enzymes, and grinding of solids into small particles. Gastric emptying reflects the coordinated motor activity of the stomach and duodenum, which is controlled by feedback from neural and humoral signals generated by the interaction of nutrients with the small intestine. As a result of this, the rate of energy delivery to the small intestine is relatively constant, and independent of the ingested nutrient load. Small intestinal feedback may be modulated by previous patterns of nutrient intake, so that gastric emptying is retarded in starvation, while emptying of glucose is more rapid after dietary glucose supplementation. The proximal region of the stomach, comprising the fundus and much of the gastric body, relaxes after meal ingestion, and acts as a reservoir for the solid component of the meal, while liquids begin to empty. Tonic contraction of the proximal stomach also generates a pressure gradient to assist gastric emptying. The distal stomach, comprising the antrum and pylorus, is responsible for grinding solids, and for generating flow across the pylorus – the latter is predominantly pulsatile, rather than continuous. Contractions of the stomach are linked to an underlying electrical rhythm of about three cycles per minute, generated by a gastric pacemaker.

Scintigraphy remains the "gold standard" for measurement of gastric emptying, and the use of dual isotopes allows both the solid and liquid components of a meal to be studied (Figure 6). Regional meal distribution can also be evaluated by defining regions of interest within the stomach.

Figure 6 Scintigraphic gastric emptying study. Proximal and distal gastric "regions of interest" are outlined

Ultrasonography and ^{13}C isotope breath tests are alternative methods of measuring gastric emptying, though the former is restricted to liquid meals. Manometry is used predominantly for research purposes to record the frequency, amplitude, and organization of lumen-occlusive contractions in the antrum, pylorus, and duodenum. Proximal gastric relaxation in response to a meal can be evaluated in the laboratory using an electronic barostat; the volume of air required to maintain a fixed pressure in an intragastric bag is used as an index of proximal gastric tone. The electrical rhythm of the stomach may be recorded from cutaneous electrodes, although the clinical significance of abnormalities of this electrogastrogram (EGG) is unclear, since they are not specific for particular gastrointestinal disorders.

Healthy aging appears to be associated with modest slowing of gastric emptying of both solids and nutrient-containing liquids, but the rate of emptying generally remains within the normal range for young subjects (Moore *et al.*, 1983; Horowitz *et al.*, 1984). The relative slowing of gastric emptying may have implications for appetite regulation, potentially contributing to the "anorexia of aging"; prolongation of gastric distension and of exposure of the small intestine to nutrients might lengthen the period of postprandial satiation. Slow gastric emptying could also influence the absorption of orally administered medications, and a slight reduction in paracetamol absorption has been reported in the healthy elderly when compared to the young. However, absorption of benzodiazepines, tetracycline, or L-dopa is not significantly altered with age *per se*. A number of systemic disorders, which occur frequently in the elderly, are associated with markedly delayed gastric emptying or gastroparesis (Table 2) – acute gastroparesis may also result from the administration of a number of drugs (Table 3).

Table 2 Causes of delayed gastric emptying

Acute
- Drugs (opiates, anticholinergics, L-dopa)
- Postoperative ileus
- Viral gastroenteritis
- Metabolic (hyperglycemia, hypokalemia)
- Critical illness

Chronic
- Idiopathic/functional dyspepsia
- Postsurgical
- GERD
- Chronic liver disease
- HIV infection
- Endocrine and metabolic (diabetes mellitus, hypothyroidism, chronic renal failure, anorexia nervosa)
- Muscular and connective tissue diseases (myotonic dystrophy, muscular dystrophy, dermatomyositis, systemic sclerosis, amyloidosis, tumor-associated)
- Neurological (central nervous system disease, spinal cord injury, chronic idiopathic intestinal pseudo-obstruction, idiopathic autonomic degeneration)

Table 3 Medications with effects on gastrointestinal motility

Decreased motility or gut transit
- Opiates
- Anticholinergics
- L-dopa
- Tricyclic antidepressants
- Calcium channel antagonists
- Nitrates
- Phosphodiesterase type 5 inhibitors (e.g. sildenafil)
- Clonidine (an α-2 agonist)
- Sumatriptan (a 5HT-1P agonist)[a]

Increased motility or gut transit
- Metoclopramide
- Domperidone
- Cisapride, tegaserod, and other 5HT-4 agonists
- Erythromycin (a motilin analog)[b]
- β-blockers
- Selective serotonin reuptake inhibitors

[a]Relaxes the gastric fundus and delays gastric emptying, but increases esophageal motility. [b]Stimulates gastric emptying but slows small intestinal transit.

There is little information about the effects of aging on the mechanics of the stomach, but fasting and postprandial antral motility did not differ between patients aged 18–39 and those aged 40–69 years who were being investigated for unexplained gastrointestinal symptoms (Fich *et al.*, 1989). Proximal gastric compliance is unchanged in the fasting state in the healthy elderly compared to the young, but perception of gastric distension is diminished (Rayner *et al.*, 2000), akin to the reduction in visceral sensitivity evident in the esophagus and stomach. Moreover, proximal gastric accommodation to a meal is delayed when compared with young controls, which might contribute to early satiation. Conversely, the antrum is more distended after a nutrient drink in the healthy elderly, and antral width correlates

with both satiation and satiety, in both young and old subjects (Sturm *et al.*, 2004). EGG recordings are similar in healthy old and young subjects, with subtle differences in the response to nutrients.

There is some evidence for altered responses to the presence of nutrients in the small intestine in the elderly compared to the young. In particular, intraduodenal nutrients stimulate greater cholecystokinin release in the healthy elderly, even allowing for elevated fasting concentrations of cholecystokinin (CCK) in this group (Chapman *et al.*, 2002), while intraduodenal glucose is more satiating than in the young. This enhanced small intestinal feedback could contribute to both delayed gastric emptying, and impaired appetite.

Postprandial Hypotension

Blood pressure can decrease markedly after meals in the elderly, and this represents an important clinical problem, leading to syncope and falls (Jansen *et al.*, 1995). Older people with type 2 diabetes are at particular risk because of the associated autonomic neuropathy. Recent studies indicate that postprandial hypotension should, in the broadest sense, be regarded as a gastrointestinal disorder. The postprandial decline in blood pressure appears to be related to the regulation of splanchnic blood flow, and the release of gastrointestinal peptide hormones, and can be attenuated by administration of the somatostatin analog octreotide. Amongst the macronutrients, carbohydrate, rather than fat or protein, is primarily responsible for the fall in blood pressure. After oral or small intestinal administration of glucose, the magnitude of the fall in blood pressure is related to the rate at which glucose enters the small intestine (O'Donovan *et al.*, 2002). Dietary and pharmacologic approaches that slow gastric emptying and small intestinal carbohydrate absorption may prove to be effective in the treatment of postprandial hypotension.

SMALL INTESTINE

While small intestinal function is critical to good nutrition in the elderly, its motility does not appear to be substantially altered with healthy aging, but can be affected by a number of systemic illnesses.

Changes in Small Intestinal Motor Function Related to Aging

The small intestine is more difficult to study than the esophagus or stomach because of its length and relative inaccessibility. Like the stomach, the frequency of its contractions are linked to an underlying electrical rhythm – in this case between eight and twelve cycles per minute. During fasting, the small bowel undergoes cyclical activity about every 90 minutes known as the *migrating motor complex* (MMC), consisting of motor quiescence (phase I), irregular contractions of increasing frequency (phase II), and a brief (5–10 minutes) period of regular contractions that propagate distally and serve to sweep the lumen of debris (phase III). After a meal, the MMC is interrupted by irregular motor activity propagated over short distances that facilitates digestion and absorption.

Small intestinal manometry is carried out in specialized research laboratories, and has limited clinical application. Transport through the small intestine can be measured more readily, by either a breath test (which detects an increase in hydrogen resulting from breakdown of ingested nonabsorbable carbohydrate, such as lactulose, by colonic bacteria, and therefore reflects orocecal transit), or by scintigraphy.

MMC periodicity was not altered in healthy elderly volunteers aged 81 to 91 years when compared with the young, using ambulatory jejunal recording, though the propagation velocity of phase III was slower. The elderly had comparable amplitude and frequency of pressure waves to the young during phase III of the MMC and postprandially, but more propagated clustered contractions during fasting and postprandial recordings (Husebye and Engedal, 1992). The functional significance of the latter phenomenon is unclear, but similar patterns are seen in patients with the irritable bowel syndrome (IBS). Nevertheless, small intestinal transit in the healthy elderly seems to be comparable to the young, in contrast with the delayed transit characteristic of the colon (Madsen and Graff, 2004). This is consistent with the observation that small bowel bacterial overgrowth is uncommon in healthy older individuals (Mitsui *et al.*, 2003).

Aging is associated with an increased prevalence of conditions, such as diabetes mellitus, that potentially affect small intestinal motility, as well as small intestinal diverticula. Such conditions may induce stasis of small intestinal contents, and together with the reduction in gastric acid secretion often seen on the elderly, predispose to bacterial overgrowth, a potential cause of malnutrition and diarrhea (Firth and Prather, 2002). Small bowel bacterial overgrowth may be diagnosed by culture of duodenal aspirates, or by hydrogen breath tests (with glucose or xylose as a substrate), although the specificity of the latter may be poor in the elderly (about 30%). A subsequent negative test following a course of antibiotics increases the diagnostic certainty. Treatment is with antibiotics such as metronidazole, tetracycline, or quinolones, given for 1 to 4 weeks, and may need to be repeated on a cyclical basis in the event of recurrence.

SYSTEMIC DISORDERS ASSOCIATED WITH DISTURBANCE OF GASTROINTESTINAL MOTILITY

Although the effects of healthy aging *per se* on gastrointestinal motility are modest, the prevalence of comorbidities increases with advancing age, and these may impact on gut

function; Parkinson's disease and diabetes mellitus are typical examples. Progressive systemic sclerosis is less common, but has profound effects on gastrointestinal motility. Furthermore, numerous medications can affect gastrointestinal motility; some of these are listed in Table 3.

Parkinson's Disease

Gastrointestinal dysfunction represents a common manifestation of Parkinson's disease (Pfeiffer, 2003). Involvement of the dorsal motor nucleus of the vagus may influence parasympathetic innervation, while abnormalities of the enteric nervous system itself (such as Lewy bodies and loss of dopaminergic neurons) are also evident.

Dysphagia is common, with prominent disturbance of the oropharyngeal phase of swallowing, as well as impaired esophageal transit, associated with nonperistaltic or tertiary pressure waves. The effects of either L-dopa or anticholinergic therapy on swallowing disorders are inconsistent; both drugs may be associated with either improvement or deterioration in dysphagia. Limited data indicate benefit from apomorphine.

Gastric emptying may be delayed, even in the absence of L-dopa therapy, which in turn slows gastric emptying further. Delayed gastric emptying may contribute to a high prevalence of symptoms such as nausea and bloating, and result in impaired nutrition and absorption of oral medications. In particular, L-dopa may be metabolized to dopamine if retained in the stomach, and become unavailable for systemic absorption. In patients suffering from the "on–off" phenomenon of motor fluctuations, gastric emptying may normalize in the "on" phase, while conversely, variations in the rate of emptying may result in erratic L-dopa absorption, and in themselves contribute to the on–off phenomenon. Metoclopramide is contraindicated in parkinsonian patients because of its effects on striatal dopamine receptors, but other prokinetic agents such as domperidone (which does not cross the blood-brain barrier) can be used. Small intestinal, colonic, and anorectal dysmotility are also common in Parkinson's disease, and may be associated with bowel dilatation and constipation. Orocecal transit time is prolonged compared with age-matched controls.

Diabetes Mellitus

Diabetes mellitus, and particularly type 2 diabetes, is increasing dramatically in prevalence worldwide, and occurs frequently in older individuals. Disordered motor function involving all segments of the gastrointestinal tract is common in diabetes, and there is a high prevalence of gut symptoms (Horowitz *et al.*, 2002), though little information specific to elderly patients with diabetes. Although both disordered motility and gut sensation have been attributed to irreversible autonomic neuropathy, it is now recognized that acute changes in the blood glucose concentration have a major influence on gut function (Rayner *et al.*, 2001).

In the esophagus, manometric abnormalities observed in diabetes include reduction in amplitude of pressure waves, abnormal waves forms, and failure of peristalsis, which are associated with delayed esophageal transit. LES pressure may be diminished, and the prevalence of GERD is increased.

Up to 50% of patients with longstanding diabetes have delayed gastric emptying for solids, liquids, or both. Motor correlates of these abnormalities include diminished antral motility and impaired coordination of antroduodenal pressure wave sequences, together with reduced fundic tone. Both the delay in gastric emptying and the underlying motor mechanisms are more marked during acute hyperglycemia, when compared to euglycemia. Disordered gastric emptying potentially contributes to upper gut symptoms, impairs absorption of nutrients and orally administered medications, and may result in, as well as arise from, poor glycemic control. While a delay in gastric emptying may actually improve the postprandial blood glucose profile in noninsulin-requiring patients due to slower release of carbohydrate to the small intestine, it is likely to result in a mismatch between the absorption of glucose and the onset of insulin action in patients receiving exogenous insulin. Patients with upper gut symptoms referable to the stomach should be investigated with endoscopy to exclude mucosal lesions or obstruction, and consideration can then be given to evaluating the rate of gastric emptying, ideally with scintigraphy. Diabetic gastroparesis is usually treated with a prokinetic drug, such as cisapride (now withdrawn in many markets owing to a risk of cardiac arrhythmia), metoclopramide, domperidone, and erythromycin (an analog of motilin).

Small intestinal motility is also frequently abnormal in diabetes mellitus. During fasting, the duration of the phases of the MMC are reduced, while postprandially, bursts of nonpropagated pressure waves may occur, together with disordered flow patterns of chyme. Small bowel transit appears widely variable in patients with diabetes, and its relationship to gastrointestinal symptoms and glycemic control remains to be clarified. Both diarrhea and constipation appear common in diabetes; small bowel bacterial overgrowth, coeliac disease, and pancreatic exocrine insufficiency should be specifically excluded when patients with diabetes present with diarrhea. Loperamide and clonidine (an α-adrenergic agonist) may be of benefit when no specific cause for diarrhea is uncovered, although older patients may be particularly susceptible to adverse reactions (constipation, urinary retention, and glaucoma for loperamide; hypotension, bradycardia, sedation, and dry mouth for clonidine).

Progressive Systemic Sclerosis

The peak incidence of progressive systemic sclerosis is in the fifth and sixth decades, and gastrointestinal involvement is common (Rose *et al.*, 1998). Esophageal dysmotility has a prevalence of about 80%, with diminished amplitude of pressure waves, and sometimes a lack of peristalsis, leading to impaired acid clearance and severe reflux disease. LES resting pressure also tends to be extremely low. Furthermore,

the stomach, small and large intestines, and anorectum may be involved, with clinical manifestations of gastroparesis, pseudo-obstruction, bacterial overgrowth (sometimes associated with small intestinal diverticula), malnutrition, and constipation or fecal incontinence. Smooth muscle atrophy and fibrosis underlie some of these disturbances, but inhibition of cholinergic transmission in the enteric nervous system by antibodies to M3 muscarinic receptors may be important in the pathogenesis. Similar effects on gastrointestinal motility may be seen in other connective tissue disorders, and in amyloidosis. PPIs are effective in the treatment of GERD, while prokinetic drugs have a role when gastrointestinal transit is delayed.

FUNCTIONAL DISORDERS

Functional gastrointestinal diseases are characterized by recurrent or persistent symptoms referable to the gut, occurring in the absence of demonstrable organic disease. This group of disorders includes functional dyspepsia (upper abdominal pain, bloating, or nausea) and IBS (abdominal discomfort, which may be relieved by defecation, associated with abnormal bowel habit), as well as other syndromes related to the esophagus, anorectum, and biliary tract.

The prevalence of IBS appears to be less in the elderly than the middle aged in the United States and United Kingdom (Bennett and Talley, 2002), and at all ages the prevalence is greater in women than men. Somewhat surprisingly, the incidence, as opposed to prevalence, of IBS appears to increase with age, in at least one US population (Locke *et al.*, 2004). This may potentially reflect an increase in health care seeking behavior in the elderly, though no information regarding consulting behavior in IBS is available specifically for this age-group. In a study of 70-year olds in a Danish community, while 6 to 18% had gastrointestinal symptoms consistent with IBS according to various definitions, symptoms had resolved in at least half within the following five years (Kay, 1994), which is probably similar to the prognosis of IBS in the general community. Similar patterns were observed for upper gut symptoms consistent with functional dyspepsia, suggesting that abdominal symptoms are frequent in the elderly, but fluctuate considerably over time. In the general population, around 10% of functional gut disorders follow a bout of infectious gastroenteritis, but recent evidence suggests the elderly are less prone to developing chronic postinfective symptoms than the young. In contrast to IBS, there is little information regarding the prevalence of functional dyspepsia in older populations.

While, as discussed, visceral sensitivity seems to decline in healthy aging, patients with functional dyspepsia or IBS have, as a group, increased sensitivity to gastric and rectal distension. Nevertheless, chronic gastrointestinal symptoms consistent with IBS are common in the elderly, though not markedly greater than in the young, with the possible exception of constipation. Visceral sensitivity has not been studied in the elderly with gut symptoms; nor has tolerance to visceral pain (the lowest level of stimulation at which a subject withdraws or asks to stop). The latter may be relevant, since pain tolerance for somatic stimuli appears to decrease with aging. The prevalence of *Helicobacter pylori* is greater in the older individuals than the young (about 60% at 60 years), but in the absence of peptic ulceration, its contribution to dyspepsia is controversial (Firth and Prather, 2002).

It is important to exclude organic diseases such as cancer and mesenteric ischemia when gut symptoms arise in older patients, particularly as the prevalence of organic disease is greater than in the young (Bharucha and Camilleri, 2001). For example, when patients present with altered bowel habit, the threshold for colonoscopic investigation should be low. Comorbidities such as Parkinson's disease, medications, thyroid disease, diabetes, depression, and small bowel bacterial overgrowth must also be considered.

Chronic gastrointestinal symptoms impair quality of life, but many elderly do not present to their doctors, so their impact may go unrecognized in older populations. Depression associated with chronic pain does not appear to be greater in the elderly than the young, but it should be borne in mind that "gut" symptoms like anorexia or bowel habit disturbance can also be features of depression. The effects of anxiety on the perception of persistent, as opposed to acute, pain have not been studied closely (Bharucha and Camilleri, 2001).

All potential therapies for functional gut disorders must be evaluated against the high placebo response rate (between 20 and 70%) associated with these syndromes, but no clinical trials have focused specifically on the elderly (Bennett and Talley, 2002). When constipation is a feature of IBS, adequate hydration and fiber supplements should be tried, with the caveat that bloating may exacerbated by high fiber intake. Tegaserod (a 5HT-4 partial agonist) may have modest benefit for symptom improvement in constipation-predominant IBS; most patients in randomized controlled trails have been female, with a minority (about 10%) over 65 years old, for whom no subgroup analysis is available.

When diarrhea and fecal urgency predominate, loperamide can be beneficial; a liquid formulation, if available, makes dose titration easier. Alosetron (a 5HT-3 antagonist) may have a place in diarrhea-predominant IBS in women, but the association of this drug with ischemic colitis suggests the need to exercise caution, especially in the elderly. As with tegaserod, randomized controlled trials have only included a few patients over 65 years old. In theory, supplemental fiber should improve the water-holding capacity of stool, but its benefit in diarrhea has not been proven.

Antispasmodics (e.g. mebeverine, hyoscine) are helpful for abdominal pain in some patients, but have anticholinergic side effects such as postural hypotension, visual blurring, and urinary hesitancy, which may affect the elderly in particular. Antidepressants may also be useful when the predominant symptom is pain, as opposed to diarrhea or constipation, and response is as good in older patients as in the young. The dose of tricyclic antidepressant used in functional gut disorders is typically lower than standard

doses used to treat depression. Selective serotonin reuptake inhibitors may be better tolerated than tricyclics, but there are less data regarding their efficacy in IBS. Probiotics may be of benefit for bloating. Psychotherapy and hypnotherapy have recently shown promise in the management of functional bowel disorders, but no information is available about their applicability to the elderly.

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KEY POINTS

- Healthy aging is associated with minimal change in gastrointestinal motor function, but visceral sensation declines with age.
- Gastrointestinal motility may be compromised by an increased prevalence of systemic illness and medication use in the elderly.
- Clinical sequelae of disturbed gut motility and sensation include swallowing disorders, impaired nutrition and absorption of medications, and altered bowel habit.
- Functional gastrointestinal disorders occur frequently in the elderly, but organic disease must be rigorously excluded.

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Gastrointestinal Bleeding

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INTRODUCTION

Gastrointestinal bleeding (GI) is a common geriatric problem (Antler *et al.*, 1981; Allen and Dykes, 1976). In the United States, about 350 000 patients are hospitalized for upper GI bleeding each year (Papp, 1991) and 35–45% of these are 60 years or older (Reinus and Brandt, 1990). The incidence of upper GI bleeding ranges between 50 and 150 per 100 000 population per year (Gilbert, 1990). Women aged 60 years and older account for 60% of upper GI bleeding (Schiller *et al.*, 1970). The mortality of upper GI bleeding has remained approximately 6–10% for the last 60 years (Warren and Marshall, 1983; Peterson *et al.*, 1981; Browder *et al.*, 1986). No difference is present in morbidity and mortality between the young and old persons (Segal and Cello, 1997). In a British study, the mortality rate for upper GI bleeding was 14% for the entire population but only 0.6% for persons younger than age 60 without malignancy or organ failure at presentation. Most deaths were reported in elderly patients or those with severe concurrent illness (Silverstein *et al.*, 1981b).

The exact incidence of lower GI bleeding is not known (Vernava *et al.*, 1997) but incidence of hospitalization is about 20 to 27 episodes per 100 000 persons per year (Longstreth, 1997; Yovarski *et al.*, 1995) with a 200-fold increase with advancing age from the third to ninth decades (Longstreth, 1997). The mortality for lower GI bleeding is 4–10% or greater (Makela *et al.*, 1993; Velanovich, 1996). Presence of selected physical findings are related to increased mortality in patients with GI bleeding compared to the situation without these findings; respiratory failure (57%), jaundice (42%), mental confusion (31.2%), shock (30%), congestive heart failure (28%), and postural blood pressure change (14%) (Silverstein *et al.*, 1981b). Similarly, the presence of some underlying diseases process are responsible for increased mortality than if they were absent; renal 29.4%, liver 24.6%, neoplasm 24.3%, central nervous system 23.5%, and lung 22.6%.

Clinical Presentation

The most common presenting complaint in both younger and older people with acute upper GI bleeding is hematamesis as apposed to hematamesis and melena or melena alone. It might be difficult at times to determine accurate clinical presentation in older people because of poor vision or poor cognition, for example, providing vague description of hematamesis versus hemoptysis.

Table 1 shows the different sign and symptoms a patient with a GI bleeding presented to Saint Louis University Hospital. The most common presenting symptom was melena in both upper and lower GI bleeding. Some of the other presenting complaints were hematamesis, nausea, coffee ground emesis, abdominal pain, anemia, rectal bleeding (these patients had massive active bleeding requiring significant number of transfusions), and reflux symptoms. The common signs and symptoms for lower GI bleeding are melena, rectal bleeding, fecal occult bleeding, nausea, abdominal pain, and anemia. Fecal occult bleeding was seen in both upper and lower GI bleeding (Tariq *et al.*, 1999, 2000).

The manifestation of GI bleeding varies with underlying medical problems; for example, a patient with underlying ischemic heart disease may present with chest pain after brisk bleeding. Coexistent heart failure, hypertension, renal disease, diabetes, and pulmonary disease may be aggravated by severe GI bleeding, resulting in a shock. Some patients with chronic blood loss may present with signs of anemia (weakness, pallor, dizziness, fatigue) or cirrhosis and portal hypotension. GI bleeding can also cause hepatic encephalopathy in patients with existing liver disease or cause hepatorenal syndrome. Orthostatic changes may be seen with lesser or moderate degree of bleeding.

Clinical Course

The hospital course of GI bleeding is similar in both young and older persons with respect to endoscopic therapy for

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Table 1 Presenting signs and symptoms of patients with gastrointestinal bleeding

	Upper gastrointestinal bleeding (%)	Lower gastrointestinal bleeding (%)	Both[a] (%)
Melena	37	38	33
Hematemesis	35	0	9
Rectal bleed	7	29	21
Anemia	12	8	20
FOB[b]	14	20	23
Coffee ground	17	0	4
Nausea	19	18	18
Reflux	2	3	3
Abdominal pain	15	15	21

[a]Both = upper and lower gastrointestinal bleeding. [b]Fecal occult bleeding.

Table 2 Factors predictive of ulcer rebleeding and mortality in older adults

Clinical factors	
Hemodynamic instability	
Bleeding manifested as hematamesis or hematochezia	
Failure of blood to clear with gastric lavage	
Age >60 years	
Coagulopathy	
Presence of underlying serious medical condition	
Hospitalization	
Endoscopic factors	*Risk of rebleeding*
Clean base	5%
Flat spot	10%
Adherent clot	22%
Nonbleeding vessel	43%
Arterial bleeding	55%

bleeding and rebleeding, need for admission to intensive care, blood transfusion requirements, need for surgery, and length of hospital stay (Antler *et al.*, 1981; Segal and Cello, 1997; Silverstein *et al.*, 1981b). The length of hospital stay has shortened since 1970–1980 into the 1990s (Silverstein *et al.*, 1981b). In 1992 and 1994, the mean hospital stay for upper GI bleeding in older adults (>60 years) was 6.0 days compared with 5.6 days in those less than 60 years of age. Table 2 describes factors predictive of ulcer rebleeding and mortality in older adults. The need for surgery is higher for adherent clot, nonbleeding vessel, and arterial bleeding compared to clean base and flat spot. Also, mortality rates are higher for arterial bleeding compared to clean base (Schiller *et al.*, 1970; Branicki *et al.*, 1990; Laine *et al.*, 1992).

Causes of GI Bleeding

In the elderly, esophagitis and gastritis in combination with peptic ulcer disease accounts for 70–91% of hospital admissions for upper GI bleeding. A greater percentage of patients with Mallory–Weiss tears, gastrointestinal varices, and gastropathy are seen in the younger population as a result of the greater degree of alcohol abuse in this age-group.

The causes of GI bleeding between the young-old and old-old are as shown in Table 3 at Saint Louis University Hospital. Gastritis was the most common endoscopic diagnosis of upper GI bleeding in the young-old and old-old group (34 vs 38%), followed by gastric ulcer (21 vs 19%), duodenitis (20 vs 16%), esophagitis (15 vs 14%), and duodenal ulcer (7 vs 12%) respectively. Esophageal varices and gastric angiodysplasia were more common in the young-old, while neither duodenal angiodysplasia nor Mallory–Weiss syndrome (2 vs 3%) was different. Table 4 shows the causes of lower GI bleeding at Saint Louis University; hemorrhoids ($p = 0.03$), diverticulosis ($p = 0.0006$), and polyps ($p = 0.06$) were more common in the old-old group as compared to the young-old group and there was no difference among the other lesions in the two groups.

The histological diagnosis of 183 patients was available with a total of 262 lesions, as shown in Table 5; gastritis was the most common lesion, which included both *Helicobacter pylori* gastritis and other gastritis. The diagnosis of gastritis included lesions such as acute gastric erosions, chronic active gastritis, and chronic active gastritis with metaplasia, chronic gastritis with inflammation, gastric atrophy with inflammation, and acute and chronic gastritis with or without inflammation. We used kappa statistics to see the agreement between the endoscopic and histological diagnosis of gastritis

Table 3 Upper gastrointestinal bleeding sites on endoscopy

	60–75 years		≥75 years (%)	
	$N = 239$(%)	$L = 359$(%)	$N = 159$(%)	$L = 224$(%)
Gastritis	82 (34)	(23)	60 (38)	(27)
Gastric ulcer	49 (21)	(14)	30 (19)	(13)
Duodenitis	48 (20)	(13)	26 (16)	(16)
Esophageal varices	37 (16)	(10)	4 (3)	(2)
Gastric angiodysplasia	16 (16)	(4)	10 (6)	(4)
Esophagitis	36 (15)	(10)	22 (14)	(10)
Duodenal ulcer	17 (7)	(5)	19 (12)	(8)
[a]Greater than one gastric lesion	18 (8)	(5)	15 (9)	(7)
[a]Greater than one esophageal lesion	29 (9)	(8)	18 (9)	(8)
Others[b]	27 (11)	(8)	20 (13)	(9)

N = Total number of patients.
L = Total number of lesions.
[a]More than one lesion in the area that could be attributed to bleeding. [b]Others include lesions such as esophageal cancer, Barrett's esophagus, duodenal angiodysplasia; one patient has duodenal and one has gastric polyp, and one has duodenal adenoma.

Table 4 Lower gastrointestinal bleeding sites on colonoscopy

	60–75 years (%)		≥75 years (%)	
	$N = 91$	$L = 114$(%)	$N = 58$	$L = 107$(%)
Hemorrhoids[a]	28 (30.7)	(25)	28 (48)	(26)
Diverticulosis[a]	29 (31.8)	(25)	35 (60)	(33)
Polyps	33 (36.2)	(29)	30 (52)	(28)
Colonic angiodysplasia	11 (12)	(10)	3 (5)	(3)
Colon masses	4 (4.3)	(4)	4 (7)	(4)
Rectal ulcer	5 (5.4)	(4)	2 (3)	(2)
Colitis	4 (4.3)	(4)	5 (9)	(5)

L = Total number of lesions.
N = Total number of patients.
[a] $p < 0.05$.

Table 5 Causes of bleeding by histological diagnosis of 183 patients with 262 lesions

Site of Lesions	N	(%)
Esophagitis	18	7
Barrett's esophagus	7	3
Non-HP gastritis	59	23
HP gastritis	24	9
Gastric ulcer	18	7
Gastric cancer	10	6
Duodenitis	18	7
Duodenal ulcer	8	3
Other upper GI lesions[a]	12	5
Colon neoplasm[b]	40	15
Polyps[b]	31	12
Colitis	11	4
Other lower GI lesions[c]	8	3

HP, *Helicobacter pylori*; N, Total number of lesions; GI, Gastrointestinal.
[a]Includes patients with esophageal ulcer and carcinoma, gastric and duodenal Angiodysplasia and duodenal adenoma. [b]See text. [c]Includes patients with diverticulitis (4) and colonic ulcer (2) and angiodysplasia (2).

in 183 patients who were biopsied. The agreement was 57%, which means both the tests agreed on the diagnosis 57% of the times. Among the lesions with gastric carcinoma, three lesions were metastatic while the rest were primary gastric lesions. The other upper gastrointestinal lesions included three lesions each with esophageal ulcer, cancer, gastric angiodysplasia, and one lesion with duodenal angiodysplasia.

The total lesions in the LGI tract were 90; polyps (31), colon neoplasm (40), colitis (11), angiodysplasia (2), colon ulcer (2), and diverticulitis (4). Among these lesions, colon neoplasm was the most common. The neoplastic lesions were leiomyosarcoma (1), villous adenoma (2), rectal adenoma (2), tubular adenoma (26), and adeno-carcinoma (9). The polyps were split into adenomatous (5), hyperplastic (16), and adenomatous change (10). Colitis included cryptitis (2), ischemic colitis (4), pseudo-membranous colitis (1), radiation colitis (1), and nonspecific colitis (3).

Tables 6 and 7 summarize the site of different studies, number of patients, age, and physician by specialty involved for both upper and lower GI bleeding. Table 8 shows the prevalence of upper GI bleeding in different studies. The prevalence of upper GI causes are gastric ulcer (5–43%), duodenal ulcer (6–42%), gastritis (6–42%), esophagitis (2–15%), and esophageal varices (1–20%), Mallory–Weiss tear (1–16%), and others are reported (combination of lesions) between 2 and 17%. The common causes of lower GI bleeding are summarized in Table 9. The prevalence of diventricular bleeding 17–56%, angiodysplasia 3–30%, hemorrhoids 3–28%, polyp as a cause of bleeding 2–30%.

Evaluation and Management of Gastrointestinal Bleeding

In this section, the general evaluation and management of GI bleeding is discussed. For disease-specific treatment, refer to gastroenterology texts.

Initial Evaluation

The first step in the management of GI bleeding patient is stabilization with blood transfusion and other treatments deemed necessary before any diagnostic evaluation. If the patient's initial blood pressure and pulse rate are normal, consider performing orthostatic blood pressure and pulse (sitting/lying and standing positions). Orthostatic changes are usually suggestive of 10–20% loss in circulatory volume, although supine hypotension suggests greater than 20% loss. Hypotension with a systolic BP less than 100 mm Hg or baseline tachycardia suggests significant hemodynamic compromise that requires urgent volume resuscitation. All patients require a complete history and physical examination; blood studies (platelet count, prothrombin time, partial thromboplastin time); liver function tests, renal functions, and complete blood counts. Determination of blood group and typing and crossing 2–4 units of blood should be performed urgently.

Restoration of intravascular volume is established by inserting two large-bore intravenous peripheral lines with 18 gauge catheter or central venous line. Fluids used for resuscitation includes normal saline, lactated Ringer's solution or 5% hetastarch, and blood transfusion as soon as it is available to improve the oxygen carrying capacity. Those patients who are in shock may need volume administration using infusion devices or vasopressors if clinically indicated.

Correction of coagulopathy is absolutely necessary, if possible, using infusion of fresh frozen plasma to correct/prolong

Table 6 Studies examining upper gastrointestinal bleeding

Author	N	Type of study	Physician	Age	Site (Hospital)
Palmer (1969)	1400	Prospective	GI	14–94	VA, East Orange, NJ
Crook *et al.* (1972)	768	Retrospective	S	53[a]	Charity Hospital, New Orleans, LA
Allen *et al.* (1973)	71	Prospective?	S/GI	15–84	Henry Ford, Detroit, MI
Sagawa *et al.* (1973)	178	Prospective	S	?	Detroit General Hospital, MI
Cotton *et al.* (1973)	208	Prospective	S/GI	2–84	St Thomas, London
Katon and Smith (1973)	100	Prospective	GI	19–84	VA, Portland, OR
Paull *et al.* (1974)	206	Prospective	GI	14–83	Queen Elizabeth, S. Australia.
Katz *et al.* (1975)	200	Prospective	GI	?	Metropolitan Hospital, NY
Lee and Dagradi (1975)	400	Retrospective	GI	29–87	Kaiser Permanente, CA
Katz *et al.* (1976)	1429	Retrospective	GI	?	Metropolitan Hospital, NY
Dagradi *et al.* (1979)	500	Retrospective	GI	40–79	VA, Long Beach, CA
Antler *et al.* (1981)	50	Prospective	GI	55–97	NYMC Metropolitan, NY
Peterson *et al.* (1981)	206	Rand. Control	GI	55 ± 0.9[b]	VA + Southern Med Sch, Dallas, TX
Silverstein *et al.* (1981a)	2097	Prosp. Data survey.	GI	57 ± 17.5	Private Practice
Brolin and Stremple (1982)	624	Retrospective	S	?	Pittsburgh Health Center, PA
Bansal *et al.* (1987)	92	Prospective	S/G	65–93	Ryhope Gen Hosp, Sunderland
Borch (1988)	684	?	S	?	Sweden
Tabibian and Sutton (1990)	605	Prospective	GI	?	Ben Taub Gen Hosp, Houston, TX
Segal and Cello (1997)	200	Retrospective	GI	Less than 60 years and older	General hospital, San Francisco, CA
Vreeburg *et al.* (1997)	1389	Prospective	GI	2–100	Amsterdam
Zimmerman *et al.* (1997)	248	Prospective	GI	64 ± 0.2 84 ± 0.4	Hadassah University Hospital Jerusalem, Israel
Wilcox and Clark (1999)	727	Prospective	GI	50 ± 15.4	Grady Memorial hospital, Atlanta
Tariq *et al.* (2000)[c]	397	Retrospective	G/GI	60–100	Saint Louis University Hospital, MO

G, Geriatrics; GI, Gastroenterology; S, Surgery.
[a]Mean age. [b]Mean with SD. [c]Unpublished data from Saint Louis University Hospital.
N = Number of subjects.

Table 7 Studies examining lower gastrointestinal bleeding

Author	N	Physician	Type	Age	Site of study
Boley *et al.* (1979)	183	GI	Retrospective	≥65	Montefiore Hospital and Medical Center, NY
Caos *et al.* (1986)	35	GI	Prospective?	6–85	University of New Mexico and VAMC, Albuquerque/ Portland, Oregon.
Leitman *et al.* (1989)	68	S	Prospective?	63[a]	New York Hospital-Cornell Medical Center, NY
Jensen and Machicado (1988)	80	GI	Prospective	21–93	UCLA Center for Health Sciences, and VAMC, LA
Makela *et al.* (1993)	266	S	Prospective	24–86	Oulu University hospital, Oulu, Finland
Richter *et al.* (1995)	107	GI	Retrospective	21–93	Massachusetts General Hospital, Boston
Peura *et al.* (1997)	635	GI	Survey	49–64	Private practice and tertiary teaching hospitals. American College of GI Bleeding Registry
Longstreth (1997)	2113	Medicine	Retrospective	20–80	Kaiser Permanente Medical Center, San Diego, CA
Wilcox and Clark (1999)	150	GI	Prospective	?	Grady Memorial Hospital, Atlanta, GA
Tariq *et al.* (2000)	149	GI/G	Retrospective	60–100	St Louis University Hospital, St Louis, MO

N = Number of patients.
[a]Mean age.

coagulation parameters. Protamine infusion can be used for immediate reversal of anticoagulation from heparin drip. Parental vitamin K may be used for prolonging prothrombin time from warfarin therapy or liver disease. Platelets transfusion may be indicated when the count is less than 50 000/mm (Papp, 1991). Protection of the airway may be needed in circumstances where there is a decrease in mental status (shock, encephalopathy), massive hematamesis, or active variceal hemorrhage is present.

History

A detailed history could point toward a possible diagnosis. Pain in the epigastric region relieved by food or antacid suggests peptic ulcer disease. Weight loss and anorexia may suggest gastrointestinal malignancy, but in the geriatric population, the most common cause of weight loss is depression and should be ruled out before initiating malignancy workup. Dysphagia can be due to stricture or cancer of the esophagus. Mallory–Weiss tear can be caused by intractable vomiting. Hematamesis usually suggests upper GI bleeding, but precautions should be taken as older people may have poor vision and are unable to provide accurate description. Melena could be seen in both upper and lower GI bleeding, and usually requires about 100 cc of blood. The stool remains positive for blood for almost 2 weeks. Patient with inflammatory bowel disease or infectious colitis (Shigella, Salmonella, Campylobacter) usually present with

Table 8 Comparison of upper gastrointestinal bleeding in percentages

Author	GU	DU	E	G	D	EV	AVM	MW	GCA	ND	OTH
Palmer (1969)	16	28	7	12	–	19	–	5	–	7	6
Crook *et al.* (1972)	9	42	–	11	–	–	–	1	2	12	5
Allen *et al.* (1973)	27	25	–	25	1	6	1	1	–	10	3
Sagawa *et al.* (1973)	18	11	2	42	1	5	1	15	4	–	–
Cotton *et al.* (1973)	27	21	7	9	1	3	1	1	2	14	–
Katon and Smith (1973)	15	23	13	9	–	16	–	8	15	4	–
Paull *et al.* (1974)	20	32+	–	20	5	6	–	6	4	–	17
Katz *et al.* (1975)[a]	5	23	0	22	0	17	–	–	–	22	11
	7[b]	8	4	37	9	7	–	–	–	18	10
Lee and Dagradi (1975)	43[a]	–	–	19	–	–	–	–	–	–	–
Katz *et al.* (1976)	3	21ø	–	36	–	16	–	–	–	14	13
Dagradi *et al.* (1979)	31[a]	–	–	34	–	16	–	6	2	11	–
Antler *et al.* (1981)[d]	29	21	14	17	0	12	–	2	2	–	–
Peterson *et al.* (1981)	18	22	–	6	–	20	–	16	2	12	–
Silverstein *et al.* (1981a)	22	23	13	30	9	15	0.5	8	4	–	7
Brolin and Stremple (1982)	10	23	–	34	–	12	–	–	–	15	6
Bansal *et al.* (1987)	25	25	–	22	–	1	–	–	9	3	14
Borch (1988)	–	–	–	11	–	–	–	–	–	–	–
Tabibian and Sutton (1990)[c]	24	19	15	5	–	25	–	6	0.4	5	2
	22	33	9	3	–	20	1	8	3	1	3
Segal and Cello (1997)[e]	35	38	11	7	–	11	–	3	1	–	–
Vreeburg *et al.* (1997)	12	20	7	5	–	9	1	5	3	22	7
Zimmerman *et al.* (1997)ψ	21	36	11	7	–	6	–	–	–	–	–
Wilcox and Clark (1999)	26	24	4	7	–	9	–	6	–	4	10
Tariq *et al.* (2000)[f]	14	6	10	24	13	7	9	3	–	–	16

GU, Gastric ulcer; DU, Duodenal ulcer; E, Esophagitis; G, Gastritis; D, Duodenitis; EV, Esophageal varices; AVM, Angiodysplasia; MW, Mallory–Weiss tear; GCA, Gastric cancer; ND, no abnormality detected; OTH, Others.
[a]Peptic ulcer, ø chronic peptic ulcer + Pyloroduodenal ulcer. ψ both patient groups added (60–69 years and ≥80 years). [b]First row is flexi rigid era and second is Panendoscopy era. [c]First row includes patients in the county hospital and the second row includes patients in community hospital. [d]Only patients aged 55 and above included. [e]Only patients >60 years reported. [f]Unpublished data from Saint Louis University Hospital, percentages of lesion, total lesions 583 of 395 patients.

Table 9 Comparison of lower gastrointestinal bleeding in percentages

Author	D	CCA	AVM	H	IBD	P	C	CU	ND	O
Boley *et al.* (1979)[a]	34	8	–	7	1	11	3	–	12	17
[b]	43	5	20	–	1	4	2	–	11	14
Caos *et al.* (1986)	23	3	20	–	–	14	1	–	23	9
Leitman *et al.* (1989)	26	7	24	2	4	2	6	–	–	9
Jensen and Machicado (1988)	17	11	30	–	–	2	9	–	6	14
Makela *et al.* (1993)	19	10	6	28	8	11	4	–	27	13
Richter *et al.* (1995)	47	10	12	3	3	–	3	–	14	2
Peura *et al.* (1997)	30	8	10	–	8	9	6	–	–	28
Longstreth (1997)	42	9	3	5	2	4	14	–	12	10
Wilcox and Clark (1999)	56	7	5	3	2	2	2	10	4	5
Tariq *et al.* (2000)[c]	29	4	6	25	–	30	4	2	–	–

D, Diverticulosis; CCA, Colon carcinoma; AVM, Angiodysplasia; H, Hemorrhoids; C, Colitis; IBD, Inflammatory bowel disease; P, Polyp; CU, Colonic ulcers; ND, No diagnosis; O, Others.
[a]Minor bleeding. [b]Major bleeding. [c]Percentages of all patients.

bloody diarrhea, fever, and abdominal pain. One needs to be very cautious initiating diagnostic workup in older patients for bleeding diathesis with skin tears and ecchymosis, since this is seen in older patients with minor trauma. Occult blood or hematochezia could be the first sign of colon cancer or polyps. Painless lower GI bleeding can also be seen in diverticulosis, angiodysplasia, or ulcerated cancerous lesion. Blood on the surface of stool or blood on toilet paper suggest internal hemorrhoids. It is equally important to determine the patient's cognitive ability by using Mini-mental status examination (Folstein *et al.*, 1975) or Saint Louis University Mental Status examination (Morley and Tumosa, 2002) to assess cognition. If a patient is demented, then it is advisable to obtain history from the caregiver accompanying the patient, or by obtaining history from the nursing home staff.

Drug history is very important, especially the use of aspirin, nonsteroidal anti-inflammatory, and anticoagulation drugs. Some over-the-counter cough medication are usually combined with aspirin and patients may not be aware of it.

Physical Examination

A detailed physical examination starting with inspection of the nose and throat is important to exclude bleeding in this

area. Look for signs of chronic liver failure (spider angiomas, hepatosplenomegaly, ascites, and jaundice). Look for arteriovenous malformation, especially of the mucous membranes, which may be associated with hereditary hemorrhagic telangiectasia (Rendu Osler–Weber syndrome), in which multiple angiomas of the gastrointestinal tract are associated with recurrent bleeding. Cutaneous nail bed and gastrointestinal telangiectasia may be associated with connective tissue disease or scleroderma. A digital rectal examination is very important to feel for masses, fissures, and obtain a sample of stool, to be tested chemically for blood. It is also mandatory to comment on the color of stools. Internal hemorrhoids, if thrombosed, could be felt by digital examination. If available, anoscopy or sigmoidoscopy should be used to confirm if internal hemorrhoids or ulcer or distal masses are the source of the problem.

If upper GI bleeding is suspected, a nasogastric lavage should be performed. Bloody nasogastric lavage is suggestive of upper GI bleeding but is negative in about 10% of cases. Coffee ground aspirates indicate bleeding that is slow or has stopped, but bright red blood indicates active bleed. Continuous nasogastric aspiration helps monitor the status of bleeding.

Esophagogastroduodenoscopy (EGD) can be performed at the bedside or in the GI suites, and is the preferred method of investigation and therapy of the upper GI tract bleeding. It has the highest diagnostic accuracy, therapeutic capacity, and low morbidity. It can be performed early in the clinical course, after the patient is hemodynamically stabilized. There is no role for barium X rays in acute upper GI bleeding. If EGD is not available or inconclusive and the patient is stable for more than 36 hours and upper GI bleed is suspected, then barium X rays should be considered.

Colonoscopy is performed if lower GI bleeding is suspected as a cause of bleeding; its yield is higher if performed in the first 24 hours. Colonoscopy is best performed in patients whose condition has clinically stabilized and who can tolerate adequate bowel purge. In order to get good results, patient should be able to drink adequate bowel prep. Many patients find polyethylene glycol (PEG)-based preparations difficult to take because of the large volume of fluid they are required to consume. Thomson *et al.* (1996) reported in a randomized prospective trial comparing sodium phosphate and PEG in a predominantly elderly population. One hundred and sixteen predominantly elderly patients were randomized to receive either sodium phosphate ($n = 61$) or PEG ($n = 55$) bowel preparations before colonoscopy. The patients found the sodium phosphate preparation slightly more tolerable than PEG. There were no significant side effects between the two groups. However, 91% of patients who had previously had PEG found sodium phosphate easier to take. The colonoscopists found no difference in the overall quality of the bowel preparation. Sodium phosphate was a safe and effective bowel preparation for colonoscopy in this carefully selected group of patients. It was preferred by patients who previously had PEG. In another study, Lashner *et al.* (1990) reported in a randomized clinical trial on 124 consecutive patients scheduled for colonoscopy who were 75 years of age or more. Sixty-three patients were randomized to receive Golytely; 17 were inpatients, 33 were outpatients, and colonoscopy was canceled in 13. Sixty-one patients were randomized to receive the enema preparation; 17 were inpatients, 30 were outpatients, and colonoscopy was canceled in 14. Both preparations were adequate but the enema preparation was superior in outpatients, while Golytely was superior in inpatients. Patients tolerated the enema preparation better, a finding present in both outpatients and inpatients. Contrary to previous reports of a significant advantage with Golytely, patients 75 years and older did not enjoy this advantage, but seemed to tolerate enemas better than Golytely with little difference in adequacy of the preparation.

When colonoscopy is negative and lower GI bleeding is suspected, a *tagged red blood cell* (*TRBC*) *scanning* should be considered. RBCs labeled with technetium 99 m remain in the circulation for 48 hours and extravasate into the lumen with active bleeding. This extravasation can be detected as a pooling of the radiotracer on scanning with a gamma camera. Bleeding rates as low as 0.1 ml/minute can be detected in research settings. When the test is positive, it is accurate in about 80% of the cases. About 20% of the localization is false positive, which precludes the use of this test alone for surgical resection of the bowel. The clinical utility of this test is for screening before arteriography.

Arteriography allows localization and potential therapy for GI bleeding when bleeding rate exceeds 0.5 ml/minute. It can provide the etiology, especially bleeding diverticula or angiodysplasia. Angiography can also be used in brisk upper GI bleeding when endocsopy is impossible. Embolization of the bleeding artery is infrequently performed because of the risk of bowel infarction. Small-bowel enteroscopes when radiological evaluation suggests jejunal bleeding source or in recurrent (obscure) GI bleeding in which conventional endoscopy is unrevealing.

Surgery is considered when the blood transfusion requirements exceeds 4–6 units over a 24-hour period or 10 units overall, as well as more than two to three recurrent bleeding episodes from the same course. It is prudent to perform EGD before undergoing emergent total colectomy. The extent of comorbid conditions and the degree of bleeding needs to be factored in when considering surgery. Therapies for specific lesions are mentioned here that require a different treatment modality than already mentioned.

Peptic Ulcer Disease

The use of high-dose proton pump inhibitors reduces the rate of recurrent bleeding, and is especially useful in patients awaiting endoscopic treatment or in those for whom endocsopy is contraindicated or postponed. The conventional PPI may suffice after endoscopic therapy has been administered. A gastric or duodenal biopsy or rapid urease assay (CLO test), histopathology, or culture is required to look for *Helicobacter pylori*. If *H. pylori* are identified, it is prudent to eradicate it by using antimicrobial therapy in addition to antisecretory medications.

Variceal Hemorrhage

Management of variceal bleeding usually requires intensive-care monitoring and endotracheal intubation for airway protection. Octreotide infusion should be initiated immediately (50–100 μg/hour bolus followed by an infusion 25–50 μg/hour). Octreotide is usually well tolerated and reduces portal pressure. Vasopressin is an alternative pharmacological agent but is used less frequently because of the side effects – myocardial ischemia and infarction, mesenteric ischemia and infarction, ventricular arrhythmias, cardiac arrest, and cutaneous ischemic necrosis. Concomitant infusion of nitroglycerin is used at times to reduce the undesirable side effects of vasopressin.

Variceal ligation or banding is the endoscopic therapy of choice. It is very effective and superior to sclerotherapy (Saeed, 1999; Saeed *et al.*, 1997; Saeed, 1996). Complications of banding include superficial ulcerations, dysphagia, transient chest discomfort, and rarely esophageal stricture.

Sclerotherapy is also effective but is used less frequently because of its complications (ulceration, stricture, perforation, pleural effusion, adult respiratory distress syndrome, and sepsis). Recurrent bleeding may be seen in up to 50% of the patients but will respond to repeated treatment. Fever may be seen in up to 40% of the patients but if it persists for more than 2 days, a bacteremia work may be necessary.

Transjugular intrahepatic portosystemic shunts (TIPS) have been used in the treatment of complications of portal hypertension. TIPS is used for the control of acute variceal bleeding, prevention of variceal rebleeding when pharmacologic therapy and endoscopic therapy have failed. TIPS is also helpful in patients with refractory ascites with adequate hepatic reserve and renal function who fail to respond to large volume paracentesis. Other indications for TIPS are Budd–Chiari syndrome uncontrolled by medical therapy, severe portal hypertensive gastropathy, refractory hepatic hydrothorax, and hepatorenal syndrome. The major limiting factors for TIPS' success are shunt dysfunction and hepatic encephalopathy. Because shunt stenosis is the most important cause of recurrent complications of portal hypertension, a surveillance program to monitor shunt patency is mandatory (Rosado and Kamath, 2003).

Shunt surgery (portacaval or distal splenorenal shunt) should be considered in patients with good hepatic reserve if the patient fails endoscopic or pharmacologic therapy, having difficulty to return for follow-up visits, increased risk of death due to recurrent bleeding, or lives away from medical care location. The morbidity and mortality is high with this procedure, as well as postoperative encephalopathy.

Balloon tamponade has a very big role in the therapy of variceal hemorrhage. It is used temporarily to stabilize patients in situations when more definite therapy is available. The commonly used balloon tamponade are the Sengstaken–Blakemore tube and the Minnesota tubes, both of which have a gastric and esophageal balloon. The following are general guidelines for the use of balloon tamponade. The details of how to use these balloon tamponades are discussed in gastrointestinal literature.

Angiodysplasia can occur anywhere in the GI tract and can be occult or overt GI bleeding. Actively bleeding angiodysplasia is best treated by endoscopic therapy (heater probe, laser, or organ plasma coagulation), intra-arterial vasopressin, or embolization during angiography or surgical resection. Endoscopic ablation is recommended even when nonbleeding angiodysplasia are found in the presence of iron deficiency anemia. The associated anemia should be treated with iron.

Stress ulcer is encountered in patients who are in the intensive-care unit and on ventilation for more than 48 hours with coagulopathy, sepsis, burns, and cerebrovascular events. Prophylactic therapy should be administered in patients who are at increased risk. Histamine-2 receptor antagonist, sucralfate, and proton pump inhibitors can be used.

Diverticulosis is usually seen on endocsopy but bleeding develops in about 5% of the patients with diverticula. Bleeding usually stops in these patients 80% of the time, but may reoccur. Persistent bleeding may require intra-arterial vasopressin at angiography or even surgical resection.

Aortoenteric fistula is an uncommon but lethal cause of GI bleeding. These patients usually have history of aortic graft surgery and present with bleeding after surgery. The fistula site is usually aortoduodenal but can be anywhere in the small and large intestine. The classic presentation is herald bleed hours to weeks before massive GI bleeding. Recognition of this condition is essential, as undiagnosed cases could be fatal. Endoscopy with examination of the fourth portion of the duodenum is essential and should be performed immediately. Angiography or CT scanning may show leak at the graft site. A negative study does not exclude an Aortoenteric fistula. If suspicion is high, a surgical consultation is absolutely necessary.

Radiation proctitis/colitis results years after exposure to radiation therapy. Intermittent hematochezia results from aberrant superficial mucosal vasculature in the distal colon. Treatment is usually supportive and laser photocoagulation of the mucosal telangiectasias may be needed.

Hemorrhoids are the most common cause of outpatient causes of hematochezia. Treatment is usually avoidance of constipation by using fiber-rich diet and supportive care. Surgical and endoscopic banding of the hemorrhoids is also available.

CONCLUSION

GI bleeding is a common geriatric problem. The incidence of GI bleeding is about 35–45% in people 60 years of age and older. The incidence of lower GI bleeding is unknown. The causes of GI bleeding vary in different studies. The diagnosis and management of GI bleeding is similar to that of young adults in many ways.

KEY POINTS

- GI bleeding in elderly.
- Causes of GI bleeding.
- Presentation and clinical course of GI bleeding.
- Diagnosis of GI bleeding.
- Management of GI bleeding.

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Liver and Gall Bladder

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The liver, that great maroon snail: No wave of emotion sweeps it. Neither music nor mathematics gives it pause in its appointed tasks. . . .

(Selzer, 1976)

AGE-RELATED HEPATOBILIARY CHANGES

Liver

Traditionally, hepatic biochemical parameters such as serum transaminases, hepatic alkaline phosphatase, γ-glutamyltranspeptidase, and serum bilirubin are considered indices of liver function. These parameters, which are indeed more reflective of disrupted hepatocyte integrity and liver dysfunction, are not altered with aging (James, 1997; MacMahon and James, 1994). However, there is an age-related compromise in more objective and sophisticated dynamic liver function indices. Available data shows that with aging hepatic volume and perfusion may decrease by approximately 30%. Other indices of hepatic metabolic function, such as nitrogen synthesis and aminopyrine clearance, also decrease with aging. Likewise, age-related reduction in hepatic microsomal cytochrome content may compromise efficient drug metabolism in the elderly (Wynne *et al.*, 1989; Fabbri *et al.*, 1994; James, 1997).

Histological studies have identified decreased smooth endoplasmic reticulum and fewer mitochondria in hepatocytes from older adults (Schmucker, 1990) Age-related reduction in hepatic regeneration is particularly concerning. Several studies suggest that the older liver is more vulnerable to stress, perhaps due to an age-related reduction in mitogen activated protein kinase activity (Liu *et al.*, 1996). These cellular changes contribute to the poorer outcomes observed in older adults following hepatic insult.

Few studies have specifically examined the effect of aging on the gallbladder and biliary tract. With aging, there is an increase in the diameter of the common bile duct, due to replacement of biliary ductal myocytes with connective tissue cells (Kialian and Aznaurian, 1995).

In addition, the lithogenicity of bile increases, resulting in an increased tendency to form cholesterol and calcium bilirubinate stones (Siegel and Kasmin, 1997). These preceding changes, set against a background of lifetime exposure to potentially hepatotoxic agents, set the stage for hepatobiliary disease as a major contender in geriatric medicine.

HEPATIC DISEASES OF THE ELDERLY

Viral Hepatitis

Classically, viral hepatitis is defined as hepatic inflammation induced by infection with specific hepatotrophic viruses. Histological features include diffuse or patchy necrosis of the liver acini. Severity of clinical presentation is variable. Some patients are asymptomatic, while others may complain of flu-like and fairly nonspecific symptoms such as myalgia, athralgia, anorexia, nausea, vomiting, and diarrhea. Physical examination may reveal fever, jaundice, hepatomegaly, and, in some cases, cutaneous manifestations such as purpura, urticaria, and other skin lesions.

Geographical distribution and prevalence of viral hepatitis vary with the infecting agent (Figure 1).

Hepatitis A Virus

Hepatitis A virus (HAV) is a 27-nm single-stranded, nonenveloped RNA picornavirus. Although infection typically occurs by fecal-oral transmission, a few cases of HAV have occurred through hematogenous transmission (Centers for Disease Control and Prevention, 1999). Onset of symptoms is usually 2–6 weeks after exposure. In younger adults, hepatitis A infection is usually subclinical with mild symptoms.

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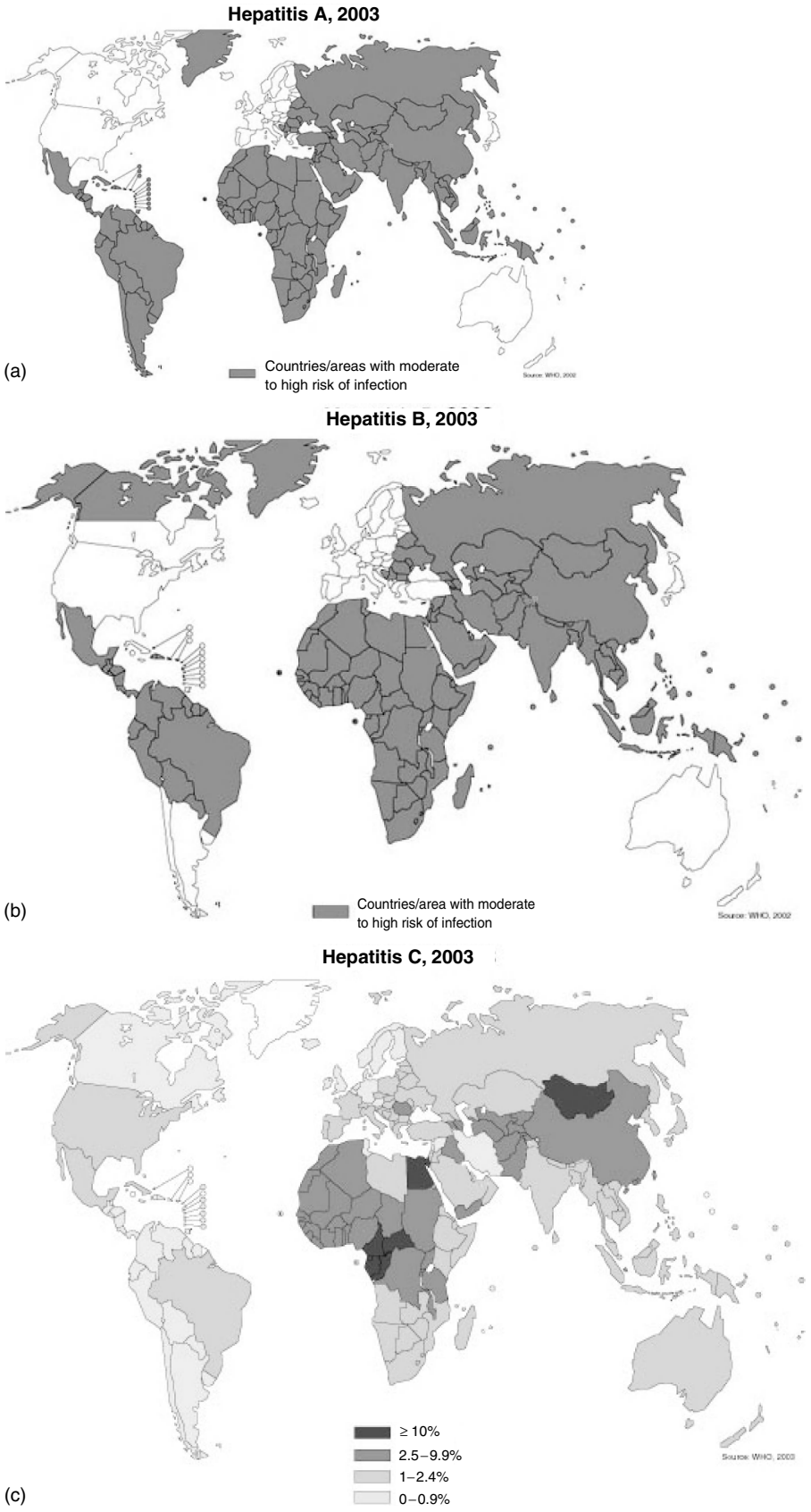


Figure 1 Geographical distribution of Hepatitis A, B, and C

Jaundice is present in less than 10% of cases. In contrast, although hepatitis A infections are less frequent in older adults, symptoms are likely to be more severe. In addition, the risk of developing and dying from complicating fulminant liver failure is far more common in infected elders. Reported case fatality rate among patients over the age of 65 years is 4% compared with 0.07% in patients aged 15–24 years (Forbes and Williams, 1988). Current recommendations state that older persons traveling to endemic areas should receive HAV vaccination. Additionally elderly food handlers and patients with chronic liver disease are also advised to receive HAV vaccination, although data regarding the efficacy and cost-effectiveness of the vaccine in older adults is lacking (James, 1997).

Hepatitis B Virus

Hepatitis B virus (HBV) is a 42-nm double-stranded, enveloped DNA hepadna virus. HBV is a highly infectious virus transmitted through sexual intercourse or contact with infected blood, blood products, and saliva. Vertical maternofetal transmission also occurs during childbirth. The incubation period of HBV is approximately 120 days (Lok and McMahon, 2001). Although most infections occur in young adulthood, serological evidence of HBV infection is threefold higher among older adults aged between 64 and 74 years. Rates of HBV infection are also higher among nursing home residents compared to those in community dwelling elders. Sporadic outbreaks of HBV infection in nursing home residents have been linked to inappropriate sharing of razors and bathing appliances. Data indicates that in older adults who contact HBV, the risk of progressing to chronic hepatitis is over 50% compared with 5% following acute infection in younger adults. Nevertheless, acute hepatitis B is rare among older adults, and older adults with acute HBV infection are usually only mildly symptomatic (Marcus and Tur-Kaspa, 1997; Reeder and Halket, 1987). Nevertheless, age remains a risk factor for the development of life-threatening fulminant hepatitis. Perhaps as a result of more prolonged exposure, older adults with HBV infection are more likely to develop hepatocellular carcinoma and liver cirrhosis (Beasley, 1988; MacMahon and James, 1994).

Hepatitis C Virus

Hepatitis C virus (HCV) is a 55-nm enveloped RNA flavivirus, with an incubation period ranging from 15–90 days. Of the six known genotypes, type 1 is the most common in the United States. Although transmission is primarily hematogenous, a few cases have been transmitted through saliva and human bites (Bukh *et al.*, 1995; Chu *et al.*, 2002). Data indicates that the prevalence of acute HCV infection among older adults equals, and, in some cases, surpasses that in the general population. Within the United States, reported seroprevalence rate among adults aged over 70 years is 1%, compared with 1.8% among the general population (Alter *et al.*, 1999). In an Italian cohort aged over 65 years, the HCV infection prevalence rate was over 4% compared with 3.2% among a comparable cohort of young subjects (Monica *et al.*, 1998). Although the incidence of new cases has declined over the past decade, projections indicate that over the next 20–30 years the prevalence of HCV among older adults will increase significantly.

As in younger adults, infection with HCV in elders is only mildly symptomatic during the acute phase. However, the clinical course in older patients is much more aggressive and lethal. Similarly, advanced age at diagnosis of the disease portends more rapid progression to fibrosis and cirrhosis (Seeff, 1997; Watson *et al.*, 1996). Other risk factors for the development of cirrhosis include alcohol use and obesity. Studies show that in patients who acquire HCV over the age of 60 years the risk of developing cirrhosis is reported to be as high as 46%, compared to approximately 7% among patients in the fourth decade of life. Reasons for the aggressive clinical course with aging are not clearly known, although age-related immunocompromise has been proffered as a likely theory (Simmonds *et al.*, 1996).

Hepatitis D Virus

Hepatitis D virus (HDV) is a single-stranded RNA viroid that is dependent on the HBV envelope protein for replication and pathogenicity. Transmission of HDV occurs hematogenously or through sexual contact and results in either coinfection or superinfection. Coinfection occurs when there is simultaneous transmission of both HDV and HBV, while superinfection refers to HDV infection of a previously HBV positive patient. Patients with coinfections have a better prognosis and progress to chronic disease in less than 5% of cases. In contrast, 70–90% of superinfected patients develop cirrhosis. Although HDV infection causes less than 5% of chronic hepatitis, it accounts for approximately 7500 new infections annually and has a mortality rate of 30% (Alter and Hadler, 1993). Data in older subjects is lacking.

Hepatitis E Virus

Hepatitis E virus (HEV) is a single-stranded RNA calicivirus that is transmitted feco-orally. This virus tends to infect younger adults and is rare in developed countries. Characteristically, pregnant women have a 20% mortality rate from this disease compared with 1% in the general population.

Older people traveling to endemic regions such as Asia, Mexico, and Africa may be at risk. Prophylaxis is ineffective and the avoidance of consumption of foods and water that may be contaminated is strongly recommended (Gilchrist, 1999).

Hepatitis F Virus

Viral particles identified in the stool of posttransfusion, non-A, non-B, non-C, non-E hepatitis cases and injected into

Indian rhesus monkeys caused acute hepatitis with elevated transaminases. Consequently, this viral enteric agent was named *hepatitis F virus* (HFV). However, to date there are no convincing corroborating scientific reports. Although sporadic cases in humans may have been identified in Europe, United States, and India, the validity of this virus remains questionable (Deka *et al.*, 1994).

GB Virus Type C (GBV-C)

This virus belongs to the *Flaviviridae* and was previously referred to as hepatitis G virus (HGV). Currently, the lack of proven association of this virus with either acute or chronic hepatitis has discouraged the use of the name HGV (Dickens and Lemon, 1997). The name GBV-C was derived from a surgeon, whose initials were GB, after marmosets inoculated with his serum developed hepatitis. On the basis of this single observation, the surgeon was erroneously thought to have posttransfusion hepatitis. Later evidence did not support this diagnosis (Almeida *et al.*, 1976). Indeed, GB virus type C (GBV–C) infection is common, but is yet to be associated with definite pathogenicity (Dickens and Lemon, 1997). Currently, the major clinical significance of this agent lies in the fact that HIV-positive patients infected with GBV-C may have prolonged survival (Xiang *et al.*, 2001). Little data exists regarding the pattern of GBV-C infection in aging adults.

Transfusion Transmitted Virus

Transfusion transmitted virus (TTV) is a single-stranded DNA virus. Despite the name, feco-oral transmission of the virus also occurs. Infection is usually acquired in childhood and may persist for years. Its role in causing hepatitis or other diseases has not been proven. Even though one of the genotypes of TTV is suspected to cause hepatitis, the pathogenicity of TTV in humans remains poorly defined (Takacs *et al.*, 2003). The prevalence of TTV is also unclear. Available data indicates that the virus has been identified in 1% of blood donors, 18% in posttransfusion subject, 15% of patients with liver cirrhosis, and 27% in patients with end-stage liver failure (Naoumov and Petrova, 1998). Notably, high TT virus load has been found to be independently associated with the occurrence of hepatocellular carcinoma among patients with HCV-related chronic liver disease (Nishizawa and Okomoto, 1997).

Autoimmune Hepatitis

Autoimmune hepatitis is characterized by severe chronic hepatitis in the presence of circulating autoantibodies. Characteristically, there is frequent progression to liver cirrhosis. Originally described as a disease of young women, autoimmune hepatitis is now known to affect all age groups and both genders. Approximately 20% of all patients diagnosed with autoimmune hepatitis are over the age of 65 years (Newton *et al.*, 1997). Diagnostic criteria for autoimmune hepatitis are unchanged with age, and the prognosis for affected older adults is no worse than for younger adults (Table 1). Nonetheless, older adults present with less acute symptoms, but are more likely to have severe histological inflammation and necrosis. Unfortunately, data indicates that older adults are less likely to be prescribed immunosuppressive therapy, even though this has been shown to prolong survival in patients with severe disease. There is no data to support the benefits of therapy in older adults with mild disease (Czaja and Freese, 2002).

Drug-induced Hepatitis

Several unique factors predispose the elderly to drug-induced hepatotoxicity. These include polypharmacy and, subsequently, an increased risk of drug-induced adverse

Table 1 Diagnostic criteria for autoimmune hepatitis (Alvarez *et al.*, 1999; Czaja and Freese, 2002)

Criteria	Definite	Probable
Genetic liver disease	Normal α1-antitrypsin, ceruloplasmin, iron, and ferritin levels	Partial α1-antitrypsin deficiency, nonspecific serum copper, ceruloplasmin, iron, and ferritin abnormalities
Viral infection	No markers of current infection with HAV, HBV, HCV	No markers of current infection with HAV, HBV, HCV
Toxic or alcohol injury	Daily alcohol $<25\,g\,day^{-1}$ and no recent use of hepatotoxic drugs	Daily alcohol $<50\,g\,day^{-1}$ and no recent use of hepatotoxic drugs
Laboratory features	Predominant serum aminotransferase abnormality, globulin, gamma globulin or immunoglobulin G level >1.5 times normal	Predominant serum aminotransferase abnormality; hypergammaglobulinemia of any degree
Autoantibodies	ANA, SMA, or anti-LKM1 >1 : 80; no AMA	ANA, SMA, or anti-LKM1 >1 : 40, or other autoantibodies[a]
Histologic findings	Interface hepatitis No biliary lesions, granulomas, or prominent changes suggestive of another disease	Interface hepatitis No biliary lesions, granulomas, or prominent changes suggestive of another disease

[a]Perinuclear antineutrophil cytoplasmic antibodies, antibodies to soluble liver antigen/liver pancreas, actin, liver cytosol type 1, and asialoglycoprotein receptor.
ANA, antinuclear antibody; SMA, smooth muscle antibody; LKM, liver kidney microsomal antibody; AMA, antimitochondrial antibody.

effects and drug–drug interactions. Age-related physiological changes, such as reduced liver mass, hepatic hypoperfusion, and reduced activity of phase 1 hepatic drug-metabolizing enzymes, further increase the likelihood of hepatic injury in response to toxic drugs. Age-related changes in body composition may compromise the volume of distribution, thereby increasing serum drug levels. Hypoalbuminemia resulting from excess cytokine elaboration, related to aging or disease, may reduce protein binding and further increase the likelihood of drugs attaining toxic levels. Finally, altered pharmacodynamics with aging affects the response to drugs at the tissue level (Regev and Schiff, 2001; Varanasi *et al.*, 1999).

Not surprisingly, drug-induced liver disease occurs more frequently, and is more severe, in older adults. In addition, older patients with coexisting renal or hepatic disease are more likely to be affected. Documented prevalence of drug-induced hepatitis ranges from 50–140 per 1 million person years in adults aged between 70 and 79 years (Almdal and Sorensen, 1990; Sgro *et al.*, 2003). Overall, the incidence of drug-induced liver disease may be higher in older adults simply because these drugs are used more frequently. Nonsteroidal agents (NSAIDs) are used extensively by older adults for a variety of arthritic and nonarthritic conditions. All NSAIDs are potentially hepatotoxic. Nevertheless, the reported rate of nonsteriodal anti-inflammatory drug NSAID-induced hepatotoxicity is less than 1%. Affected patients are usually asymptomatic, with elevated hepatic transaminases. Hepatic alkaline phosphatase may also be mildly elevated. Notably, patients with piroxicam-induced hepatitis may present with severe cholestatic features. NSAID hepatitis usually responds well to withdrawal of the offending agent. All older adults started on NSAIDs should have their liver function evaluated within two to three months of starting therapy (Hepps *et al.*, 1991; Solomon *et al.*, 2003).

Following a decline in the use of methyldopa, hepatic disease associated with the use of cardiac medications exhibited a decline. However, with the increased use of amiodarone, hepatocellular disease related to cardiac medications has begun to increase. Affected patients are usually asymptomatic. Approximately half of all patients on amiodarone exhibit a rise in serum transaminase levels. Amiodarone-induced hepatitis may occur with both oral and intravenous administration. These changes resolve if amiodarone is withdrawn early in the course of treatment. Other histological findings of amiodarone-induced hepatitis include steatohepatosis, cholestatic hepatitis, and micronodular cirrhosis (Tameda *et al.*, 1996; Traverse *et al.*, 1994; Gonzalez Galilea *et al.*, 2002)

With most medications, the increased prevalence of drug-induced hepatotoxicity in older adults is a consequence of increased exposure. However, certain drugs such as benoxaprofen, halothane, and several antituberculous agents – isoniazid (INH), rifampicin, and pyrazinamide – are inherently more likely to cause hepatotoxicity in older adults (Varanasi *et al.*, 1999; Nagayama *et al.*, 2003). Benoxaprofen is a nonsteroidal agent, which was withdrawn by the United States Food and Drug Administration (FDA) following several reports of fatal liver failure occurring specifically in adults over the age of 70 years. Similarly, animal studies indicate an age-related increase in sensitivity to the effects of halothane, resulting in an increased risk of hepatic failure and death among older adults exposed to this agent.

INH hepatitis is rare in young patients but occurs in more than 2% of patients aged over 50 years. Increased sensitivity to INH in older adults is related to changes in hepatic physiology and altered pharmacokinetics. INH metabolism produces toxic reactive metabolites presumably from acetylation. Traditionally, persons with the rapid INH acetylator phenotype were considered more prone to toxicity. Most recent studies have failed to confirm this relationship. Indeed, convincing data suggest that slow acetylators may divert larger amounts of INH to an alternate metabolic pathway (Cytochrome P450 2E1) that results in production of a toxic reactive metabolite (Huang *et al.*, 2003). The precise mechanism underlying INH toxicity is still unknown.

Presenting features of INH toxicity range from asymptomatic elevation of transaminases to fulminant hepatic failure requiring liver transplantation (Vasudeva and Woods, 1997). Thus, patients on INH should receive serial serum transaminase measurements to facilitate early detection of hepatotoxicity.

Diagnosis and Management of Hepatitis

Clinical presentation of hepatitis varies widely and affected patients may be entirely asymptomatic. Some patients present with flu-like symptoms, such as fever, chills, skin rash, nausea, vomiting, myalgia, athralgia, or malaise. System-specific symptoms such as jaundice, abdominal discomfort, dark urine, easy bruising, and hepatomegaly may also occur. Certain hepatitides, such as hepatitis C, are characteristically asymptomatic during the acute phase. Diagnosis in such cases is usually delayed until several years after infection. In autoimmune hepatitis, despite the chronic nature of the disease, 40% of patients present acutely with fever, jaundice, polyarthralgias, myalgias, thrombocytopenia, and biochemical evidence of severe hepatic dysfunction (Krawitt, 1996).

Serum testing in most cases of hepatitis will reveal elevated transaminases. In mild cases, elevation usually does not exceed three times normal, while in severe cases there may be a 20-fold increase. Clinical detectable jaundice is usually not present until serum bilirubin exceeds $3\,\mathrm{mg\,dl^{-1}}$. With severe disease, prothrombin time increases, and this is usually indicative of impending liver failure. Additional blood testing should be done in all cases to determine etiology of the hepatitis. Thus, viral antigen and antibody studies are conducted to screen for hepatitis A–E. GBV-C RNA may be identified using a reverse transcriptase polymerase chain reaction test. This test is not available for commercial use. There are also no serological assays routinely available for the diagnosis of GBV-C (HGV) or TTV (Stapleton, 2003).

An autoantibody profile for circulating autoantibodies should be conducted to screen for autoimmune hepatitis. Most patients will have elevated levels of circulating autoantibodies. However, only two-thirds will have one of the more specific autoantibodies. Patients are frequently screened for antinuclear and/or antismooth muscle antibodies (Lohse *et al.*, 1995; Czaja and Freese, 2002). Tests for other autoantibodies such as soluble liver antigen, liver cytosol antigen and the asialoglycoprotein receptor antibody are also helpful diagnostic tools with high specificity (Manns *et al.*, 1987; Martini *et al.*, 1988; Treichel *et al.*, 1994). Lab tests for autoimmune hepatitis should include serum protein electrophoresis. This may reveal hypergammaglobulinemia with a selective increase in IgG levels. Human leucocyte antigen (HLA) typing may be helpful as most patients are positive for HLA B8, DR3, or DR4 (Donaldson *et al.*, 1994).

The diagnosis of drug-induced hepatitis is usually one of exclusion based on the patient's medication history, which should include questions pertaining to the use of prescription, over-the-counter and herbal medications.

Imaging techniques, such as ultrasound, computed tomography (CT) scans, and MRI are helpful in further evaluation of patients with suspected hepatitis for etiology and severity of disease. Definitive diagnosis, assessment of severity, acuity, and activity of disease are based on histological findings and requires a liver biopsy.

On the basis of liver biopsy findings, hepatitis may be characterized as acute or chronic. Autoimmune hepatitis and all the viral hepatitides except HAV, HEV, and HFV exist in both the acute and chronic phases. Histologically, chronic hepatitis may be further characterized into four stages: (i) chronic persistent to mild chronic active hepatitis; (ii & iii) chronic active hepatitis with scarring; and (iv) cirrhosis (Bach *et al.*, 2000). Rapidity of clinical progression through these stages cannot be predicted.

The cornerstone of treatment of any hepatitides is primarily supportive care. Rest, adequate nutrition, and avoidance of additional injury from alcohol or other toxic insults should be stressed. Currently no specific medication is recommended for hepatitis A, D, E, or G. In 25–50% of patients with chronic HBV infection, treatment with interferon α-β results in disease remission within 6 months. Oral nucleoside analogs, such as lamivudine and famciclovir, have been shown to reduce HBV levels and the risk of fulminant hepatic failure in more than 50% of patients treated with these agents (Hoofnagle and DiBalart, 1997; Lai *et al.*, 1998). The decision to treat patients with HCV is usually made on an individual basis, using factors such as compliance, disease severity, and likelihood of favorable response. Standard therapy consists of pegylated interferon alpha and ribavarin. Following 24 weeks of therapy, undetectable levels of HCV RNA are achieved in over 50% of patients, indicating a sustained response. Patients infected with HCV genotype 1 are less likely to respond, with only 42–46% of patients achieving a sustained response with treatment. Forty-eight weeks of therapy is advised to maximize chances of favorable response. Patients infected with HCV genotype 2 or 3 have a sustained response exceeding 75% and generally require only 24 weeks of therapy. If HCV RNA remains detectable following the course of treatment, therapy should be discontinued, as less than 2% of patients will subsequently respond (Manns *et al.*, 2001; Fried *et al.*, 2002; Hadziyannis *et al.*, 2002).

Currently vaccinations are available only for HAV and HBV (Figure 2).

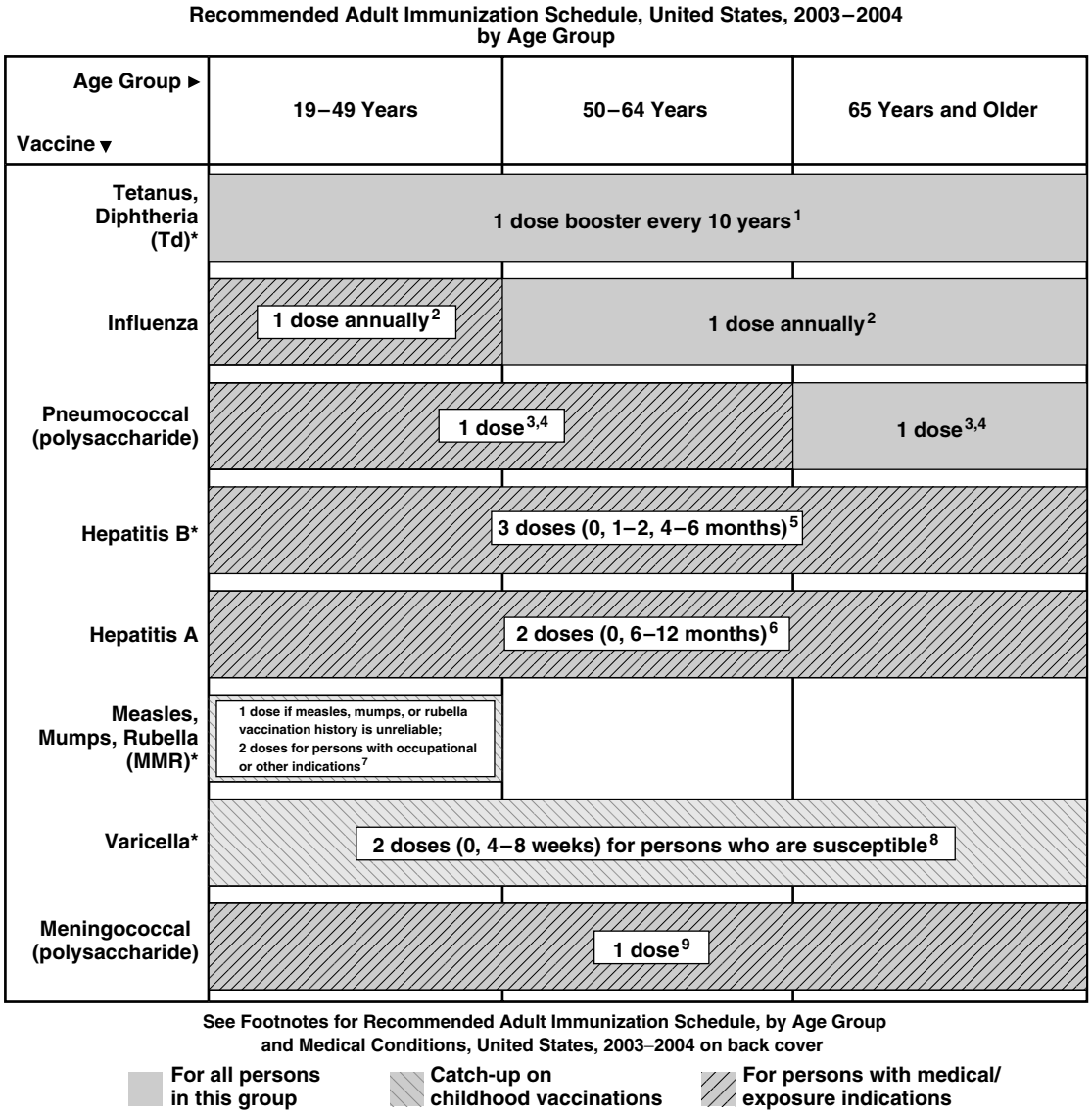
Patients with severe autoimmune hepatitis (aspartate transaminase (AST) > than 10-fold or AST > fivefold and serum gamma globulin > twofold) are definite candidates for treatment. Combination therapy using azathioprine and corticosteroids has been shown to prolong survival and improve outcomes in affected adults. Patients with mild autoimmune hepatitis do not benefit from treatment (Newton *et al.*, 1997).

Alcoholic Liver Disease

Excessive alcohol use is a major cause of liver disease. Approximately 10% of men and 2% of women over the age of 60 years suffer from an alcohol use disorder. Although age does not alter alcohol dehydrogenase activity, studies suggest a difference in the clinical course and outcomes of alcoholic disease in older adults compared with younger subjects. Older adults who present with alcoholic liver disease are more likely to have severe symptoms and present with complications such as portal hypertension or liver cirrhosis. Prognosis in older patients is directly related to age. Patients presenting with alcoholic liver disease over the age of 70 years have a mortality rate at one year of about 75% compared with 5% in patients aged less than 60 years (Varanasi *et al.*, 1999; Beresford and Lucey, 1995; Corrao *et al.*, 1997; James, 1997)

Laboratory testing reveals elevated serum aspartate aminotransferase, bilirubin, and alkaline phosphatase. Liver biopsy reveals a spectrum of histological changes ranging from steatosis, through acute hepatitis to cirrhosis. Animal models indicate that toxic oxidative stress and proinflammatory cytokine elaboration, arising from metabolism of ethanol to acetate, contributes significantly to the onset of alcohol-related steatosis and progressive forms of liver damage. Elevated serum concentration levels of tumor necrosis factor alpha (TNF α), interleukin (IL)-6, IL-8, IL-18, and transforming growth factors, occur in patients with alcoholic liver disease. Cytokine levels have been shown to correlate with liver dysfunction and clinical outcome. Cessation of alcohol intake results in resolution of steatosis and restoration of normal hepatic architecture within a few weeks. Acute alcoholic hepatitis, which comprises cellular inflammation and fibrosis, also responds to alcohol cessation. Persistent alcohol intake results in progressive fibrosis and subsequent cirrhosis within 5 years in 40% of affected patients (McClain *et al.*, 2004; McClain *et al.*, 1999).

Treatment of alcoholic liver disease does not vary with age. Abstinence is the cornerstone of effective management and is critical to the success of all other adjunctive therapy. Most patients with alcohol dependence are undernourished, which



*Covered by the Vaccine Injury Compensation Program. For information on how to file a claim call 800-338-2382. Please also visit www.hrsa.gov/osp/vicp To file a claim for vaccine injury contact: U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington D.C. 20005, 202-219-9657.

This schedule indicates the recommended age groups for routine administration of currently licensed vaccines for persons 19 years of age and older. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

Report all clinically significant post-vaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available by calling 800-822-7967 or from the VAERS website at www.vaers.org.

For additional information about the vaccines listed above and contraindications for immunization, visit the National Immunization Program Website at www.cdc.gov/nip/ or call the National Immunization Hotline at 800-232-2522 (English) or 800-232-0233 (Spanish).

Approved by the Advisory Committee on Immunization Practices (ACIP), and accepted by the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Family Physicians (AAFP)

Figure 2 Summary of recommendations published by The Advisory Committee on Immunization Practices – Centers for Disease Control. Department of Health and Human Services

further increases their mortality risk. Severely undernourished veterans with acute alcoholic hepatitis had a 30-day mortality rate of 52% compared with a 2% mortality rate in their counterparts with only mild undernutrition. Protein energy undernutrition compromises the immune system and may therefore have a permissive effect on the toxicity of alcohol. In addition, hepatic regeneration may be compromised by impaired protein synthesis. Thus, aggressive nutritional support is recommended for patients with alcoholic liver disease.

Corticosteroids have been shown to ameliorate cytokine production, suppress acetaldehyde catabolism and thereby

blunt the hepatic inflammatory response. Nevertheless, data from several meta-analyses have failed to demonstrate consistent benefit from corticosteroid therapy in alcohol-related liver disease. Paucity of data in addition to potential side effects of steroid therapy in older adults renders steroid therapy an unwise choice in older adults. Several research studies are aggressively exploring the role of cytokine antagonism in the treatment of alcohol liver disease. Theoretically, TNFα antagonists could prove useful in suppressing alcohol-related hepatic inflammation. Recent studies suggest that anti-TNF therapy may improve histological features and enhance survival (Spahr *et al.*, 2002; Tilg *et al.*, 2003). However, well-controlled randomized trials are lacking. Pentoxifylline, a phosphodiesterase inhibitor, has proved useful in reducing the risk of hepatorenal syndrome (Akriviadis *et al.*, 2000).

Several studies have evaluated the effect of antioxidants, such as *S*-adenosyl methionine and silymarin (milk thistle), in the treatment of alcoholic liver disease. Available evidence fails to confirm benefit from any of these agents (Pares *et al.*, 1998; Mato *et al.*, 1999). Other potentially antioxidative agents such as propylthiouracil and phosphatidylcholine have also been studied. They had no effect on outcomes or survival (Rambaldi and Gluud, 2001; Lieber *et al.*, 2003). Colchicine, an inhibitor of collagen synthesis produced a paradoxical increase in the risk of adverse events (Rambaldi and Gluud, 2001).

Hepatocellular Carcinoma

In North America, hepatocellular carcinoma is predominantly a disease of older adults, with 50% of cases occurring in adults over the age of 60 years. In contrast, the peak incidence of hepatocellular carcinoma (HCC) in Sub-saharan Africa and China occurs in young to middle adulthood. Older adults are more likely to present with advanced disease and their survival rates are significantly lower than those of younger patients (10.5 weeks compared with 18.5 weeks in younger adults, Collier *et al.*, 1994; Regev and Schiff, 2001).

Hepatocellular carcinoma in older adults is more likely to be related to HCV than HBV (Hoshida *et al.*, 1999). Data from a Korean study identified a serological positivity ratio of 29.7 for hepatitis B surface antigen in patients younger than 50 years compared with 0.9 in patients older than 60 years (Lee *et al.*, 1993). Infection with HBV in the earlier years of life as opposed to in adulthood, as is the case with HCV, probably accounts for this difference. Additionally, the latent interval between acquisition of HCV and the development of hepatocellular is significantly longer than with HBV.

Available data indicate that treatment outcomes of hepatocellular carcinoma are unaffected by age. There is difference in morbidity, early mortality, or long-term survival between older and younger patients treated with either surgical resection or chemo-embolization (Bismuth, 1999; Hanazaki *et al.*, 2000). Thus, age should not be used as the sole determining criterion for deciding treatment options.

DISEASES OF THE GALLBLADDER AND BILIARY TRACT

Gallstone Disease

Age-related changes in biliary metabolism result in increased cholesterol saturation of bile and gallbladder dysmotility. In addition, there is increased activity of HMG-CoA reductase and reduced activity of 7-alpha hydroxylase. These changes enhance the lithogenicity of bile. Consequently, there is an increase in the prevalence and severity of gallstone disease, specifically cholesterol, and calcium bilirubinate stones, in older adults (Bowen *et al.*, 1992; Affronti, 1999).

In the United States, the incidence of gallstones in Caucasian women increases from 5% in the third decade of life to 25% in the seventh decade. Complications such as choledocholithiasis, emphysematous cholecystitis, ascending cholangitis, and pancreatitis are more apt to occur with aging. Although the precise reasons are yet to be defined, it has been proffered that atherosclerosis in older adults may cause gallbladder ischemia, thereby enhancing susceptibility to disease (Kahng and Roselyn, 1994).

Clinical Features

Although asymptomatic cholelithiasis is a common occurrence in older patients, most of them never experience complications. However, in older adults the frequent coexistence of multiple illnesses and the atypical presentation of diseases render complications more sinister and possibly life threatening when they do occur. Approximately one-fifth of older adults presenting with cholecystitis are likely to have coexisting choledocholithiasis and biliary colic, compared with about 5% of younger subjects. Ascending cholangitis is also more likely to occur in older patients. Following emergent cholecystectomy, approximately 50% of older subjects will develop choledocholithiasis (Siegel and Kasmin, 1997; Reiss and Deutsch, 1985; Rosenthal and Anderson, 1993).

Older adults are more likely to manifest with atypical features that may confound early diagnosis. Blunted febrile responses and minimal leucocytosis in the face of infection may delay diagnosis of cholecystitis. Abdominal pain in patients with impaired cognitive function may be poorly localized. Data indicates that in patients over the age of 65 years, 56% may be afebrile on presentation, 84% have poorly localized abdominal pain and 5% may be completely pain free. Delirium resulting from infection in cholecystitis may misdirect clinical focus toward the nervous system.

Physical diagnosis is less accurate in older patients. Murphy's sign in older adults is poorly sensitive (48%) compared with a sensitivity of 90% in younger patients. In older patients, Charcot's triad (right upper quadrant pain, jaundice, and fever) is more likely to present as Reynold's pentad with the additional features of delirium and hypotension (Hendrickson and Naparst, 2003; Parker, 1997; Adedeji, 1996). The onus rests with health professionals to

maintain a keen sense of awareness of the likelihood of this disorder in older patients.

Diagnosis and Management

Ultrasound is the imaging modality of choice in suspected cholelithiasis and cholecystitis. However, health professionals should be aware that older adults have a higher incidence of acalculous cholecystitis, which may not be identified on ultrasound. Utilization of hydroxy iminodiacetic acid (HIDA) scans as an adjunct in such cases may be helpful. Increasingly sophisticated endoscopic procedures have considerably enhanced diagnostic and therapeutic options in biliary tract disease (Hendrickson and Naparst, 2003). Ideally, an endoscopic retrograde cholangiopancreatography (ERCP) should always precede a cholecystectomy to facilitate accurate definition of the required surgical procedure. Endoscopic ultrasound is a newer technique that is just as sensitive as, but less risky than, ERCP. This may become the preferred procedure for older frail patients (Canto *et al.*, 1998).

ERCP is a safe and effective procedure in older adults. With experienced operators, the success rate is approximately 98%. Evidence suggests that older adults tolerate ERCP better than younger patients. In a cohort of 64 patients over the age of 90 years undergoing therapeutic ERCP, Kasmin *et al.* (1995) identified a complication rate of 3% with no incidents of pancreatitis and no procedure related deaths. Within the general population the expected overall complication rate ranges from 5 to 10% (Affronti, 1999).

Newer techniques such as endoscopic ultrasound, intraductal ultrasonography, magnetic resonance cholangiopancreatography and three-dimensional computed tomography continue to improve diagnostic accuracy (Domagk *et al.*, 2004).

Adoption of a "wait and see" approach is advocated as a reasonable therapeutic option in the management of cholelithiasis. However, data to support this was derived from studies of younger patients. The increased risk of complications and mortality following emergent surgery make this a less favorable solution for older adults. Reported mortality rates for elective procedures range from 4 to 10%, which is comparable to data obtained from younger adults. In emergent situations the mortality rate in older patients rises as high as 20% (Rosenthal and Anderson, 1993). Accordingly, the risks of expectant therapy in older adults with apparently asymptomatic disease must be carefully weighed against the benefits of elective intervention.

Laparoscopic cholecystectomy is the preferred therapeutic option in symptomatic cholelithiasis. Advantages of this procedure over open cholecystectomy include reduced length of stay and less patient discomfort. Anecdotal reports suggests that this minimally invasive procedure is well tolerated by older adults who are otherwise reasonable candidates for surgery. However, studies have yielded conflicting results with regards to morbidity and mortality data. The decision to perform laparoscopic cholecystectomy is still operator dependent. Nevertheless, increased proficiency at this procedure is rapidly relegating open cholecystectomy to the position of a salvage procedure following failure of a laparoscopic cholecystectomy (Kahng and Roselyn 1994; Ido *et al.*, 1995).

Pharmacological dissolution has rapidly fallen out of favor as a viable primary therapeutic option. Chenodeoxycholic acid was the first agent developed to reduce lithogenicity of bile and dissolve gallstones. Complete dissolution was rarely achieved and occurred in less than 15% of patients. Added disadvantages to the use of this agent were a high recurrence rate (50%), significant adverse effects and high cost. A newer and similar agent ursodeoxycholic acid is better tolerated and may be more effective. However, definitive evidence in older adults is lacking (Kahng and Roselyn 1994; Weinstein *et al.*, 1990).

Similarly, there is a striking lack of data concerning the safety and efficacy of contact dissolution in older adults. Methyl *tert*-butyl ether (MTBE), a potent cholesterol solvent, is instilled into the gallbladder during percutaneous transhepatic cholangiography to facilitate direct contact dissolution of gallstones. Catheter-related complications, MTBE toxicity, the high recurrence rate and the virtual absence of any data in older adults render this an inadvisable and obsolete option (Thistle and May, 1989).

Finally, biliary electroshock wave lithotripsy is a noninvasive procedure that appeared to be a potentially favorable option for older adults. However, efficacy of this technique depends on multiple factors, including size, calcium content and number of stones, and adequate gallbladder function and motility. Few patients qualify for this procedure (Magnuson *et al.*, 1989). There is no data in elders.

Gallbladder Perforation

Gallbladder perforations are more likely to occur in the fundus because, compared to the rest of the gallbladder, the fundal portion is relatively poorly vascularized. Type 1 gallbladder perforations are acute and associated with biliary peritonitis. Type II perforations are subacute and characterized by the presence of a pericholecystic abscess. Type III perforations generally result in a fistulous tract between the gallbladder and the duodenum.

Type III perforations occur most frequently and are more likely to be complicated by gallstone ileus. Though uncommon in the general population, gallstone ileus is the commonest cause of small bowel obstruction in older women, occurring in 25% of such cases. Definitive management is surgical enterotomy and stone extraction (Kahng and Roselyn, 1994)

Emphysematous Cholecystitis

This is a life-threatening condition characterized by gangrene of the gallbladder due to an infection with gas-forming organisms. Emphysematous cholecystitis is more likely in older patients with diabetes. Clostridial organisms are implicated in most patients. Cholelithiasis is present in only half of

affected patients. Ischemia has been implicated in this condition although the precise pathogenetic mechanisms remain unclear. Mortality is very high and emergent cholecystectomy is indicated (Affronti, 1999).

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune disease characterized by progressive destruction of intrahepatic biliary ducts and chronic cholestasis. Although predominantly a disease of middle-aged women, over one-third of patients are over the age of 65 years (Metcalf *et al.*, 1997). Several large case series indicate that the mean age at presentation is approximately 60 years with the peak incidence occurring between 70 and 79 years (Metcalf *et al.*, 1997; Howel *et al.*, 1997).

In patients who are symptomatic at presentation, advanced age is an independent adverse prognostic factors (Regev and Schiff, 2001). Treatment is generally reserved for selected older patients who are symptomatic. Outcomes for asymptomatic patients do not differ from that of the general population. Asymptomatic patients often come to attention following investigation of an unexplained elevation of serum alkaline phosphatase. Diagnosis of PBC is usually confirmed by the detection of antimitochondrial antibodies. Extrahepatic manifestations of PBC include hypothyroidism, sicca syndrome, hypothyroidism, and cutaneous xanthoma. Fat-soluble micronutrient deficiencies may occur resulting in an increased risk of osteoporosis and impaired coagulation (James, 1997).

Medical therapy is not very helpful in treating PBC. Colchicine may retard progression of liver fibrosis and improves laboratory values in patients with PBC but it has no effect on signs or symptoms of the disease. Corticosteroids and D-penicillamine are ineffective treatment options. Conflicting results have been obtained regarding other immunosuppressive agents such as Azathioprine (Imuran), methotrexate, and cyclosporin A. Ursodeoxycholic acid is a promising pharmacological agent. Data demonstrates not only improved symptoms and biochemical parameters but also retarded progression of PBC following ursodeoxycholic acid therapy. Recent evidence also suggests a role for selective estrogen receptor modulators in the treatment of PBC. Tamoxifen therapy has been associated with a decrease in serum alkaline phosphatase level in two women with coexistent PBC. Authors of these case reports suggest that Tamoxifen may act on cholangiocyte estrogen receptors to inhibit cholangiocyte proliferation. Further evidence is needed to support this hypothesis (Bergasa *et al.*, 2004; Reddy *et al.*, 2004). In contrast, orthotopic liver transplantation has very good outcomes in patients with end-stage liver disease resulting from PBC (Bergasa *et al.*, 2004).

Liver Transplantation

Liver cirrhosis, portal hypertension, and liver failure have a major impact on both hepatic and all-cause mortality in older adults. Indeed, the presence of liver cirrhosis in the setting of concomitant disease is an adverse prognostic factor. Subjects with chronic liver disease and complicating cirrhosis aged over 80 years had a cumulative survival rate of 59 and 19% at 5 and 9 years respectively, compared with 86 and 69% in their noncirrhotic counterparts with chronic liver disease (Hoshida *et al.*, 1999; del Olmo *et al.*, 2000; O'Mahony and Schmucker, 1994). Although management of liver cirrhosis in older adults is similar to younger adults, long-term survival rates are much worse in the elderly.

Previously, advanced age was considered a contraindication to liver transplantation and patients older than 55 were rarely accepted as transplant recipients. More recent evidence indicates a survival rate among older transplant recipients comparable to that of younger subjects. Age, as an isolated criterion, is therefore no longer considered a contraindication to liver transplantation (Tran *et al.*, 2004; Fattovich *et al.*, 1997).

Currently, approximately 20% of transplant recipients in the United States are over the age of 60 years compared with less than 10% in 1989 (Seaberg *et al.*, 1998). Additionally, quality of life, morbidity, and one year survival rates in older transplant recipients are comparable with those in their younger counterparts. Five year survival rates in older transplant recipients are worse due to excess cardiac, neurological, infective, and neoplastic deaths (Zetterman *et al.*, 1998; Varanasi *et al.*, 1999). Incidentally, the incidence of organ rejection following transplantation has consistently been shown to be lower in older adults possibly as a result of age-related immune dysfunction (James, 1997).

Although, the scarcity of donor organs has inappropriately fostered the use of age as a prioritizing factor, the absence of significant differences in outcomes does not justify this practice in older patients who would otherwise qualify for liver transplantation.

Similarly, available data indicates that livers harvested from elderly donors (50–70 years) may be transplanted with reasonable success rates. However, eligible older donors must be carefully screened to avoid the risk of early postoperative liver dysfunction and compromised graft survival (Hoofnagle *et al.*, 1996).

KEY POINTS

- Age-related pathophysiological changes include hepatic hypoperfusion, decreased hepatic mass, reduced activity of phase 1 hepatic drug-metabolizing enzymes, compromised hepatic regeneration, relative dilatation of the common bile duct, and increased lithogenicity of bile. These changes result in enhanced vulnerability of the aging hepatobiliary system to disease.
- Hepatobiliary diseases are a major cause of morbidity and mortality in older adults. The mortality rate from chronic liver disease in adults aged over 65 years

is 3–6 times higher than that in middle-aged adults. Biliary disease is the leading indication for acute abdominal surgery in older adults. Older adults with viral hepatitis are more likely to develop complications such as fulminant hepatic failure, liver cirrhosis, and hepatocellular carcinoma

- Twenty percent of all patients diagnosed with autoimmune hepatitis are over the age of 65 years. Drug-induced hepatitis is more common in older adults due to multiple factors including increased exposure to drugs, compromised hepatic metabolism and increased risk of hepatotoxicity with the use of certain drugs in older adults.
- Older adults are more likely to present with atypical features of biliary tract disease, and life-threatening complications such as gallbladder perforation and emphysematous cholecystitis. Emergency biliary surgery has worse outcomes in older adults. The risks of expectant therapy in older adults with asymptomatic biliary tract disease must be weighed against the benefits of elective intervention.
- Advanced age is not an absolute contraindication to liver transplantation. Quality of life, morbidity, and one year survival rates in older transplant recipients are comparable with those in their younger counterparts.

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34

Sphincter Function

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INTRODUCTION

Fecal incontinence is a common condition which affects up to 21% of community dwelling elderly individuals over the age of 65 (Campbell *et al.*, 1985; Kok *et al.*, 1992; Talley *et al.*, 1992). Prevalence in the institutionalized elderly (nursing homes) exceeds 50% (Chassagne *et al.*, 1999; Prather *et al.*, 2001). An attack of acute diarrhea can result in an incontinence episode even in healthy people, when the rectal reservoir is overwhelmed by the liquid/loose stools. Patients with fecal incontinence experience anxiety, fear of embarrassment, emotional and social devastation, silent suffering, isolation, and depression (Johanson and Lafferty, 1996). Patients underreport fecal incontinence unless prompted, placing the onus on the physician to ask about anorectal problems and to encourage patients toward the effective treatment options that are available. Fecal incontinence, along with urinary incontinence, is among the leading reasons for nursing home admission (Nelson *et al.*, 1998). In this chapter, we will discuss only the anal sphincter, its anatomy, physiological changes with aging, prevalence, importance, risk factors, causes of incontinence, evaluation, and treatment options of fecal incontinence.

ANATOMY AND PHYSIOLOGY OF THE ANAL CANAL AND RECTUM

In order to better understand the clinical presentation, evaluation, and treatment options for fecal incontinence, the anatomy and physiology of the anal canal and rectum are briefly reviewed along with changes that occur with aging.

The *rectum* is a tubular structure, 12–15 cm in length with the anal canal extending about 4 cm, from the anal verge to the anorectal ring. The anal canal is separated by a dentate line into an upper mucosal lining and lower cutaneous segment of the anal canal. The area above the dentate line is supplied by the sympathetic and parasympathetic systems, while below the dentate line the somatic nervous system provides innervation. Just above the dentate line there are 8–12 rectal columns (anal cushions) with their bases connected to each other. The high-pressure zone of the anal sphincter is formed by the combination of muscles (internal anal, external anal, and the puborectalis) and anal cushions (Lestar *et al.*, 1989; Schweiger, 1979).

The *internal anal sphincter* is a circular muscle layer that starts from the rectum. The internal anal sphincter is tonically contracted at rest, preventing the involuntary loss of stool and gas.

Tone of the anal sphincter:

The internal anal sphincter contributes 50–85% of the resting tone of the sphincter with the external anal sphincter contributing 25%–30%, the remaining 15% coming from the anal cushions (Lestar *et al.*, 1989; Schweiger, 1979; Taylor *et al.*, 1984; Gibbons *et al.*, 1986). In response to rectal distention, the internal anal sphincter tone increases initially, followed by decreased tone constituting the recto-anal inhibitory response (Lestar *et al.*, 1989).

Changes with Aging:

The thickness of internal anal sphincter increases with age and is confirmed by ultrasound and magnetic resonance imaging (Papachrysostomou *et al.*, 1994; Rociu *et al.*, 2000; Burnett and Bartram, 1991; Nielsen and Pedersen, 1996). The functional significance of this change is unclear. It could be a compensatory change for the maintenance of continence (Papachrysostomou *et al.*, 1994). This is unlikely as the age-related changes in anal sphincter pressures are quite modest in healthy individuals (Loening-Baucke and Anuras, 1985; Barrett *et al.*, 1989). The most likely explanation is increased connective tissue or "sclerosis" of the internal anal sphincter with aging (Klosterhalfen *et al.*, 1990).

The external anal sphincter is a striated muscle surrounding the inner smooth muscle and terminating distal to the internal anal sphincter. Both the puborectalis and the external anal sphincter provide the voluntary control of

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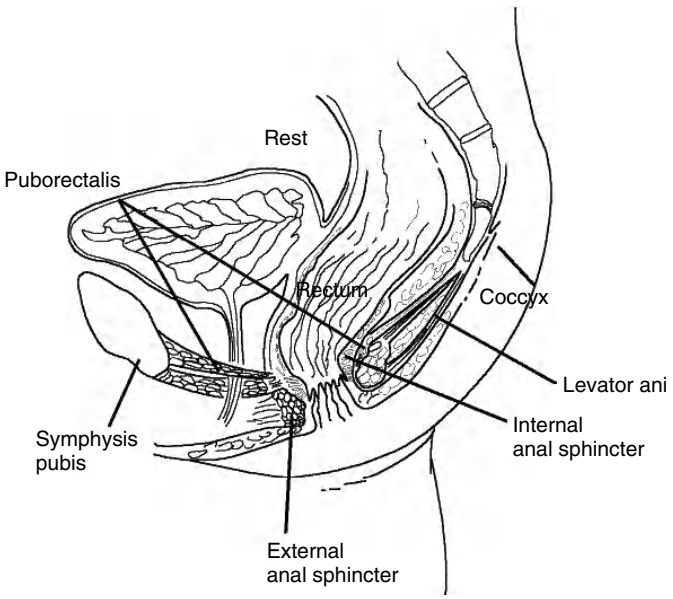

Figure 1 Anatomy of the anorectum at rest

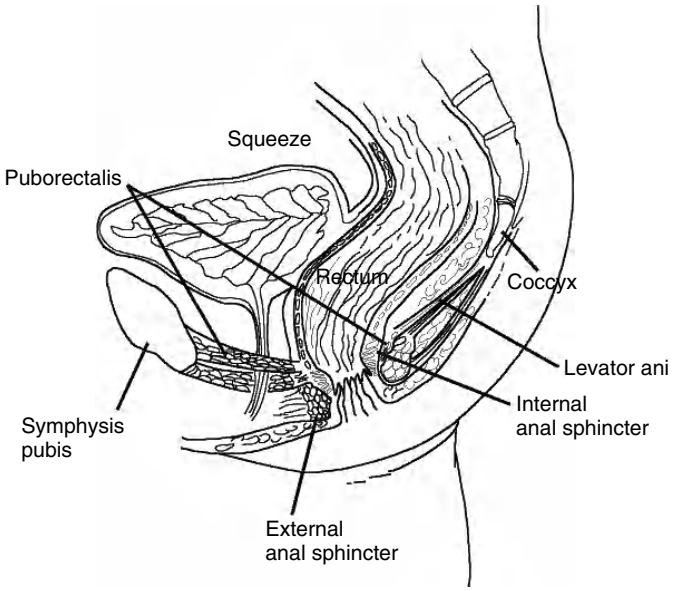

Figure 2 Anatomy of the anorectum during squeeze

continence in response to various stimuli such as increased intra-abdominal pressure that occurs with coughing, rectal distention, and anal dilatation (Schweiger, 1979; Sun *et al.*, 1990). Voluntary anal sphincter pressures decrease with age and pressures are lower in women than in men (Enck *et al.*, 1989).

The levator ani muscle is a major component of the pelvic floor and is composed predominantly of three striated muscles: iliococcygeus, pubococcygeous, and puborectalis. The puborectalis muscle plays the largest role in continence and is a U shaped loop of striated muscle slinging around the posterior aspect of the external anal sphincter, pulling the anal canal forward creating the anorectal angle (Figure 1). The puborectalis and resultant anorectal angle aid in the maintenance of continence, as this angle becomes more acute with voluntary sphincter contraction providing an anatomic obstruction to the distal movement of stool retained above the angle (Hajivassiliou *et al.*, 1996).

Physiology of Defecation:

Both the sensory and motor neurons of the anorectum interact to maintain continence and control the process of defecation. The desire to defecate is usually preceded by propagation of contractions in the proximal colon resulting in the movement of feces into the rectum with relaxation of the distal colon/rectum, relaxation of internal anal sphincter, and contraction of the external anal sphincter until the socially appropriate time for defecation is desired (Gowers, 1877; Gordon, 2001). The sensory receptors in the anal canal determine the nature of luminal contents, that is, whether the contents are solid, liquid, or gas (Miller *et al.*, 1988). When voluntary defecation is desired, intra-abdominal pressure rises from abdominal wall contraction. The muscles of the pelvic floor (external anal sphincter, puborectalis, and other muscles of the levator ani) relax. Relaxation of the puborectalis results in straightening of the anorectal angle providing a straightened conduit for stool movement (Figure 2). The anal canal relaxes with the increased rectal pressure resulting in the evacuation of stool.

Mechanism of Continence:

It is maintained through the combined action of several muscles:

(a) The external and internal anal sphincters and the puborectalis muscle.
(b) Determinants of continence include resting anal tone, resistance to opening at the anus, rectal compliance, normal anorectal sensation, and the consistency of stools (Tobin and Brocklehurst, 1986). In addition, mobility and intact cognition is required to have a bowel movement. Impairment in any of these mechanisms may result in fecal incontinence.

PREVALENCE AND IMPORTANCE

The prevalence of fecal incontinence in the general population is 2.2% (Nelson *et al.*, 1995). This study did not include individuals residing in nursing homes. When individuals above the age of 65 years were studied, the frequency of fecal incontinence increased from 3.7 to 27% (Table 1). The greatest prevalence of fecal incontinence is found in nursing homes with more than 50% of the long-term care residents affected by chronic fecal incontinence (Chassagne *et al.*, 1999). Higher prevalence of fecal incontinence is seen in geriatric hospital wards (20–32%) and geriatric psychiatry centers (up to 56%) (Thomas *et al.*, 1987; Issac and

Table 1 Prevalence of fecal incontinence

Country	Author (ref)	Prevalence in general population	Prevalence age > 65 years (%)
New Zealand	Campbell *et al.* (1985)	–	3.1
Switzerland	Faltin *et al.* (2001)	4.4[a]	–
Germany	Giebel *et al.* (1998)	5	–
Netherlands	Kok *et al.* (1992)	2.3	4.2–16.9
Japan	Nakanishi *et al.* (1999)	–	8.7 M; 6.6 F
Wisconsin (USA)	Nelson *et al.* (1995)	2.2	–
Boston (USA)	Resnick *et al.* (1994)	–	17
Minnesota (USA)	Robert *et al.* (1999)	8.3 M; 13.1 F	17 M; 27 F[b]
Minnesota (USA)	Talley *et al.* (1992)	–	3.7
France[c]	Chassagne *et al.* (1999)	–	58
Wisconsin (USA)[c]	Nelson *et al.* (1998)	–	47
England[c]	Peet *et al.* (1995)	–	20.8

M, male; F, female.
[a]Only women studies. [b]Age greater than 50 years. [c]Studies reporting prevalence in long-term care.

Table 2 Risk factors and causes of fecal incontinence

Risk factors (Gordon, 2001; Nelson *et al.*, 1995)
Prior history of urinary incontinence
Presence of neurological disease
Presence of psychiatric disease
Poor mobility
Age greater than 70 years
Dementia

Causes of fecal incontinence (Madoff *et al.*, 1992)
A. Fecal impaction
B. Loss of normal continence mechanism
   1. Local neuronal damage (e.g. pudendal nerve)
   2. Impaired neurological control
   3. Anorectal trauma/sphincter disruption
C. Problems overwhelming normal continence mechanism
D. Psychological and behavioral problems
   1. Severe depression
   2. Dementia
   3. Cerebrovascular disease
E. Neoplasm (rare)

Walkley, 1964). Eighty percent of patients hospitalized with dementia also experienced fecal incontinence (Taylor *et al.*, 1984). Double incontinence (i.e. fecal incontinence and urinary incontinence) occurs twelve times more commonly than fecal incontinence alone with 50 to 70% of patients with urinary incontinence also suffering from fecal incontinence (Nelson *et al.*, 1995; Thomas *et al.*, 1987; Issac and Walkley, 1964; Ouslander *et al.*, 1982). This is not surprising, as the combination of urinary and fecal incontinence is the second most common cause of institutionalization in elderly persons (Nelson *et al.*, 1998; O'Donnell *et al.*, 1992).

Fecal incontinence is a marker for poorer overall health and is associated with increased mortality (Chassagne *et al.*, 1999; Nakanishi *et al.*, 1999). Incontinent nursing home residents experience more urinary tract infections and pressure ulcers (Borrie and Davidson, 1992). The total health-care costs attributable to fecal incontinence are difficult to determine as few studies examine health-care costs for fecal incontinence alone. Most health-care cost information comes from nursing homes caring for patients with fecal incontinence, urinary incontinence or both. The nursing home related costs for incontinence were $3.26 billion in 1987 and the yearly cost of adult diapers alone is $400 000 000 (Hu, 1990; Mandelstam, 1985). The additional health expenditures reach in excess of $9000 per patient year of incontinence (Borrie and Davidson, 1992).

RISK FACTORS AND CAUSES OF FECAL INCONTINENCE

The risks and causes of fecal incontinence are summarized in Table 2. Risk factors for fecal incontinence include a prior history of urinary incontinence, the presence of neurological or psychiatric disease, poor mobility, age greater than 70, and dementia (Nelson *et al.*, 1995; Madoff *et al.*, 1992; Tobin and Brocklehurst, 1986). Possibly the most common predisposing condition to fecal incontinence is fecal impaction, which is reported in up to 42% of elderly patients admitted to geriatric units (Read and Abouzekry, 1986). These patients are often chronically constipated and receive large doses of laxatives resulting in incontinence from leakage around the large fecal impaction (Read and Abouzekry, 1986). The problem is further complicated by the presence of decreased rectal sensation allowing the progressive accumulation of stool in the rectum (Read *et al.*, 1985). Fecal incontinence in diabetes mellitus occurs from autonomic neuropathy and is exacerbated in the presence of diabetic diarrhea (Schiller *et al.*, 1982). Pelvic neuropathy may result from prolonged straining and birth trauma. Fecal incontinence results in these patients because of sphincter damage and pudendal neuropathy (Sultan *et al.*, 1994). Trauma to the anal canal such as anal surgery including hemorrhoidectomy, anal fissure repair, and anal dilatation may disrupt the anal sphincter muscles resulting in impaired continence (Rieger *et al.*, 1997; Read *et al.*, 1982b). Patients with total internal sphincterotomy have a 40% risk of fecal incontinence, while partial sphincterotomy carries a risk of 8–15% (Bennet and Goligher, 1962; Walker *et al.*, 1985; Pernikoff *et al.*, 1994). Altered cognition is commonly associated with fecal incontinence (Chassagne *et al.*, 1999). The combination of altered cognition and fecal incontinence are important factors leading to institutionalization (Borrie and Davidson, 1992).

CLINICAL SUBGROUPS

There are three main types of fecal incontinence:

1. Overflow
2. Reservoir and
3. Rectosphincteric

Overflow incontinence is specially seen in cognitively impaired, bed ridden nursing home individuals and the risk factors are outlined in Table 3. Reservoir incontinence is seen

Table 3 Risk factors for overflow incontinence

Inadequate fiber
Inadequate water intake
Immobility
Inadequate toileting facilities
Mental status changes
Metabolic abnormalities
Hypothyroidism
Hypercalcemia
Hypokalemia
Medication
Narcotics
Antipsychotics
Antidepressants
Calcium channel blockers
Diuretics

in individuals with diminished colonic or rectal capacity. This condition is commonly seen with radiation proctopathy, chronic rectal ischemia, idiopathic inflammatory bowel disease, and proctocolectomy with ileoanal anastomosis. Rectosphincteric incontinence is seen in conditions associated with structural damage to one or both anal sphincters, pudendal neuropathy affecting the external anal sphincter and or puborectalis muscle and or rectal sensation, or to degenerative or myogenic disorders affecting internal anal sphincter or external anal sphincter.

EVALUATION OF FECAL INCONTINENCE

The goals in evaluating fecal incontinence include establishing the severity of incontinence, understanding the pathophysiology present and directing the patient to appropriate therapy for their condition. This is accomplished through the history, physical examination, and investigations targeted to determine the etiology of fecal incontinence.

HISTORY AND PHYSICAL EXAMINATION

The physician may find it difficult to recognize fecal incontinence since patients usually will not volunteer information about incontinence unless asked (Johanson and Lafferty, 1996). This information is best elicited through direct questioning regarding bowel habit and continence. It is helpful to identify when the symptoms first occurred, determine if the patient has any sensation such as the passage of stool or gas, fullness in the rectum, or warning symptoms such as abdominal cramps and urgency. Inquiry about the home environment may reveal barriers to bathroom facilities especially in nursing homes, particularly in patients with walkers. Table 4 summarizes important areas to address during history. Colitis of any cause may result in loose stools that overwhelm the continence mechanisms. Patients with perianal Crohn's disease may also develop fecal incontinence from fistula formation. In the evaluation of fecal incontinence, several components of the neurological history deserve attention. A cerebrovascular accident may limit the patient's physical ability to use the toilet facility. The new onset of fecal incontinence may also herald the presence of cord compression, especially when associated with other neurologic symptoms.

Table 4 Evaluation of fecal incontinence

1. History
Chronic medical condition
Diabetes and chronic diarrhea or constipation
Cerebrovascular accidents or cord compression
Dementia and depression
Immobility
Trauma during child birth
Surgeries history
Hemorrhoidectomy
Sphincterotomy
Fistulectomy
Colon resection and dilatation
Radiation to the prostate or cervix for carcinoma
Review of medications such as antipsychotic, sorbitol base medications (theophyline)
2. Physical examination
Saint Louis University Mental Status examination or Mini-Mental State Exam
Geriatric depression scale
Neurological examination
Rectal examination

A thorough review of prescription, over-the-counter medicine, and supplements may reveal an underlying cause for the altered bowel habit. Medicines causing diarrhea include magnesium containing antacids and poorly absorbed sugars such as sorbitol and mannitol (used in dietetic products). Sorbitol is also frequently used as a base in elixirs, for example, theophyline elixir. The intentional or inadvertent use of cathartics may contribute to diarrhea and incontinence. Similarly, a medication responsible for constipation may cause a worsening of incontinence through overflow.

The physical examination helps to identify the pathophysiology of fecal incontinence and can guide the ordering of appropriate tests for further evaluation (Rosen, 1990). The usual physical examination may be supplemented by a Mini-Mental Status Examination, or Saint Louis University Mental Status Examination, which help identify patients with cognition problems (Crum *et al.*, 1993; Morley and Tumosa, 2002). The neurological examination includes assessment of general patient mobility, motor strength, and sensory testing. The "anal wink" is elicited by stroking the skin lateral to the anal canal and observing the contraction. Absence of this reflex suggests significant neural damage. Anal gaping can be seen when the buttocks are parted in patients with paraplegia (Read and Sun, 1991). The perineum is inspected for dermatitis, hemorrhoids, fistula, surgical scars, skin tags, rectal prolapse, soiling and ballooning of the perineum (suggesting weakness of the pelvic floor). Following inspection, the next step is digital rectal examination to note the baseline sphincter tone, squeeze pressure, any asymmetry of the sphincter on squeeze (especially anteriorly), and the amount and character of the stool (hard and ball like or soft). The positive predictive value of digital exam is 67% for detecting

decreased anal tone when compared to anal manometry (Hill *et al.*, 1994). Patients with high or normal sphincter tone can also be incontinent especially in the setting of large rectal volumes or altered rectal sensation. In patients with lesions of the spinal cord or cauda equina the sphincter tone may be normal, but when pressure is applied to any part of the anorectal ring the phenomena of gaping can be seen. Findings in the normal elderly patient typically reveal lower anal canal pressures (Bannister *et al.*, 1987).

DIAGNOSTIC TESTS

A number of tests are available to provide data on colonic and anorectal function (Barnett *et al.*, 1999). Table 5 outlines most of the tests necessary for the investigation of fecal incontinence. In the elderly population the most important thing is to exclude fecal impaction. Even in the absence of stool in the rectal vault, a higher impaction may be present. If the patient is at risk, a plain abdominal radiograph is required to exclude high impaction. A flexible sigmoidoscopy or colonoscopy examines the colorectal mucosa for evidence of colitis, neoplasia, inflammatory bowel disease, colonic and rectal ischemia, laxative abuse, and other structural abnormalities. Anorectal manometry provides comprehensive information regarding anorectal function as it quantifies anal sphincter tone and assesses anorectal sensory responses, the recto-anal inhibitory reflex, and rectal compliance (Rao and Patel, 1997). Anorectal manometry gives either new information or confirms the suspected diagnosis in patients with fecal incontinence (Wexner and Jorge, 1994). A finding of decreased rectal compliance may point to fecal incontinence from increased stress on the continence mechanism as the stool is received in the rectum (i.e. a stiff rectum does not accommodate the stool bolus resulting in overflow) (Rasmussen *et al.*, 1990). Electromyography measures the neuromuscular integrity between the distal portion of pudendal nerve and the anal sphincter muscle (Rao, 1997). Electromyography correlates well with anorectal manometry but its use in the routine assessment of fecal incontinence is controversial (Barnett *et al.*, 1999; Wexner *et al.*, 1991). Anal ultrasound defines the internal and external anal sphincters (Law *et al.*, 1991). Anal ultrasound can be used to identify isolated sphincter defects present in about two-thirds of incontinent patients (Chen *et al.*, 1999; Liberman *et al.*, 2001). Ultrasonographic findings correlate with both surgical and electromyographic findings (Deen *et al.*, 1993; Meyenberger *et al.*, 1996). Magnetic resonance imaging (MRI) has also been used to evaluate the sphincter defects with definition superior to anal ultrasound as it provides higher spatial resolution and better contrast for lesion characterization (Beets-Tan *et al.*, 2001). Given the added expense and need for special coils, the clinical relevance of the improved resolution in debatable. Not all patients require all tests. An algorithm outlining one possible management strategy is shown in Figure 3.

Table 5 Diagnostic test for fecal incontinence

Diagnostic tests
Plain abdominal X ray
Sigmoidoscopy/colonoscopy
Anorectal manometry
Electromyography
Anal ultrasound or magnetic resonance imaging (MRI)

TREATMENT

The treatment of fecal incontinence depends on the underlying etiology and severity of the incontinence. Table 6 summarizes the main treatment options for fecal incontinence. Minor degrees of fecal incontinence can be treated conservatively, whereas patients with severe fecal incontinence require more aggressive treatment (Tariq, 2004; Tariq *et al.*, 2003).

Conservative Therapy

Patients with mental impairment such as in dementia may simply need to be directed to the toilet or reminded of such use. Physical limitations and environmental obstacles need to be addressed if these are contributing to incontinence as they can often be overcome by simple measures. *Habit training* involves a regular schedule of defecation, usually after breakfast, often incorporating the use of supplemental fiber and regularly scheduled enemas when defecation is delayed more than 2 days. Habit training is particularly effective for patients with overflow incontinence (Ouslander *et al.*, 1996). It has been shown that *prompted voiding* increases the number of continent bowel movements and reduces the number of incontinent movements; this study was designed primarily for urine incontinence (Ouslander *et al.*, 1996). *Sphincter training exercises* ("Kegel" exercises) alone do not increase the number of continent episodes (Whitehead *et al.*, 1985). Nocturnal diarrhea is primarily seen in diabetic patients. In cases where gut dysmotility is suspected, clonidine may be used. Topical application is

Table 6 Summary of treatment options

Conservative
Redirection in persons with cognitive impairment
Habit training
Adding Fiber into the diet
Prompt voiding
Kegel exercise
Anti diarrheal agents (once infection is excluded)
Biofeedback
Surgical (little or no data in older persons)
Sphincter repair
Neosphincter operation
Alternative therapy
Artificial anal sphincter implantation
Injection of glutaraldehyde
Sacral nerve stimulation
Colostomy

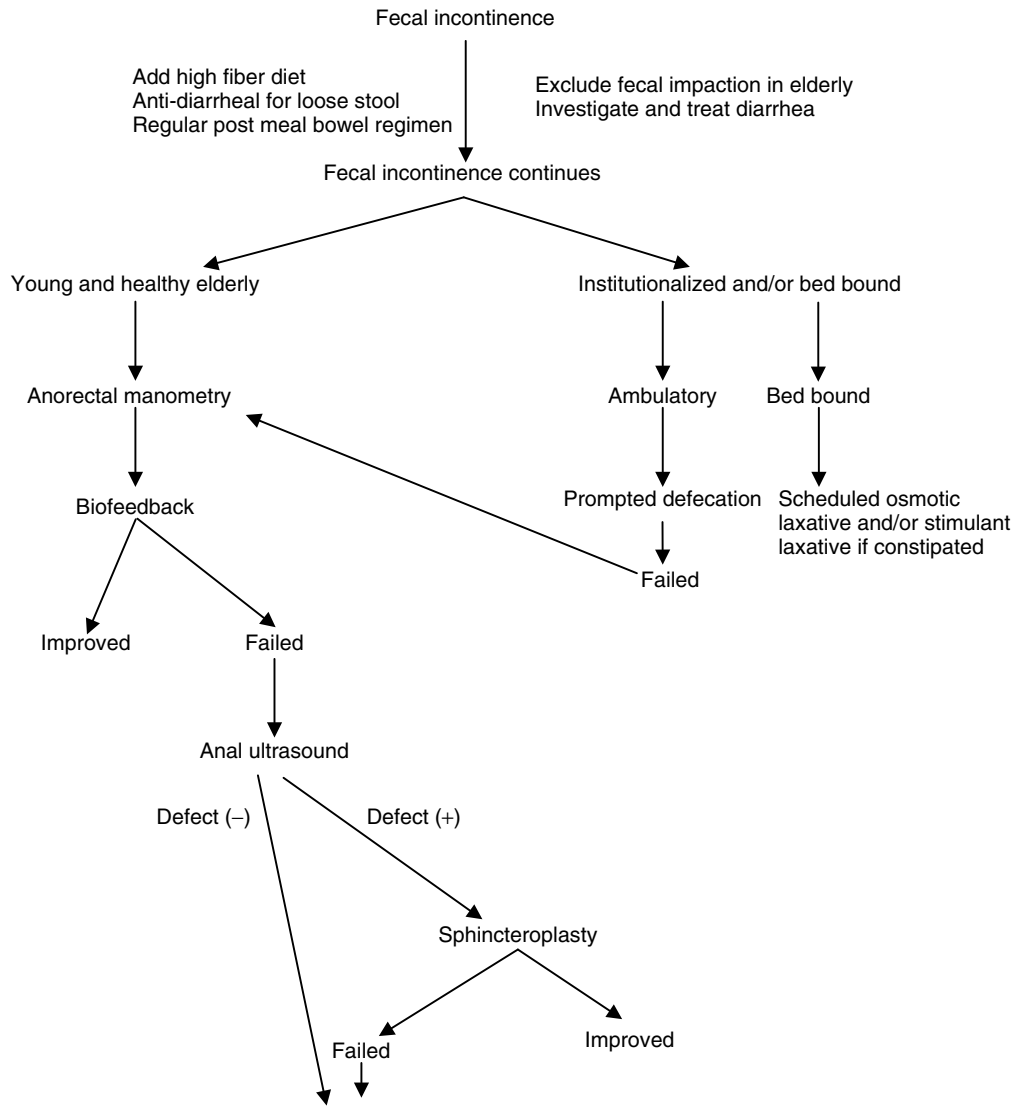

Figure 3 Algorithm for the management of fecal incontinence (Reprinted from *American Journal of Medicine*, V115, Tariq SH *et al.*, Fecal incontinence in the elderly patient, pp 217–226, Copyright 2003, with permission from Excerpta Medica Inc.)

preferred over the oral preparation. A trial of cholestyramine may be helpful if bile acid malabsorption is suspected. Antidiarrheals such as loperamide are helpful when the stool is loose (Read *et al.*, 1982a). A double-blind crossover study of 30 patients receiving loperamide, codeine, or diphenoxylate with atropine for 4 weeks found that all reduced the stool frequency but loperamide and codeine were more effective in reducing fecal incontinence compared to diphenoxylate (Palmer *et al.*, 1980). Diphenoxylate and codeine have more central nervous system side effects than loperamide and are generally best avoided in the elderly in this setting.

Biofeedback is classically described as a learning theory with operant conditioning as its theoretical basis and was first described by Engel *et al.* (1974). Biofeedback is a nonsurgical, noninvasive, relatively inexpensive outpatient method of treating fecal incontinence (Wald, 1981). Biofeedback for fecal incontinence involves improving the strength of the external sphincter and improving anorectal sensation (Whitehead *et al.*, 1985). Biofeedback provides immediate and long-term improvement of fecal incontinence (Enck *et al.*, 1994). Biofeedback training teaches the patient to recognize small volumes of rectal distension and to contract the external anal sphincter while simultaneously keeping intra-abdominal pressure low. This is accomplished by measuring anal canal pressure, showing this on a visual display to the patient, and providing verbal feedback. Table 7 shows the success rate, age range, and number of sessions involved in different studies. Better results are achieved when treating motivated, mentally capable patients. Patients should also have some degree of rectal sensation and be able to contract the external anal sphincter (Latimer *et al.*, 1984). Miner *et al.* (1990) compared active sensory biofeedback with sham retraining. In the active group, biofeedback training reduced incontinent

Table 7 Technical details and results of biofeedback therapy

Author (ref)	N	Age Range (mean)	Control group	Biofeedback Modality	Outcome Measure	Improved	Follow-up duration months (mean)
Miner *et al.* (1990)	25	17–76	Yes Randomized	Strength Sensory Coordination	Stool diary	77% BF 42% sham	24
Whitehead *et al.* (1985)	18	65–92 (73)	Yes Randomized	Strength Sensory Coordination	Diary ≥75% improvement	77% 50% 42%	post BF 6 12
Guillemot *et al.* (1995)	24 16 BF 8 control	39–72 (60)	Yes Not randomized Patients chose therapy	Strength	Clinical score	75% 19%	6 24–36 (30)
Loening-Baucke (1990)	17 8 BF 9 medical therapy	35–84(64)	Yes Not randomized	Strength Sensory Coordination	Stool diary ≥75% improved	50%[a] 38%[a]	3 12
MacLeod (1983)	50	25–76 (55)	No	Strength	≥90% decrease in FI frequence	72%	12
Rao *et al.* (1996)	22	15–78 (50)	No	Strength Sensory Coordination	Diary/VAS FI Severity scale	≥ 75% = 53% ≥ 50% = 100%	12
Goldenberg *et al.* (1980)	12	12–78	No	Strength	Not described	83%	3–24
Wald (1981)	17	10–79 (48)	No	Strength Sensory Coordination	Interview Questionnaire ≥75% improvement	71%	2–38 (15)
Sangwan *et al.* (1995)	28	30–74 (52.9)	No	Strength Sensory	Manometry Excellent or good results	75%	4–47 (21)
Glia *et al.* (1998)	26	32–82 (61 median)	No	Strength Sensory	FI questionnaire ≥50% reduction FI	64%	12–48 (21)
Chiarioni *et al.* (1993)	14	24–75 (49)	No	Strength	Diary cards ≥75% reduction FI Monthly interviews × 5 Then Q 3 months	75%	3–21 (15)
Cerulli *et al.* (1979)	50	5–97 (46)	No	Strength Sensory Coordination	≥90% reduction FI	72%	4–108 (32)

(*continued overleaf*)

Table 7 (*continued*)

Author (ref)	N	Age Range (mean)	Control group	Biofeedback Modality	Outcome Measure	Improved	Follow-up duration months (mean)
Berti Riboli *et al.* (1988)	21	14–84 (60)	No	Strength Sensory Coordination	≥90% reduction FI	86%	1.5 or 3
Patankar *et al.* (1997)	72	34–87 (70)	No	Strength	Questionnaire ≥75% improvement Subjective satisfaction	85%	not stated
Rieger *et al.* (1997)	30	29–85 (68 median)	No	Strength	VAS Incontinence score >80% improved = cure Any improvement	27% 23% 23% 67%	1.5 6 12
Ryn *et al.* (2000)	37	22–82 (61 median)	No	Strength	FI score Subject rating VAS	59% good or v. good 41% some improved	12–59 (44)
Buser and Miner (1986)	13	13–66	No	Strength Sensory Coordination	Manometry Resolution of FI	92%	16–30
Norton and Kamm (1999)	100	14–82 (49 median)	No	Strength Sensory Coordination	Bowel diary Symptom questionnaire	43% (cure) 24% (improved)	end of BF
Ko *et al.* (1997)	25	31–82 (63)	No	Strength Coordination	Symptom improvement Number FI episodes	92%	7
Leroi *et al.* (1999)	27	29–74 (53)	No	Strength Sensory Coordination	Clinical improvement Good versus poor	30%	Not reported

FI, Fecal Incontinence; VAS, Visual Analog Scale; BF, Biofeedback.

[a]Unchanged from controls.

episodes by 80% per week in this study, whereas the control group showed no change from the baseline. This improvement lasted over 2 years in 73% of the patients available for follow-up. Whitehead *et al.* (1985) reported a study in the geriatric population, who were treated initially for fecal impaction but in whom 13 patients continued to be incontinent. These patients were then treated with biofeedback, which improved sphincter strength and reduced incontinence episodes by more than 75%. Enck *et al.* in his review of biofeedback showed improved continence in 13 of 14 studies (Enck, 1993). In a recent review of 46 studies involving the use of biofeedback for fecal incontinence in 1 364 patients (76% female), less than 20% of these studies included randomization and most involved a relatively small number of subjects. Improvement in continence occurred in at least one-half of the patients. No specific details regarding age-related differences were noted (Norton and Kamm, 2001).

Surgical Therapy

Surgical intervention is generally considered when more conservative measures have failed in patients with severe incontinence and identifiable anatomic defects. Although surgery is more commonly recommended in younger patients, the appropriately selected elderly patient fairs well with surgical intervention (Simmang *et al.*, 1994).

Sphincter Repair

In the setting of an isolated sphincter defect, especially anterior sphincteroplasty, surgery is very successful (Mavrantonis and Wexner, 1998; Karoui *et al.*, 2000). Three basic approaches are described: direct apposition, overlapping anterior sphincteroplasty, and plication procedures (anterior, posterior, and total pelvic floor repair). It is reported that an improvement is seen in anal function demonstrated by anal manometry before and after anterior sphincter repair (Fleshman *et al.*, 1991). There was 96% improvement in anal function as compared to preoperative symptoms (all women aged 22–75 years, mean age 37.8 years). The outcome of surgical repair is variable as some patients may continue to have incontinence and others develop new bowel problems postoperatively (Karoui *et al.*, 2000; Yoshioka and Keighley, 1989).

Neosphincter Operations

Muscle transposition may be considered for severe fecal incontinence where standard therapy has failed. Techniques include graciloplasty, dynamic graciloplasty, and gluteus maximus transposition. The result of graciloplasty varies significantly (Leguit *et al.*, 1985; Corman, 1985; Corman, 1980). The result of graciloplasty is improved by electrical stimulation after the implantation of electrical electrodes and a pulse generator (Baeten *et al.*, 1995). Electrical stimulation provides the gracilis muscle with the properties to function as a sphincter (George *et al.*, 1993). In a prospective multicenter trial, 66% of patients with graciloplasty achieved continence in a follow-up at 2 years (Madoff *et al.*, 1999). The performance of graciloplasty in the elderly has not been reported.

Alternative Therapies

Newer techniques have been developed for the treatment of fecal incontinence, but these procedures are described predominantly in younger age-groups. Wong *et al.* published a multicenter prospective trial in 12 patients who failed in conventional management for severe fecal incontinence and had an artificial anal sphincter implanted (Wong *et al.*, 1996). A successful outcome was achieved in 75% of the patients with a mean age of 33 years. The result of this surgical technique has not been specifically addressed in the elderly.

Injections of glutaraldehyde cross-linked collagen are simple and well-tolerated for patients who do not respond to conservative therapy and have a surgically incorrectable problem (internal sphincter dysfunction). Seventeen patients (mean age = 53 years) participated in a study. Sixty-five percent of the patients had symptomatic improvement, 12% had minimal improvement, while 18% had no improvement (Kumar *et al.*, 1998).

Sacral nerve stimulation for fecal incontinence has been shown to improve fecal continence along with improved quality of life in selected patients (Vaizey *et al.*, 2000). In a nonrandomized study, the application of radiofrequency energy to the sphincter may improve continence and quality of life (Takahashi *et al.*, 2002; Takahashi *et al.*, 2003). Finally, for severe fecal incontinence, when all the other procedures have failed, a diverting colostomy is usually the surgical procedure of choice.

CONCLUSION

Fecal incontinence is a common problem in the elderly population, particularly affecting individuals in the community and nursing homes. In addition to the inconvenience of the incontinence for the patient and caregiver, it is a marker of poor health and associated increased mortality. Patients and their caregivers must be questioned specifically about the presence of fecal incontinence and its severity and the patients must be treated accordingly. All patients with fecal incontinence warrant an initial medical evaluation including the exclusion of fecal impaction by rectal exam and X-ray film of the abdomen. Cognitively impaired patients benefit most from habit training. Several surgical procedures are available and may be helpful in selected older persons in selected centers. Future studies are needed to identify which patients will obtain the most benefit from these interventions and to determine the most cost-effective evaluation and treatment regimens in the aging population.

KEY POINTS

- Fecal incontinence is a common problem that is often not reported to the physician.
- In persons with fecal incontinence, fecal impaction should always be excluded.
- In healthy elderly with fecal incontinence, anal manometry and biofeedback should be utilized.
- Anal ultrasound can also be used to identify a defect suitable for treatment with sphincteroplasty.
- Common causes of fecal incontinence include cognitive impairment and fecal impaction.

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35

Constipation

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DEFINING CONSTIPATION

Constipation most classically refers to reduced defecation frequency. Physicians usually define constipation as less than three bowel movements per week. Patients more frequently describe constipation as defecatory difficulty with predominant complaints of straining or hard stools. Understanding the patient's view of "constipation" assists in the evaluation and treatment process.

The normal defecatory process requires normal colon transit and normal pelvic floor function. Normal colon transit ranges from 24 to 72 hours. Increased colonic contractions occur in response to meals, particularly those with higher concentrations of calories and fat. Once stool is delivered to the rectum, defecation may be voluntarily initiated through a set of coordinated actions, including relaxation of the puborectalis muscle, opening of the anorectal angle, and relaxation of the anal sphincters, accompanied by a simultaneous rise in intra-abdominal pressure (i.e. Valsalva maneuver). An abnormality affecting any of these areas results in the development of an altered bowel pattern.

Primary constipation refers to constipation without an obvious cause. Secondary constipation implies that the altered bowel function results from external etiologies such as metabolic abnormalities, medications, insufficient diet, or mechanical factors obstructing the movement of stool. Chronic constipation indicates that symptoms have been present for more than three months. Patients with chronic constipation, not responding to usual treatments, require further investigation to evaluate for evidence of slow transit constipation or dyssynergic defecation (also called *pelvic outlet dysfunction*). Although constipation commonly occurs in the setting of the irritable bowel syndrome (IBS), new onset IBS occurs less frequently in elders than in younger patients. Specific criteria have been defined for identifying constipation by different investigators. The most commonly used are the Rome criteria, a consensus definition by experts for the primary purpose of use in clinical trials (Thompson *et al.*, 1999).

EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND IMPACT

Constipation has long been misunderstood as a common problem associated with aging. The prevalence of self-reported constipation, physician visits, and laxative use increases with aging (Harari *et al.*, 1996; Everhart *et al.*, 1989; Sonnenberg and Koch, 1989). In contrast, reported stool frequency does not change with age (Harari *et al.*, 1996; Everhart *et al.*, 1989). Challenges in defining the prevalence of constipation in elders relates to the variety of criteria used in different studies. Self-reported constipation affects 27% of individuals aged 65 years and older, whereas only 17% of elders meet more stringent (e.g. Rome criteria) diagnostic criteria for constipation (Pare *et al.*, 2001). Data from the National Health Interview Survey reveal a "U" shaped distribution to constipation with individuals aged 60–69 reporting the least constipation (Harari *et al.*, 1996). When adjusting for race and laxative use, odds ratios for less than three bowel movements per week in individuals aged 70–79 and $\geq$80 years were 0.61 (95% CI: 0.51–0.72) and 0.85 (95% CI: 0.68–1.03), respectively, compared to individuals less than 40 years (Harari *et al.*, 1996). Thus, age alone is not an independent risk factor for reduced stool frequency. Likewise, there exists little evidence to support low fiber diets, lack of fluid or reduced exercise as contributing to constipation in the otherwise healthy older patient (Annells and Koch, 2003; Muller-Lissner *et al.*, 2005). Women report fewer bowel movements per week than do men. Nonwhites and individuals of lower socioeconomic status report fewer stools (Higgins and Johanson, 2004).

In frail elders, up to 45% report constipation as a health concern (Wolfsen *et al.*, 1993). The prevalence of constipation is higher in nursing home residents, a finding partially explained by use of constipating medications (van Dijk *et al.*, 1998). Nursing home residents frequently (58%) use laxatives, usually on an as-needed basis (Lamy and Krug, 1978). Comorbidities and medication use explain much of the higher prevalence of constipation in older persons. However, the

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traditional perceptions of constipation and aging no longer hold; the healthy older person is not predestined to develop constipation.

Elders' perceptions of what constitutes constipation differ from that of their physicians. Rather than reduced frequency, the presence of straining and hard bowel movements correlate most closely with self-reports of constipation in elders (Harari *et al.*, 1997). Bowel frequency clearly provides an inadequate measure of constipation in elders. Elders report a high prevalence of straining and defecatory difficulty (Harari *et al.*, 1996; Whitehead *et al.*, 1989). Population-based prevalence of constipation has been reported at 40% of community-dwelling adults over the age of 64 (Talley *et al.*, 1996). The risk factor most commonly reported for constipation is medication use, including nonsteroidal anti-inflammatory drugs (Talley *et al.*, 1996).

Despite the lack of difference in risk factor–adjusted constipation rates between elders and younger individuals, elders more frequently use laxatives. Up to 50% of elder women reporting use laxatives, typically due to difficulties with straining, rather than to infrequent defecation. Overall, 20–30% of community-dwelling elders use laxatives on at least a weekly basis. In nursing homes, 58% of residents receive laxatives on at least an intermittent basis (Lamy and Krug, 1978). Few economic studies in the United States outline the costs of laxative use by elders. One study in the United Kingdom estimated the annual cost to the National Health Service for prescription laxatives at 43 million pounds (Petticrew *et al.*, 1997). Most elders self-treat with over-the-counter products; thus, the economic impact of laxative use is likely considerably higher than this estimate.

The findings of similar stool frequency but increased defecatory difficulty parallel the reported physiologic changes occurring with the digestive tract with aging. Colon transit overall is generally well preserved with aging in humans (Melkersson *et al.*, 1983). Changes in pelvic floor function may contribute to defecatory difficulty, with older women demonstrating reduced opening of the anorectal angle and a greater degree of perineal descent compared to younger women (Bannister *et al.*, 1987). Pudendal neuropathy also occurs more commonly with aging and may negatively affect pelvic floor function (Pfeifer *et al.*, 1997). Other factors correlated with constipation in aging include reduced caloric intake, use of multiple medications, hemorrhoids, and pain in the abdomen (Towers *et al.*, 1994; Stewart *et al.*, 1992). Many diseases occurring more commonly in elders also contribute to the development of constipation, such as diabetes mellitus, Parkinson's disease, and stroke (Bytzer *et al.*, 2001; Doshi *et al.*, 2003; Quigley, 1996). Prior surgery may also affect bowel function in elders. In women over 50 years, hysterectomy results in prolonged colon transit time and greater complaints of constipation and straining than in controls (Heaton *et al.*, 1993). Since aging alone has little influence on the development of constipation, when complaints of constipation occur in elders, it commonly relates to medical comorbidities and increased defecatory difficulty.

The consequences of constipation in elders make it a significant health problem. The presence of chronic constipation impacts functioning in daily living, and elders with these complaints rate their health lower than people without gastrointestinal symptoms (O'Keefe *et al.*, 1995). These findings were not confounded by the presence of other chronic illnesses or medication use. Health-related quality of life is reduced in patients with chronic constipation (Glia and Lindberg, 1997). The presence of constipation has also been hypothesized to increase urinary tract symptoms, with treatment of constipation resulting in reduced urinary frequency, urgency, and dysuria (Charach *et al.*, 2001). Constipation is also associated with bowel incontinence and treatment of constipation reduces incontinence episodes (Lynch *et al.*, 2001; Chassagne *et al.*, 2000). Immobile or cognitively impaired individuals with constipation face an increased risk of fecal impaction and stercoral ulceration (Lynch *et al.*, 2001; Maull *et al.*, 1982). Constipation reduces quality of life and diminishes self-perceived health in community-dwelling elders (O'Keefe *et al.*, 1995). Effective strategies are needed for reducing the burden of illness and costs associated with constipation.

ETIOLOGY OF CONSTIPATION

Of the multiple causes of constipation in older persons, most relate to medication use or coexistent medical illness (Tables 1 and 2). The most commonly implicated medications are opiates, nonsteroidal anti-inflammatory drugs, and medications with anticholinergic effects. Although immobility, reduced fluid, and fiber intake are often implicated in the development of constipation, there exists little evidence to support this folklore. Increased physical activity does not reliably improve constipation (Meshkinpour *et al.*, 1998). Reduced caloric intake correlates more closely with constipation in elders than do differences in fiber intake (Towers *et al.*, 1994). Likewise, reduced liquid intake does not appear to cause constipation in most elders (Whitehead *et al.*, 1989). Increased psychological distress correlates with reports of constipation by elders, although the mechanism for this association remains unknown (Whitehead *et al.*, 1989; Towers *et al.*, 1994).

Table 1 Medications commonly associated with constipation

Antidepressants (SSRIs and TCAs)
Antihistamines
Antipsychotics
Bromocriptine
Calcium channel blockers
Calcium supplements
Diuretics
Ferrous gluconate and ferrous sulfate
Levo-dopa
Nonsteroidal anti-inflammatory drugs
Opiates

SSRI, Selective Serotonin Reuptake Inhibitors; TCA, Tricyclic Antidepressants.

Table 2 Medical conditions commonly associated with constipation

Mechanical obstruction
Colonic neoplasia
Colonic stricture (intrinsic or extrinsic)
Anal stenosis
Metabolic
Amyloidosis
Chronic renal failure
Diabetes mellitus
Electrolyte disturbance (hypercalcemia, hypomagnesemia)
Hyperparathyroidism
Hypothyroidism
Scleroderma
Neurologic
Autonomic neuropathy
Cerebrovascular accident
Dementia
Parkinson's disease
Psychiatric
Depression

CLINICAL APPROACH

History

The evaluation of constipation begins first with understanding the patients' perspective on their altered bowel function and the time course of constipation development. The acute or subacute onset of constipation requires a more aggressive diagnostic approach to exclude structural lesions, including colon neoplasia, stricture, and volvulus. Likewise, the presence of weight loss, rectal bleeding, history of inflammatory bowel disease, family history of colorectal neoplasia, or presence of iron deficiency anemia requires a structural examination to exclude cancer or other etiology. Additional helpful details in the patient history include onset of constipation, frequency of bowel movements, sensation of incomplete evacuation, straining to defecate, consistency of the stool, associated abdominal pain, the need for digitation, perineal splinting, or unusual postures for defecation to occur, episodes of bowel incontinence, prior abdominal or pelvic surgery, prior abdominal or pelvic radiation therapy, and prior pregnancies. It is also necessary to review current medications and supplements, current and previously used laxatives with their degree of effectiveness, use of enemas, and use of complementary therapies to treat constipation (e.g. high colonics, herbs, teas, etc.). Dietary history includes a general survey of calories ingested, fiber intake, and restricted foods. Given the consistent association of constipation with depression and anxiety, a brief psychological assessment is also warranted. In general, the ideal, evidence-based approach to the diagnostic evaluation of constipation remains to be identified.

Physical Examination

The physical examination is directed to identifying underlying medical causes for constipation, excluding fecal impaction and providing a preliminary assessment of anorectal function. A fecal mass may be palpable on abdominal palpation. Rectal examination includes inspection of the perineum at rest and with strain. Normal perineal descent during strain is 1–4 cm. No perineal descent suggests failure of the pelvic floor to relax and allow the passage of stool. Excessive perineal descent, sometimes characterized as a ballooning of the perineum, indicates excess laxity to the pelvic floor musculature and dyssynergic defecation. This finding is most common in multiparous women. The strength of the anal sphincter muscle at rest and with squeeze is assessed. Puborectalis and anal sphincter relaxation during strain provide a measure of the appropriateness of pelvic floor function. Failure of relaxation or very high anal sphincter resting pressure suggests dyssynergic defecation. The presence of weak anal sphincter pressures may place the patient at risk for incontinence during treatment of the constipation. Rectal prolapse can be associated with difficult evacuation due to blockage of the anal canal with rectum. These patients usually also described episodes of bowel incontinence. A more severe rectal prolapse can be identified during strain in the left lateral decubitus position. A better way to assess for rectal prolapse is to have the patient strain over a commode. The examiner places a gloved hand below anus and can feel the rectal prolapse descend and touch the glove. The degree of rectal prolapse can be assessed by visual inspection. The physical examination, including rectal exam, is a necessary part of the evaluation of any constipated patient.

Diagnostic Tests

Laboratory tests often recommended in the evaluation of constipation include a complete blood count, metabolic panel that includes electrolytes, creatinine, magnesium and calcium, and sensitive thyroid-stimulating hormone (sTSH). Stool examination for occult blood should be assessed. The need for a colonic structural examination is dictated by the need for routine colorectal screening, presence of worrisome signs such as bleeding or anemia or recent change in bowel habit. The yield of colonoscopy in identifying neoplasia is no different in the individual with constipation compared to what would be identified in an asymptomatic population undergoing screening. Many patients with long-standing constipation and no warning symptoms can undergo a therapeutic trial with fiber or an osmotic laxative, preserving further evaluation for those who fail to respond to simple interventions.

Patients with more severe or medication-unresponsive constipation may benefit from further evaluation, including physiologic testing. It is difficult to predict the underlying pathophysiology of chronic constipation by symptoms alone (Glia *et al.*, 1999). The presence of slow transit constipation or dyssynergic defecation may be suspected by a poor response to a trial of supplemental fiber (Voderholzer *et al.*, 1997). Additional tests include colon transit measurement, colonic manometry, anorectal manometry, balloon expulsion testing, and defecography. Colonic transit measurements may

be performed scintigraphically or using radio-opaque markers and plain abdominal radiographs. Practically, few centers have scintigraphy readily available. A variety of techniques have been described for measuring colonic transit using radio-opaque markers, some providing data on regional colon transit. Since treatments have not yet been identified to treat regional colonic abnormalities, total colon transit measurements suffice. The 5-day colon transit measurement involves ingestion of a commercially available capsule containing 24 radio-opaque markers (Sitzmark®) and performing a plain abdominal radiograph 5 days later (Hinton *et al.*, 1969). Transit is considered prolonged when five or more markers remain (Figure 1). Although markers remaining predominantly in the rectum suggest dyssynergic defecation or outlet dysfunction, the distribution pattern of the markers throughout the colon does not reliably differentiate between primary slow transit versus colon transit delayed as a result of outlet dysfunction (i.e. dyssynergic defecation).

Dyssynergic defecation refers to physiologic difficulty with the rectal evacuation process. Synonyms include pelvic outlet dysfunction, pelvic floor dysfunction, anismus, and paradoxical puborectalis contraction. Uncommonly, difficult rectal evacuation may be due to an anal stricture, obstructing rectocele, or internal intussusception. The latter two findings are most often the result of abnormal straining, rather than a primary problem themselves. The presence of dyssynergic defecation can be evaluated by anorectal manometry, electromyography of the anal sphincter, balloon defecation, and defecography. Anorectal manometry involves measuring the pressures of the anal sphincter with a manometric probe in response to different maneuvers, including straining. During strain, a rise should occur in intrarectal pressure and the anal sphincter should relax. The presence of a paradoxical increase in sphincter pressure suggests the possibility of dyssynergic defecation. False positives occur at least 10% of the time with all tests of pelvic floor function. Thus, two tests that independently confirm the same findings are required to make a secure diagnosis of dyssynergic defecation. Balloon expulsion testing is performed by placing a small balloon in the rectum and filling the balloon with 50–60 cc of warm water. The patient is asked to sit on a commode and expel the balloon. Normal expulsion occurs in 60 seconds or less. A prolonged time or failure to expel the balloon suggests dyssynergic defecation (Beck, 1992). Anorectal manometry and balloon expulsion testing are the most commonly performed tests to identify dyssynergic defecation. Electromyography will also assess for proper anal sphincter muscle relaxation and contraction. The need to place needles in the anal sphincter has made this technique less attractive for most patients. Defecography involves placing a paste in the rectum. The patient sits on a commode and radiographs are obtained during defecation. Defecography assesses the opening of the anorectal angle, provides an assessment of sphincter opening, perineal descent, and rectal emptying. Defecography typically is reserved for cases where an underlying structural abnormality is suspected or when other tests for dyssynergic defecation are equivocal. Additional physiologic tests of colon transit and pelvic floor function are required in only the subset of patients refractory to medical management. Even in this highly selected group of patients, an abnormality is identified only 50% of the time (Surrenti *et al.*, 1995). Patients with refractory symptoms and normal physiologic studies are defined as having "normal transit constipation". Many of these patients meet criteria for IBS, particularly if their symptoms have been long standing.

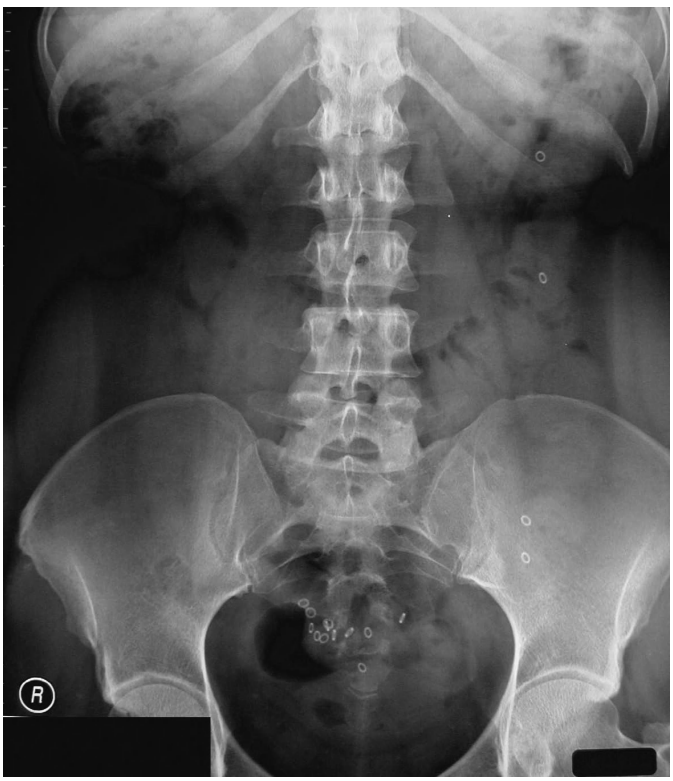

Figure 1 An abdominal radiograph obtained 5 days after ingestion of a capsule containing 24 radiopaque (small circles) markers. The presence of 16/24 markers on day 5 indicates the presence of slow colonic transit. The majority of the markers reside in the rectum with a few markers scattered in the sigmoid and descending colon

TREATMENT

The initial treatment strategy for constipation nearly always includes the ingestion of more dietary or supplemental fiber. Increased fiber intake improves stool consistency and accelerates colon transit in many individuals (Badiali *et al.*, 1995). However, constipated elders actually consume more fiber at baseline than nonconstipated controls (Johnson *et al.*, 1988). Nonetheless, fiber generally provides a safe, inexpensive first-line approach. Increased fluid intake is also frequently recommended. While this may have value in the dehydrated patient, increasing fluid intake in chronic constipation rarely improves constipation symptoms (Muller-Lissner *et al.*, 2005). Likewise, increased physical activity is also recommended without clear evidence of efficacy (Muller-Lissner *et al.*, 2005; Meshkinpour *et al.*, 1998). General nonpharmacologic advice given first line includes information

Table 3 Agents used in the treatment of constipation

Agent	Usual dosages
Fiber	
Oat bran	1–6 tbsp in divided dosages mixed with food
Psyllium	1–2 tbsp PO 1 to 4 times /day
Methylcellulose	1 heaping tbsp (2 g) PO 1–3 times /day
Osmotic laxatives	
Lactulose	15–60 ml PO in divided doses
Sorbitol 70% solution	15–150 PO in divided doses
Magnesium citrate	120 to 300 ml PO in divided doses daily
Magnesium hydroxide	15–60 ml PO at bedtime
Polyethylene glycol	17 g PO daily
Stimulant laxatives	
Senna	8.6 g–17.2 g PO daily
Castor oil	15–60 ml PO times one
Bisacodyl	10–30 ml PO daily
Enemas	
Tap water	500–1000 ml up to twice weekly
Sodium biphosphate	1 or 2 enemas weekly
Oil retention	4.5 oz as needed up to 1 to 2 times weekly

about a normal bowel habit, ingestion of a healthy, fiber rich diet, and taking advantage of the meal-related increase in colonic motor activity. Given the strong association of constipation in older persons with medication use, elimination or adjustments should be made in medications, substituting less constipating alternatives where possible. Agents used in the treatment of constipation are listed in Table 3.

Pharmacologic Management

Bulking Agents

Bulking agents commonly used include wheat or oat bran, psyllium, calcium polycarbophil, carboxymethylcellulose, and partially hydrolyzed guar gum. There are few high-quality randomized controlled studies assessing the efficacy of these agents. Studies with psyllium generally show improved stool form and frequency (Ashraf *et al.*, 1995; Cheskin *et al.*, 1995). Studies assessing the efficacy of wheat bran, oat bran, calcium polycarbophil, carboxymethylcellulose, and partially hydrolyzed guar gum are inadequate for assessing the efficacy of these agents.

Stool Softeners

Stool softeners such as dioctyl sodium sulphosuccinate (Colace®) or dioctyl calcium sulphosuccinate (Surfak®) are reported to soften the stool, easing defecation. Despite the widespread use of these agents, there are no randomized controlled trials showing efficacy. One study comparing dioctyl sodium sulphosuccinate to placebo showed no improvement in stool frequency or consistency (Castle *et al.*, 1991). Another study comparing dioctyl sodium sulphosuccinate to psyllium found psyllium to be superior (McRorie *et al.*, 1998). The therapeutic use of stool softeners appears limited for the treatment of chronic constipation.

Osmotic Laxatives

Osmotic laxatives improve stool form and bowel movement frequency by increasing the amount of water retained in the lumen of the gut. Polyethylene glycol (PEG) and lactulose have therapeutic value in the treatment of constipation. Other osmotic laxatives include sorbitol, magnesium salts, and saline salts. Polyethylene glycol, lactulose, and sorbitol have the greatest safety margins. Use of saline or magnesium salts comes with a risk for significant electrolyte disturbance, especially in older persons. Elders with normal renal function may become hypermagnesemic with chronic use, especially at higher doses (Golzarian *et al.*, 1994). Magnesium salts should not be used in renal disease and saline salts should be avoided in chronic renal failure, end stage liver disease, and heart failure. Polyethylene glycol appears to be the best tolerated overall in elders. Lactulose and sorbitol undergo bacterial metabolism in the gut, leading to increased symptoms of bloating, abdominal cramping, and flatulence in some patients.

Several randomized, placebo-controlled trials of PEG show efficacy in the treatment of chronic constipation. Compared to placebo, PEG improves stool consistency and frequency (Andorsky and Goldner, 1990). One study compared PEG to lactulose, showing improved efficacy with PEG and fewer side effects (Attar *et al.*, 1999). No studies using PEG directly assessed efficacy in older adults. One study in adults with a mean age of 45 showed efficacy, safety, and few side effects over a 6-month period of an isosmotic PEG electrolyte solution (Corazziari *et al.*, 2000).

Lactulose improves stool frequency and consistency with a success rate of 80% compared to a placebo response of 60% (Wesselius-De Casparis *et al.*, 1968). A study of nursing home residents with constipation compared lactulose to a glucose solution. Lactulose improved stool frequency, reduced need for enemas and fecal impaction over a 12-week period (Sanders, 1978). The difference in number of fecal impactions between the two groups was an astounding difference of 6 for lactulose versus 66 for glucose. A literature review revealed no placebo-controlled randomized trials assessing the primary efficacy of sorbitol in the treatment of constipation. One randomized comparative trial of lactulose and sorbitol in elders found no difference in laxative effect and no strong preference of one laxative over the other by the study subjects (Lederle *et al.*, 1990). Abdominal symptoms were similar between the two groups except for greater complaints of nausea in the lactulose group. The cost for sorbitol is generally less than for lactulose, making it the preferred agent for many patients.

Magnesium hydroxide is the most commonly used magnesium-containing osmotic laxative. Despite quite widespread use of this laxative, there are no high-quality studies demonstrating efficacy and safety in treating constipation. Nonetheless, magnesium intake is well known

to cause diarrhea, supporting its use in the treatment of constipation. Magnesium salt intake in normal subjects results in a linear increase in stool weight with a 7.3 g increase in fecal weight for every millimole increase in stool magnesium (Fine *et al.*, 1991). A cross-over study comparing magnesium hydroxide and 8.7 g of a bulk laxative in geriatric long-stay patients showed increased stool frequency in the magnesium hydroxide group (Kinnunen and Salokannel, 1987). Magnesium salts must be used cautiously in older patients with consideration given for periodic monitoring serum magnesium levels in those taking magnesium-containing laxatives chronically. The use of sodium-containing laxatives has not been well studied in the treatment of constipation. Sodium-containing laxatives are better absorbed systemically than magnesium-containing laxatives. When oral phosphosoda was used as a colonic preparation for diagnostic examination, significant changes in electrolytes occurred (Gumurdulu *et al.*, 2004). Even in the setting of a normal creatinine, an age-related increase in phosphate occurred (Gumurdulu *et al.*, 2004). Sodium-containing laxatives cannot currently be recommended for the routine treatment of constipation in older persons.

Stimulant Laxatives

The adverse effects stimulant laxatives have in the treatment of constipation remain one of the most steadfast medical myths (Muller-Lissner *et al.*, 2005). Stimulant laxatives have been reported to damage the colon and cause laxative dependency. This perception may relate to the occurrence of melanosis coli, a dark brownish discoloration of the colon that occurs with long-term use. The presence of melanosis coli has no functional significance. Prior studies reporting damage to the colonic enteric nerves and smooth muscle were anecdotal and uncontrolled. It is likely that many of these patients had preexisting abnormalities of the colon. When used at recommended doses, stimulant laxatives are unlikely to harm the colon. Stimulant laxatives do result in abdominal discomfort and electrolyte imbalance in some patients (Xing and Soffer, 2001).

No high-quality, placebo-controlled studies have assessed the efficacy of stimulant laxatives. Most commonly available stimulant laxatives include the anthraquinones, diphenylmethane derivatives, and ricinoleic acid. Anthraquinone laxatives include senna-containing products and aloe. An observational (uncontrolled and not blinded) study using a senna-containing concentrate as part of a program that included a stool softener, increased fiber, fluid intake resulted in improved bowel evacuation in 86% and prevented fecal impaction in nursing home patients with constipation (Maddi, 1979). Stimulant laxatives are typically reserved for patients who do not respond to other laxatives.

Prokinetic Agents

Prokinetic agents stimulate propulsion along the gastrointestinal tract. Tegaserod, a $5HT_4$ agonist, improves the symptoms of constipation in adults (Johanson *et al.*, 2004). Data regarding efficacy in individuals over the age of 65 has not been demonstrated. Neostigmine, an acetylcholinesterase inhibitor, produces prompt colonic decompression. The use of neostigmine is reserved for hospitalized patients with acute colonic pseudo-obstruction (Ponec *et al.*, 1999).

Miscellaneous Agents

Misoprostol, a prostaglandin agonist, stimulates intestinal secretion and intestinal transit. Its use is limited by the common occurrence of side effects, including abdominal pain and cramping (Roarty *et al.*, 1997). Its use is reserved for patients with refractory constipation. Colchicine, well known for causing diarrhea in the acute treatment of gout, may be used in patients refractory to other medications (Verne *et al.*, 2003). Colchicine frequently causes increased symptoms of abdominal pain, limiting its use. Glycerin suppositories have long been used as over-the-counter agents for stimulating bowel movements. The medical literature is lacking to assess their effectiveness.

Enemas

The use of enemas in the treatment of constipation is typically limited to the acute situation. There is no medical evidence to support the routine use of phosphate enemas in the treatment of constipation (Davies, 2004). The use of phosphate enemas is well described to cause serious hyperphosphatemia, especially in patients with renal insufficiency (Knobel and Petchenko, 1996). Any enema must be used with caution owing to the risk of colonic perforation (Paran *et al.*, 1999). Soap suds enemas should not be used. Small-volume tap water enemas may be helpful in emptying the rectum. Larger-volume tap water enemas may be used on occasion, but even these can result in hyponatremia (Chertow and Brady, 1994). In patients with very refractory constipation, the use of antegrade enemas has been described (Rongen *et al.*, 2001; Wills *et al.*, 2003). Antegrade enemas involve creating a cecostomy placed surgically or endoscopically. Water or PEG is flushed through the tube periodically to facilitate colonic emptying. No high-quality, controlled trials have assessed any of these enema therapies.

SPECIAL CATEGORIES OF CONSTIPATION

Medication use is strongly correlated with the development of constipation in older persons. Where possible, unnecessary medications should be discontinued and necessary medications switched to a less constipating alternative when one is available. For example, verapamil causes more constipation than other calcium channel blockers. Chronic opiate use results in constipation in up to 50% of individuals (Schug *et al.*, 1992). Methadone and fentanyl may be less constipating than other morphine derivatives (Mercadante *et al.*, 2001; Allan *et al.*, 2001). Methylnaltrexone, a peripheral μ-receptor antagonist, improves oral cecal transit and

induces laxation without inducing opiate withdrawal symptoms (Yuan, 2004). Its use has been limited due to the need to administer the medication intravenously. Naloxone-3-glucuronide, an oral opiate antagonist that remains in the gut lumen without being absorbed, shows promise in reducing morphine-induced constipation in healthy subjects in a preliminary study (Netzer *et al.*, 2005). Opiates potently slow gastrointestinal transit and allow enhanced intestinal absorption of fluids. A rational approach involves outlining a strategy to prevent constipation at the initiation of opiate use. There are no high-quality studies to indicate the best strategy. Polyethylene glycol improved stool form in methadone-induced constipation (Freedman *et al.*, 1997). Stimulant laxatives are also commonly used.

Constipation occurs commonly in Parkinson's disease related to dyssynergic defecation from incoordination of the pelvic floor musculature during defecation and the constipating effect of medication used to treat Parkinson's disease. Psyllium has been used successfully to treat constipation in these patients (Ashraf *et al.*, 1997). Individuals with dementia frequently develop constipation. Sorbitol and lactulose have been reported as successful in an observational study (Volicer *et al.*, 2004).

The use of combinations of laxatives has rarely been addressed in the literature but is commonly encountered in practice when a single agent is ineffective. The most common combination is an osmotic laxative with a stimulant laxative. In patients with continued complaints of constipation, despite the use of a single laxative, obtaining a plain abdominal radiograph to assess the degree of stool retention may be helpful. Patients with a large amount of stool (and no evidence of fecal impaction) may be treated with a colon preparation such as balanced electrolytes plus PEG (e.g. Nulytely®) to cleanse the colon. The patient may be then started on an osmotic laxative with a stimulant laxative available on an as needed basis every two to three days if a satisfactory bowel movement does not occur. Patients without significant stool loading should be assessed for the presence of IBS. Eleven percent of elders have symptoms consistent with IBS (O'Keefe *et al.*, 1995). Patients with IBS may benefit from medications directed at neuromodulation, although caution must be used owing to the anticholinergic effects of many of these agents (Clouse, 2003).

Patients with refractory constipation and slow transit constipation benefit from subtotal colectomy and ileorectostomy (Nyam *et al.*, 1997). Fortunately, this is rarely required as nearly 90% of patients with slow transit constipation respond to laxatives (Rex *et al.*, 1992). When dyssynergic defecation is present, biofeedback improves defecatory function in approximately 70% of patients (Enck, 1993). Patients with both slow transit constipation and dyssynergic defecation should be treated with biofeedback first. When slow transit constipation persists after successful treatment of dyssynergic defecation, subtotal colectomy may be considered. Surgical therapy is most successful in patients without upper gut motility disorders or significant psychological symptoms (Redmond *et al.*, 1995).

The optimal treatment for fecal impaction is not clear. Patients able to tolerate oral therapy may benefit from PEG or other osmotic laxatives with or without the use of enemas (Puxty and Fox, 1986). Patients with a hard or very large fecal bolus in the rectum may require manual removal of the feces. Hyperosmotic, water-soluble contrast enemas have also been used with success in relieving fecal impaction (Culp, 1975).

CONCLUSIONS

Complaints of constipation and use of laxatives remain quite common in older persons. When controlling for comorbidities, constipation is no more common in elders than in younger persons. Stool frequency remains unchanged with aging. Elders more commonly complain of straining and hard stools. Risk factors for constipation include medication use, chronic medical illness, and psychological distress. Healthy elders are no more likely to develop constipation than younger persons. Constipation adversely affects elders' sense of well-being and quality of life. The economic impact is also significant due to the cost of laxatives alone. In patients with up-to-date colorectal cancer screening, who lack worrisome symptoms such as bleeding or weight loss, empiric treatment is appropriate with bulking agents or simple laxatives. Patients who fail to respond require a more detailed evaluation. Identifying the most effective treatment strategy for constipation in elders, whether in the community or long-term care setting, remains unclear due to the lack of high-quality therapeutic trials for most laxatives. Data support the use of psyllium, lactulose, sorbitol, and PEG in elders with constipation. The safest, best tolerated, and least expensive laxatives (including the use of bulking agents) should be implemented first before prescribing the more expensive laxatives. Improved research in this area is needed to identify the most effective, economically viable therapeutic agents.

KEY POINTS

- Reports of constipation and use of laxatives are very common in older persons.
- Stool frequency is no different in elders compared to younger persons, with elders complaining most of straining and hard stools.
- The use of medications and chronic medical illnesses correlate more closely with the development of constipation in elders.
- Patients lacking worrisome symptoms may undergo an empiric therapeutic trial, reserving diagnostic testing for those who fail to respond.
- The best available evidence supports the use of psyllium and osmotic laxatives in the treatment of constipation in elders.

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36

Diseases of the Pancreas

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THE AGING PANCREAS

The pancreas has considerable functional reserve so that any anatomical changes associated with age have little, if any, effect on pancreatic function. Morphological changes, however, do occur as part of the aging process. Ectasia of the main pancreatic duct occurs, which can cause confusion in the interpretation of the appearances on endoscopic pancreatography. Additionally, ductal epithelial hyperplasia and intralobular fibrosis, which rarely lead to pancreatic atrophy, can occur (Kreel and Sandin, 1973). In this autopsy study of the elderly in the United Kingdom, ductal narrowing not due to strictures, space occupying lesions due to the superior mesenteric artery, splenic artery, aorta, vertebral osteophytes, sympathetic ganglia, and lymph nodes were noted. The study also showed metastases in the pancreas, which could be mistaken for primary pancreatic tumors. Finally, aging can be associated with impaired pancreatic blood supply due to atherosclerosis.

Functional studies have been done in elderly patients and compared with those in younger patients. The volume of pancreatic secretion falls in the elderly as do the outputs of lipase, trypsin, and phospholipase (Laugier and Sarles, 1985). There does not appear to be a corresponding fall in fat absorption (Gullo *et al.*, 1986).

INFLAMMATORY DISEASES OF THE PANCREAS

Acute Pancreatitis

Although alcohol abuse is the major cause of acute pancreatitis in the middle aged, it is less common as a cause in the elderly. Acute pancreatitis, however, occurs with increasing frequency in the elderly because of an increased prevalence of gallstones. A recent English study showed that hospital admission rates for acute pancreatitis had doubled over a 30-year period in all age groups but the case fatality rates had not altered (Goldacre and Roberts, 2004). Hospital admissions for acute pancreatitis per 100 000 were 13 or more for both men and women over 65 years of age and the case fatality rates were 8 per 100 patients at 29 days after presentation and 7.4 at 30–364 days after presentation. Corresponding rates in the over 75-year age group were even higher. Besides alcohol and gallstones, other predisposing factors of acute pancreatitis in the elderly include hypercalcemia (usually due to hyperparathyroidism), hypertriglyceridemia, and obstruction to pancreatic flow such as that caused by tumors, endoscopic pancreatography, and uremia. Acute pancreatitis occurs in up to 30% of patients following cardiac bypass surgery perhaps because of the administration of large doses of intravenous calcium chloride (Castillo *et al.*, 1991). Acute pancreatitis is also associated with biliary sludge and cholecystectomy or endoscopic papillotomy may prevent recurrence (Lee *et al.*, 1992). Elderly patients are more likely to be taking prescribed medication but whether drugs are a major cause of acute pancreatitis is debatable. Most reports of drug-related pancreatitis are anecdotal and the potential severity of the disease precludes drug challenges. A large retrospective German study of acute pancreatitis implicated drugs as a possible cause in only 1.4% of the patients. The disease was mild and ran a benign course (Lankisch *et al.*, 1995). In almost 25% of patients, no cause can be found and this is especially the case in the elderly.

Pathophysiology of Acute Pancreatitis

The basic underlying pathophysiologic mechanism in acute pancreatitis is pancreatic duct obstruction. This allows autodigestion of the gland by its own enzymes. Reflux of bile and duodenal juices into the pancreatic duct are also important. In the majority of patients, the process is self-limiting but in some the disease becomes fulminating. This leads to pancreatic necrosis and activation of inflammatory cytokines, which can result in generalized organ failure (systemic inflammatory response syndrome). If the necrosed

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pancreas becomes infected by gut bacteria, the disease is often fatal.

Presentation of Acute Pancreatitis

The illness characteristically presents with severe abdominal pain, often leading to acute hospital admission. The pain usually occurs in the epigastrium and radiates through to the back and is often relieved by sitting forward. This presentation, however, may differ in the elderly when the illness may be confused with myocardial infarction or a perforated abdominal viscus.

The physical signs are those of an acute abdomen. Jaundice, vomiting, fever, tachycardia, and hypotension may occur. If severe, hemorrhagic pancreatitis supervenes with retroperitoneal hemorrhage which leads to bruising in the flanks (Grey Turner's sign), around the umbilicus (Cullen's sign) or even below the inguinal ligament (Fox's sign).

Diagnosis of Acute Pancreatitis

The diagnosis is supported by the finding of high levels of amylase in the serum. A recently introduced urinary dipstick for the detection of trypsinogen-2 appears a simple and sensitive diagnostic aid (Kemppainen *et al.*, 1997). Elevated levels of serum lipase are more specific than elevated amylase levels. The serum lipase rises within 4–8 hours, peaks at 24 hours, and returns to normal in 8–14 days (Frank and Gottlieb, 1999).

Radiological examinations are increasingly important and sophisticated. Straight abdominal X rays may show a sentinel loop – an area of small bowel ileus adjacent to the inflamed pancreas. In severe pancreatitis, the chest X ray can reveal a pleural effusion, areas of atelectasis, and pulmonary edema. These appearances occur in patients of all ages.

Ultrasonography is important. Gallstones and dilated bile ducts suggest pancreatitis of biliary origin. Overlying gas shadows often impair visualization of the pancreas, but when seen, the gland appears swollen. Ultrasonography is important in detecting pancreatic pseudocyst and fluid collections within the abdomen. Enhanced computerized tomography (CT scanning) is useful in showing evidence of pancreatic necrosis and localized fluid collections both in and outside the pancreas (Figure 1). CT scanning may also reveal gallstones, bile duct, or pancreatic duct dilatation not obvious in ultrasound scanning. In selected patients, endoscopic retrograde cholangiopancreatography (ERCP) is useful in showing dilated bile ducts and gallbladder stones (Figure 2) and has the added advantage that bile duct stones can be cleared. When acute pancreatitis is diagnosed by these imaging methods, biochemical tests (serum levels of amylase and lipase) are elevated in over 90% of patients (Clavien *et al.*, 1989).

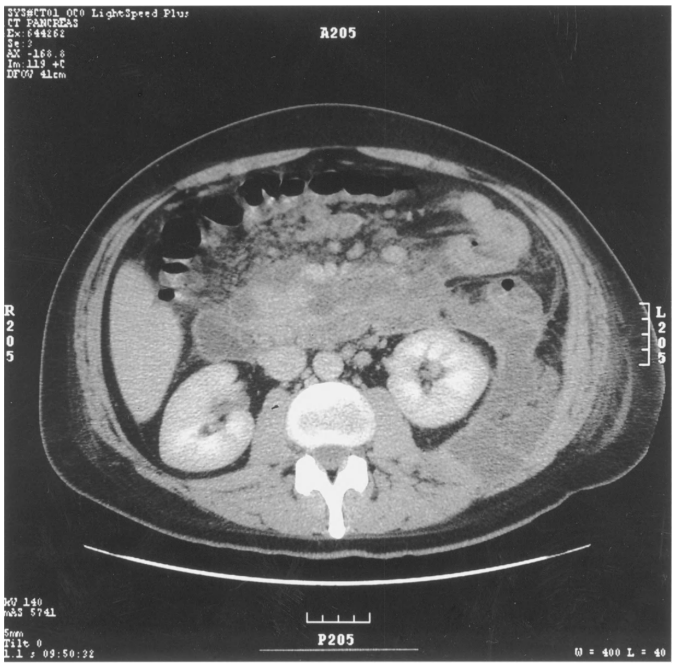

Figure 1 Acute pancreatitis with necrosis. (Courtesy of Dr N Al-Mohktar)

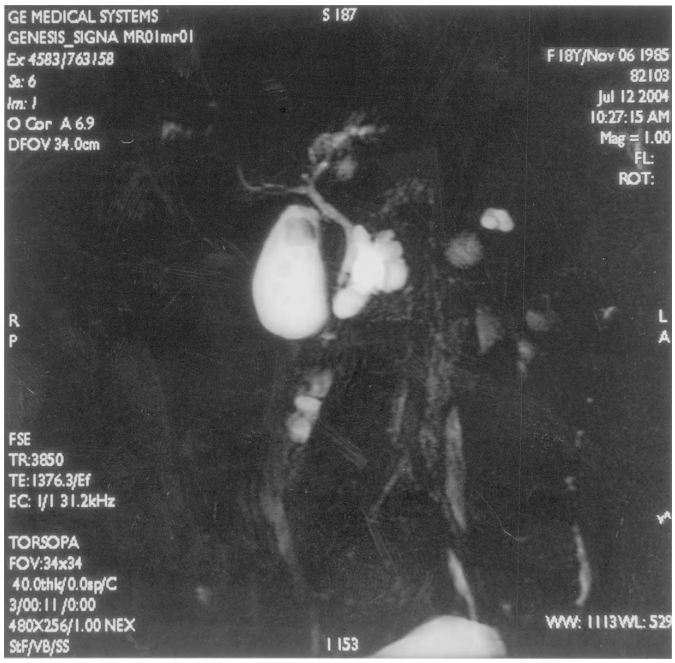

Figure 2 ERCP showing dilated bile ducts and gall bladder stone. (Courtesy of Dr WT Young)

Assessment of the Severity of Acute Pancreatitis

In an individual patient, the severity of disease is judged by clinical observation. In an attempt to compare disease severity between centers, assess the results of therapeutic intervention, and perhaps decide referral to specialized centers, various scoring systems have been introduced. One of the earlier scoring systems was introduced by Ranson *et al.* (1974). The index takes account of age, white blood cell counts, glucose levels, LDH, and AST levels at admission

and the decrease in hematocrit, elevation of the blood urea, decrease in serum calcium, pO_2, base deficit, and fluid balance at 48 hours. Using similar measurements, modified "Glasgow Criteria" were later introduced (Blamey *et al.*, 1984). These prognostic indices are of proven value in predicting severe disease but suffer from the disadvantage that measurements are made over a period of 48 hours. A score of over 3 by either system indicates severe disease. The "APACHE II" can be calculated on admission and is more sensitive and specific at 48 hours after admission. The APACHE II grading system has the advantage that it can be measured from admission and throughout the hospital stay (Knaus *et al.*, 1985). Assessment of disease activity using CT scanning has also been studied and shown good correlation with local complications and mortality (Balthazar, 2002).

Management of Acute Pancreatitis (See United Kingdom Guidelines for the Management of Acute Pancreatitis 1998 Gut (suppl 2): S1–S13)

Mild disease requires only observation and symptom control. Antibiotics are not routinely given. The 20–30% more ill patients need admission to an intensive care unit and careful monitoring. Nutrition is important and there is a debate as to whether the patient should be nourished by enteral routes or by parenteral routes. A recent meta-analysis suggested that enteral feeding was more appropriate. Compared with parenteral feeding, enteral feeding reduced the number of surgical interventions and the number of infections. Additionally, parenteral feeding is immunosuppressive and favors inflammation (Marik and Zaloga, 2004). The feeding tube should be placed in the jejunum to prevent pancreatic stimulation.

Routine antibiotic therapy in severe acute pancreatitis is controversial. Although the evidence is slight, a Cochrane review suggests that patients with proven pancreatic necrosis should be given broad-spectrum antibiotics active against gut organisms for up to 2 weeks (Bassi *et al.*, 2003). In patients with bile duct stones, endoscopic duct clearance, particularly if there are signs of concomitant biliary disease, should be done as soon as possible. Patients with gallstones who develop mild acute pancreatitis should undergo cholecystectomy during their index admission.

Indications for surgery in acute pancreatitis include pancreatic pseudocyst and pancreatic abscess. Removal of necrosed pancreas should be considered in patients with continuing fever after antibiotics who have clear signs on CT scanning. The surgery is hazardous and best done by surgeons skilled in pancreatic surgery. Surgical intervention can be life saving and age alone does not preclude it.

Chronic Pancreatitis

Whereas the pancreas is normal before and after an attack of acute pancreatitis, the gland is always histologically abnormal in chronic disease. The histological changes include an increase in the intralobular fibrous tissue, atrophy of the acini, and a chronic inflammatory infiltrate. Macroscopically, ductal changes, mainly duct dilatation, occur when there is an obstructive cause of the disease. Pancreatic tissue is hard to obtain and histological changes are patchy so that the diagnosis of chronic pancreatitis is seldom made histologically.

Incidence and prevalence rates for chronic pancreatitis, particularly in the elderly, are uncertain. Chronic pancreatitis is rarely diagnosed for the first time in patients over 65 years of age. The commonest cause of the disease is alcohol, so most cases of chronic pancreatitis present in the fourth and fifth decade of life. Estimated prevalence rates for all ages range from 0.04 to 5% (Steer *et al.*, 1995). In an English study of hospital admissions, age-standardized admission rates for chronic pancreatitis rose by 100% in the decade ending in the year 2000 (Tinto *et al.*, 2002). In the United States, the National Discharge Survey indicated that only 12% of patients were 65 years of age or older (Go, 1994).

Causes of Chronic Pancreatitis

Alcohol is the commonest cause of chronic pancreatitis overall but is less common as a cause in the elderly. In the elderly, an underlying cause is not always apparent and the disease is labeled "idiopathic". Idiopathic chronic pancreatitis in the elderly has a different natural history and displays different clinical manifestations; pain, for example, is less severe and less common (Gloor *et al.*, 2002). Chronic pancreatitis occurs in chronic ductal obstruction such as that caused by a periampullary tumor, in pancreas divisum in which the head and body of the pancreas develop separately and each has its own duct, in hyperlipoproteinemia, and in hyperparathyroidism.

Postmortem examinations reveal that pancreatic stones occur in some 15% of patients over the age of 90 years and that changes of chronic pancreatitis are seen. The significance of these findings is uncertain for there is no correlation with clinical disease (Nagai and Ohtsubo, 1984).

Pathogenesis of Chronic Pancreatitis

The underlying cause of chronic pancreatitis is unknown. When the disease is induced by alcohol, it is suggested that changes in pancreatic secretion occur that lead to precipitation of pancreatic protein in the ducts. Ductal obstruction leads to the histological changes of chronic pancreatitis. Lithostatine, a protein secreted by acinar cells, inhibits the precipitation of calcium in pancreatic juice. Reduced concentrations of lithostatine could result in the precipitation of calcium carbonate in ducts, although this hypothesis is uncertain (Steer *et al.*, 1995).

Mutations of the cystic fibrosis gene may increase the chances of developing chronic pancreatitis. Braganza and her colleagues studied 134 consecutive patients with chronic pancreatitis. Their study suggested that mutations of the CFTR (cystic fibrosis transmembrane conductance regulator) gene and the 5T genotype are associated with chronic pancreatitis (Sharer *et al.*, 1998).

Clinical Presentation of Chronic Pancreatitis

Severe abdominal pain, a characteristic of chronic pancreatitis in younger patients, is less severe or even absent in the elderly. Weight loss, diabetes, and fat malabsorption occur.

Occasionally, chronic pancreatitis is recognized when pancreatic calcification is noted on a straight X ray of the abdomen (Figure 3).

Clinical examination is usually normal, although there may be localized tenderness in the epigastrium. Signs of malnutrition occur late in the disease.

The Diagnosis of Chronic Pancreatitis

Establishing a diagnosis is difficult. Serum amylase and lipase levels are usually normal or only slightly elevated. If there is associated obstruction of the intrapancreatic bile duct, bilirubin and alkaline phosphatase levels are elevated. Steatorrhea results from exocrine insufficiency and can be recognized by Sudan staining of the stool and quantified when the patient eats a daily diet containing 100 g of fat. Faecal fat excretion resulting from chronic pancreatic disease is usually higher than that seen in other causes of fat malabsorption.

Tubeless pancreatic function tests are increasingly valuable in suggesting the diagnosis. The *para*-aminobenzoic acid (PABA) excretion index is based on the ability of pancreatic chymotrypsin to split orally administered *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid. The released PABA is then measured in the urine. The pancrealauryl test is similar. Pancreatic esterases release fluorescein, which is again measured in the urine. Provided hepatic, renal, and intestinal functions are normal, low levels of PABA or fluorescein in the urine suggest pancreatic insufficiency. Analysis of intestinal volume, concentrations of pancreatic enzymes and bicarbonate following a standard test meal or the intravenous administration of cholecystokinin can indicate exocrine insufficiency. The conditions under which the test is performed need to be carefully controlled so that its use is confined to those with special experience.

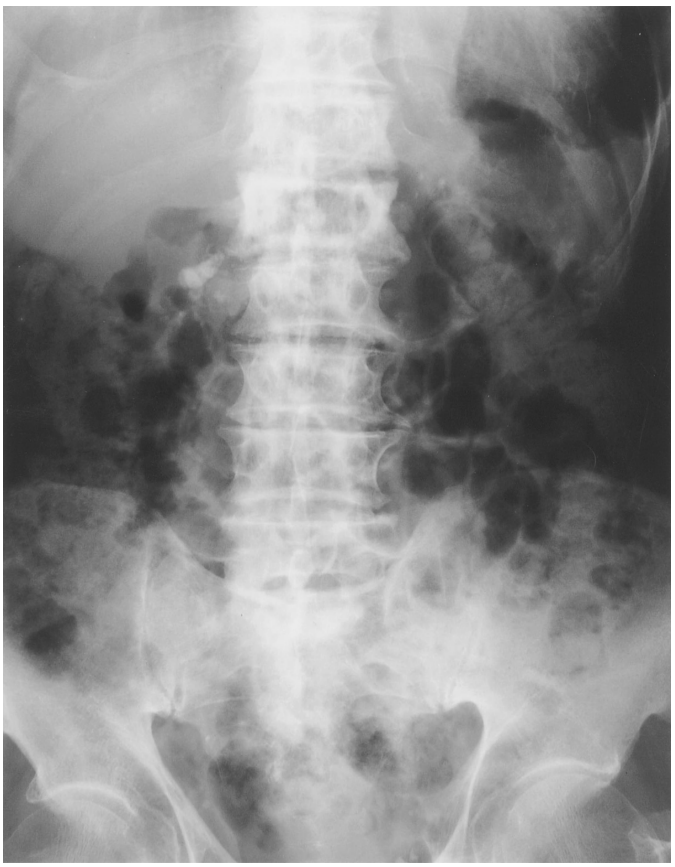

Figure 3 Plain abdominal X ray showing pancreatic calcification in chronic pancreatitis. (Courtesy of Dr N Al-Mohktar)

Imaging procedures

Imaging procedures have superseded function studies in the diagnosis of chronic pancreatitis. Plain abdominal radiography may show calcification. Calcification appears more rapidly in patients with alcoholic rather than idiopathic pancreatitis and consequently is less common in the elderly. In some two-thirds of patients, ultrasonography shows swelling of the gland or duct dilatation. CT provides similar information but may be more sensitive.

Endoscopic retrograde pancreatography has become essential in the diagnosis and assessment of chronic pancreatitis. It demonstrates duct abnormalities, which are classified as mild, moderate, or severe. Endoscopic pancreatography shows minor abnormalities of the smaller pancreatic ducts, allowing a diagnosis of chronic pancreatitis to be made in patients in whom other imaging procedures have been normal.

Pancreatography is of particular value therapeutically. Duct strictures amenable to dilatation, stenting, or partial gland resection may be apparent only endoscopically. Finally, endoscopy is a valuable aid in the diagnosis of pancreatic cancer.

Complications of Chronic Pancreatitis

Diabetes is more difficult to control in chronic pancreatitis and episodes of hypoglycemia are likely because of poor diet or malabsorption. Hyperglycemia is an inevitable consequence of major pancreatic resections (*see* **Chapter 122, Type 2 Diabetes Mellitus in Senior Citizens**). Pancreatic pseudocysts in chronic pancreatitis are less likely to resolve spontaneously than those in acute pancreatitis and often have to be drained. Rupture of a pseudocyst into the peritoneum leads to pancreatic ascites. High amylase levels in the ascitic fluid confirm the diagnosis. Octreotide may help control the ascites by reducing pancreatic secretion. Occasionally, the cyst ruptures into the pleural space, usually on the left side, leading to a pleural effusion. Rarely a chronic pancreatic pseudocyst may be the source of hemorrhage which can be life threatening. Hemorrhage may also result from esophageal varices arising from obstruction to the splenic or portal vein by the inflammatory process in the pancreas (see Law and Freeman, 2003).

Management of Chronic Pancreatitis

Pain is less common in the elderly, but when it occurs, it impairs the quality of life. Opiate drugs should be avoided because of the danger of addiction. Nonsteroidal antiinflammatory drugs and tricyclic antidepressants may be useful. The pain is often related to high intraductal pressures and pharmacological attempts to lower the pressures have been made. Cholecystokinin stimulates the release of pancreatic enzymes. Theoretically, increasing intraluminal levels of pancreatic enzymes by orally administered pancreatic enzymes should decrease native cholecystokinin production and lower intraductal pressure, hence relieving pain. The evidence in favor of this approach is slight because of the difficulty in conducting double-blind trials and high placebo response.

Octreotide is a powerful inhibitor of pancreatic secretion and has been used to reduce pancreatic secretion. Its disadvantage is that it has to be given subcutaneously on a daily basis, although long-acting preparations are now available. Its value remains uncertain.

If drug therapy fails to control pain, celiac axis block is often successful. If endoscopic pancreatography shows duct strictures, stent placement often relieves pain. Surgical pancreatic resection or total pancreatectomy should seldom be considered as a method of pain relief in the elderly.

Attempts to control steatorrhea by orally administered pancreatic enzymes are useful and the dose should be titrated to achieve maximum effect. Malabsorption of fat-soluble vitamins occurs and should be treated with appropriate supplements.

Sclerosing Pancreatitis

This form of chronic pancreatitis has been recently described mainly in the Japanese literature. It can occur at any age and is distinguished from other causes of chronic pancreatitis by the finding of high serum IgG4 levels. There is irregular narrowing of the main pancreatic duct and lymphoplasmacytic infiltration of the pancreas. It may respond to corticosteroids (Hamano *et al.*, 2001).

PANCREATIC TUMORS

Endocrine Tumors of the Pancreas

Endocrine tumors of the pancreas are rare. Some of the tumors also occur in extrapancreatic sites. The tumors are classified according to the hormone they excrete. The commonest tumor is insulinoma, which secretes insulin and gives rise to episodes of hypoglycemia or even coma. Glucagonoma is associated with weight loss, diabetes, or rash and somatostatinoma gives rise to diabetes, gallstones, weight loss, and steatorrhea. Gastrinoma gives rise to peptic ulcer and weight loss, tumors secreting growth hormone release hormones that give rise to acromegaly, tumors producing ACTH give rise to Cushing's syndrome, and tumors producing pancreatic polypeptide result in abdominal pain, GI (gastrointestinal) bleeding, and diarrhea (Mullan *et al.*, 2001). Most of the tumors have a malignant potential and may be part of the multiple endocrine neoplasia syndrome.

Cystic Tumors of the Pancreas

These tumors are rare. Serous cystadenomas are small, rarely over 2 cm in size, and are of little clinical import. Mucinous cystic neoplasms range from benign to dysplastic to frankly malignant types. Intraductal papillary mucinous tumor is recently described and is yet to be studied in detail (Sarr *et al.*, 2001).

Cancer of the Pancreas

Pancreatic cancer is diagnosed in over 7000 people in the United Kingdom each year. The diagnosis is difficult to make and only some 15–20% of patients have tumors amenable to surgery at presentation. One-year survival rate is around 20% and only 5% of patients are alive 5 years after diagnosis.

The predominant risk factor is old age (Figure 4), although there is a relationship to cigarette smoking. Genetic and

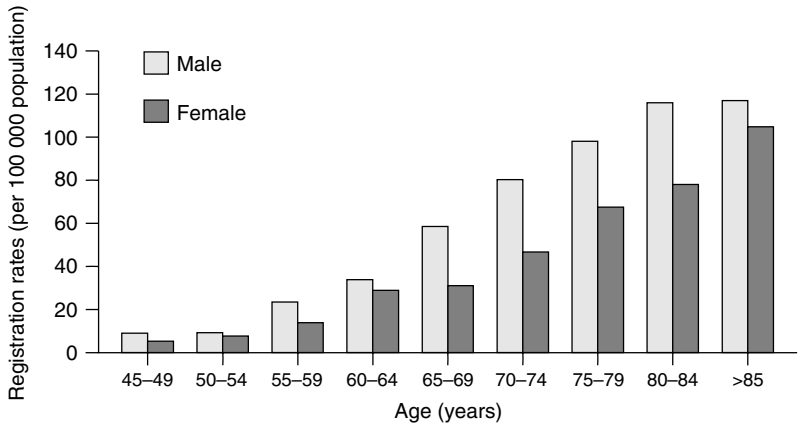

Figure 4 Registration rates of pancreatic cancer in Wales. The Welsh Office. Cancer Registration in Wales 1974–1984 and 1984–1988; HMSO, Cardiff

general medical conditions such as familial breast cancer, hereditary chronic pancreatitis, chronic pancreatitis, and diabetes are also risk factors (Li *et al.*, 2004). In many patients, there is a preceding history of depression, often requiring psychiatric help.

Clinical Features

Cancer of the head of the pancreas presents with jaundice often with epigastric or back discomfort. Later in the clinical course, other symptoms of cholestatic jaundice such as itching, pale stools, and dark urine occur. Anorexia and weight loss are common. Tumors of the body and tail of the pancreas present more insidiously and are often recognized only when distal spread of the disease has occurred.

Diagnosis of Pancreatic Cancer

Following initial assessment, ultrasonography is usually the first imaging procedure. The tumor is seldom seen because of overlying gas shadows. If the tumor is in the head of the pancreas, however, bile duct obstruction may occur and the level of the obstruction visualized. CT scanning provides similar information and may help in identifying tumor expansion outside the confines of the gland such as metastatic tumor in the liver or adjacent lymph nodes (Figure 5). Endoscopic cholangiopancreatography allows more precise delineation of ductal anatomy and, taken in conjunction with other investigations, helps to decide whether the tumor is resectable. Stent insertion to relieve ductal obstruction at this stage is controversial, should surgery become a management option. A recent meta-analysis suggested that preoperative biliary drainage was associated with a greater complication rate compared to those patients who underwent surgery alone (Sewnath *et al.*, 2002).

Pancreatic cancer can be confused with chronic pancreatitis. Attempts should be made to verify histologically the diagnosis of a tumor. Tissue or cytological preparations can be obtained by ultrasound or CT-guided fine needle aspiration although there may be a risk of cancer seeding.

Management of Pancreatic Cancer

Surgery alone offers the hope of cure and even if performed only offers a five-year survival rate of 20%. Adjuvant therapy with fluorouracil-based chemoradiation is an option, although others recommend chemotherapy alone (Li *et al.*, 2004). In patients with unresectable disease, chemoradiation can be used. Gemcitabine is currently under investigation as a radiosensitizer and the agent may also be used as part of a combined chemotherapy protocol.

Palliation is often the only management option. The relief of bile duct obstruction and pain control remain the only treatment modalities that can be offered.

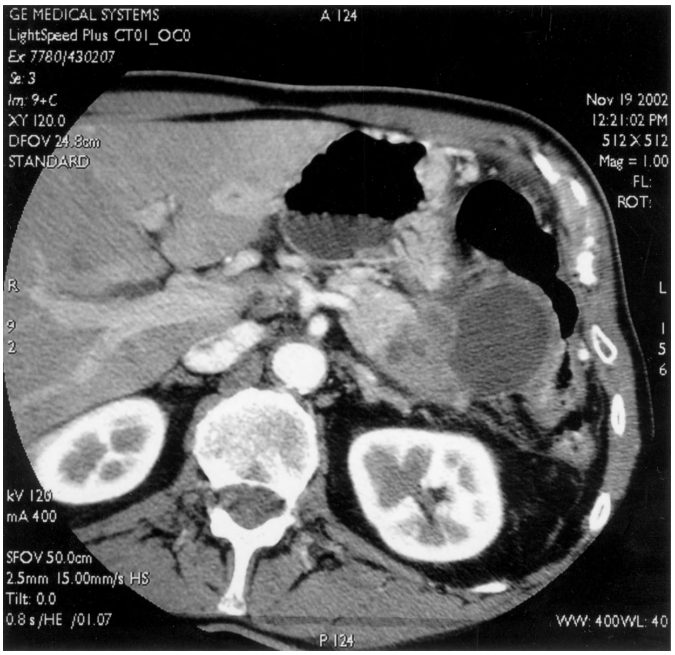

Figure 5 Tumor of the pancreatic tail with solid and cystic components. (Courtesy of Dr N Al-Mohktar)

KEY POINTS

- Pancreatic cancer is the main pancreatic disease associated with aging.
- Acute pancreatitis associated with gall stone disease is the commonest cause of acute pancreatitis in the elderly.
- There is no good evidence that relates drugs to the development of pancreatitis.
- Although morphological change occurs in the elderly, pancreatic function appears to be maintained.

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PART III

Medicine in Old Age

Section 3

Hematological Disorders

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Anemia in Older Persons

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Anemia has been associated with both frailty (Kamenetz *et al.*, 1998) and mobility impairment (Chaves *et al.*, 2002) in older persons, and is an independent risk factor for increased mortality over 5 years (Izaks *et al.*, 1999). Anemia has been shown to lead to functional impairment (Chaves *et al.*, 2002; Kamenetz *et al.*, 1998), and is a risk factor for falls in older persons (A Report of the Kellogg International Work Group on the Prevention of Falls by the Elderly, 1987; Baker and Harvey, 1985; Herndon *et al.*, 1997). Anemia is associated in older adults with muscle density and decreased muscle strength, as measured by ankle extension (Cesari *et al.*, 2004). Women with a hemoglobin concentration between 13 and 14 g dl^{-1} have better mobility and lower mortality compared to those with a hemoglobin concentration of less than 12 g dl^{-1} (Chaves *et al.*, 2002).

Anemia is strongly associated with an increase in subsequent myocardial infarction and poor outcomes following a myocardial infarction (Wu *et al.*, 2001). Among a population-based cohort of older patients with congestive heart failure, anemia was present in 17% of subjects. Mortality risk was 34% higher in anemic patients (Ezekowitz *et al.*, 2003). In a Medicare cohort of patients with congestive heart failure, mortality rate increased by 1.6% for every 1% decrease in hematocrit (McClellan *et al.*, 2002). Prolonged anemia also results in left ventricular hypertrophy (Levin *et al.*, 1996).

Anemia is often a comorbid condition complicating other conditions. Subjects who have anemia tend to be older, have a higher prevalence of a stroke and gastric ulcer, use more medications, and have higher creatinine levels. These factors suggest that anemia may result from underlying disease; however, the association held even when these diseases were excluded (Izaks *et al.*, 1999).

Quality of life is impaired in persons with anemia, and anemia produces a high level of fatigue (Cella, 1998). Vascular dementia, but not Alzheimer's dementia, has been associated with anemia (Milward *et al.*, 1999).

Treatment of anemia increases hemoglobin concentration, improves the quality of life, and may decrease mortality (Valderrabano, 2000; Cella, 1998; Quirt *et al.*, 2001). Patients with congestive heart failure and an ejection fraction of less than 40% who received treatment for anemia had a 42% improvement in New York Heart Association class score, compared with the control patients who had a decrease of 11.4% (Silverberg *et al.*, 2001). Correction of anemia also produces a decrease in the left ventricular hypertrophy (Levin *et al.*, 1996).

Despite the growing evidence of these poor outcomes associated with anemia in older persons, the diagnosis is often overlooked and, more important, undertreated (Thomas, 2004).

DEFINITION AND PREVALENCE

Hemoglobin and hematocrit values differ little between the healthy elderly population and the younger population. Thus, anemia is not a normal finding in older persons, and hemoglobin concentration should not be adjusted downward in older persons (Tran *et al.*, 1993; Zauber and Zauber, 1987). The World Health Organization defines anemia as a hemoglobin concentration of less than 13 g dl^{-1} in men and less than 12 g dl^{-1} in women.

The prevalence of anemia increases with each decade of life over the age of 70. In the Established Population data for adults aged 71 years or older, hemoglobin concentration was inversely associated with age. In men and women aged 71–74 years, 9% were anemic. The proportion of anemic persons increased differentially with age, reaching 41% for men and 21% for women, aged 90 years or older, respectively (Salive *et al.*, 1992). A similar trend was reported in the third National Health and Nutrition Examination Survey, where the prevalence jumps from 11% in males aged 70–79 years to 22% in males aged 80–89 years (Hsu *et al.*, 2002).

There is a marked sex difference in the frequency of anemia. In a population-based study, the corrected annual incidence of anemia was higher in men older than 65 years (90.3

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per 1000 subjects) as compared to women older than 65 years (69.1 per 1000 subjects) (Ania *et al.*, 1997). Sex differences in hemoglobin concentration result chiefly from differences in testosterone concentration. Hypogonadism in older males (andropause) is commonly associated with approximately a $1\,g\,dl^{-1}$ fall in hemoglobin concentration (Weber *et al.*, 1991). Furthermore, men who have functional hypogonadism from pituitary adenomas are anemic (Ellegala *et al.*, 2003), and men with prostate cancer who are undergoing therapy with total androgen blockade are anemic (Bogdanos *et al.*, 2003).

A very high prevalence of anemia occurs in long-term care settings. In 481 long-term care patients with an average age of 81.4 years, the prevalence of anemia was 31.4% (Chaves *et al.*, 2002). In another study, the prevalence of anemia was 40% (Wu *et al.*, 2001).

Iron deficiency anemia occurs in 3% of children aged 1–2 years, 2% of adolescent girls, 1% of adolescent boys and men, and 5% of women of childbearing age. In persons older than 50 years, 7% have iron deficiency anemia (Looker *et al.*, 1997). Little data exists about the population prevalence of pernicious anemia. Data is largely based on surveys of subjects with florid manifestations or from retrospective analyses of previously diagnosed disease. In one population-based survey, the estimated prevalence was 2.7% in women and 1.4% in men. The frequency of pernicious anemia was higher in both black women (4.3%) and white women (4.0%) (Carmel, 1996).

Anemia associated with chronic renal insufficiency is common. Approximately 13.5 million adults in the United States have a creatinine clearance of $50\,ml\,minute^{-1}$ or less, and about 800 000 adults have chronic renal insufficiency–associated anemia, defined as a hemoglobin concentration of $<11\,g\,dl^{-1}$, according to a study of the National Health and Nutrition Examination Survey (NHANES) III data (Ania *et al.*, 1997). In that study, a statistically significant decrease in hemoglobin concentration was seen among men starting at a creatinine clearance of $70\,ml\,minute^{-1}$ or less and among women starting at $50\,ml\,minute^{-1}$ or less. At any given level of creatinine clearance, men had a larger decrease in hemoglobin concentration than women. For example, compared to subjects with a creatinine clearance more than $80\,ml\,minute^{-1}$, the decrease in hemoglobin concentration for subjects with a creatinine clearance of $20–30\,ml\,minute^{-1}$ was $1.0\,g\,dl^{-1}$ in women and $1.4\,g\,dl^{-1}$ in men.

A substantial number of subjects with chronic renal insufficiency may not have sufficient iron stores to support erythropoiesis. In the National Health and Nutrition Epidemiological Study III, among those persons with a creatinine clearance of $20–30\,ml\,minute^{-1}$, 46% of women and 19% of men had a transferrin saturation of less than 20%, and 47% of women and 44% of men had a serum ferritin of less than $100\,ng\,ml^{-1}$ (Hsu *et al.*, 2002).

The most common cause of anemia in a prevalence study of older persons was anemia of chronic disease, accounting for 35–40% of cases. Iron deficiency anemia was responsible for 8–15% of cases. Chronic kidney disease was responsible for 6–8% of cases. Blood loss accounted for 7% and myelodysplasia for about 5%. Vitamin B_{12} deficiency was responsible for another 5%. As in most studies of older persons, a large number of anemias were undiagnosed despite evaluation (Joosten *et al.*, 1992).

In the older population, anemia of chronic disease and anemia associated with chronic renal disease are the most common causes of anemia. Renal insufficiency accounts for the greatest percentage of anemic individuals with the diagnosis of anemia of chronic disease (27%). Most of these patients have an erythropoietin deficiency. However, other causes of anemia of chronic disease account for about 73% of cases. These conditions include cancer (nonchemotherapy patients), congestive heart failure, hepatitis C, inflammation, diabetes, and rheumatoid arthritis, osteoarthritis, hypertension, stroke, asthma, and recent surgery. Often, patients can have more than one cause of anemia of chronic disease (e.g. iron deficiency, chronic kidney disease, and rheumatoid arthritis). For this reason, nutritional anemias including deficiency in iron, vitamin B_{12}, or folate, and anemia due to blood loss and drug side effects should be excluded in persons with chronic disease.

DIFFERENTIAL DIAGNOSIS

Manufacture of blood proceeds in the bone marrow in a complex, regulated manner. Anemia can be due to failure of the bone marrow to manufacture adequate blood components, gradual or rapid blood loss from hemorrhage, or a rapid breakdown of blood components (hemolysis) in the marrow or peripherally. Causes of failure of the bone marrow to produce adequate blood components includes primary impairment of hemoglobin synthesis (hemoglobinopathy), or an altered maturation of blood cells (myelodysplastic syndromes), or inadequate nutrients (vitamin B_{12}, folate, pyridoxine, or iron) necessary for blood production (Table 1).

A careful differential diagnosis is the cornerstone of management. Several schemes for a differential diagnostic approach have been proposed – none of which is perfect. A corrected reticulocyte count is useful to determine bone marrow function. Anemia associated with an increased reticulocyte count occurs when the bone marrow responds to red cell destruction (hemolysis) or hemorrhage. The presence of elevated concentrations of unconjugated bilirubin and lactic dehydrogenase usually accompanies hemolysis. If these concentrations are normal, hemorrhage from an occult source of blood loss should be sought. A stool occult blood should be obtained, as gastrointestinal bleeding is the most common

Table 1 Causes of anemia

Bone marrow failure
Genetic
Inadequate nutrients
Inadequate erythropoiesis
Hemorrhage
Hemolysis

cause of occult blood loss. A low or normal corrected reticulocyte count in the presence of anemia indicates an inadequate bone marrow response. In the presence of a low corrected reticulocyte count, determination of red cell morphology indices is useful (see Figure 1).

An elevated mean corpuscular volume (macrocytosis) suggests vitamin B_{12} or folate deficiency, hepatic disease, myelodysplasia, hypothyroidism, certain drugs or alcoholism. Measurement of vitamin B_{12} and folate concentrations will determine anemia due to these causes in the majority of cases. Confirmation of vitamin B_{12} deficiency in those patients who have values in the lower normal range should be obtained, since about 50% of patients with subclinical disease may have normal B_{12} levels. A more sensitive method of screening for vitamin B_{12} deficiency is the measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B_{12} deficiency. A homocysteine level will be elevated in both vitamin B_{12} and folate deficiencies, but a methylmalonic acid level will be elevated only in vitamin B_{12} deficiency. Renal failure is the only other confounding cause of an elevated methylmalonic acid concentration.

Myelodysplasia syndrome (MDS) can be associated with a normal LDH, normal bilirubin, and low reticulocyte count. An elevated mean corpuscular volume with abnormalities in red cell corpuscular shape suggests myelodysplastic anemia when nutritional deficiency, drugs, and chemotherapy have been excluded. MDS anemia is a bone marrow failure state associated with varying degrees of pancytopenia. About half of these patients will have a neutropenia. A blood smear may show hyposegmented nuclei in the neutrophils (pseudo Pelger–Huët phenomenon) or abnormal granular content in the white cells. Approximately one-quarter of the patients have thrombocytopenia with megakaryocytes in the peripheral smear. Bone marrow examination confirms the diagnosis with increased cellularity, maturational abnormalities, ringed sideroblasts, and an increase in blasts as well as karyotype abnormalities making the diagnosis (e.g. loss of the long arm of chromosome S). The bone marrow examination may reveal different abnormalities that are useful in classifying the subtype of MDS.

In subjects with a low or normal mean corpuscular volume, the likely diagnoses include anemia of chronic disease, anemia of renal disease, or iron deficiency anemia. Persons with microcytosis, a low serum iron, and low ferritin concentrations have iron deficiency anemia. If the iron is low and the ferritin is high, it is suggestive of anemia of chronic disease (Wians *et al.*, 2001). Thalassemia syndromes and sideroblastic anemias (either primary or secondary) may be associated with a microcytic morphology.

Unfortunately, iron deficiency anemia and anemia of chronic disease commonly coexist in older persons. In

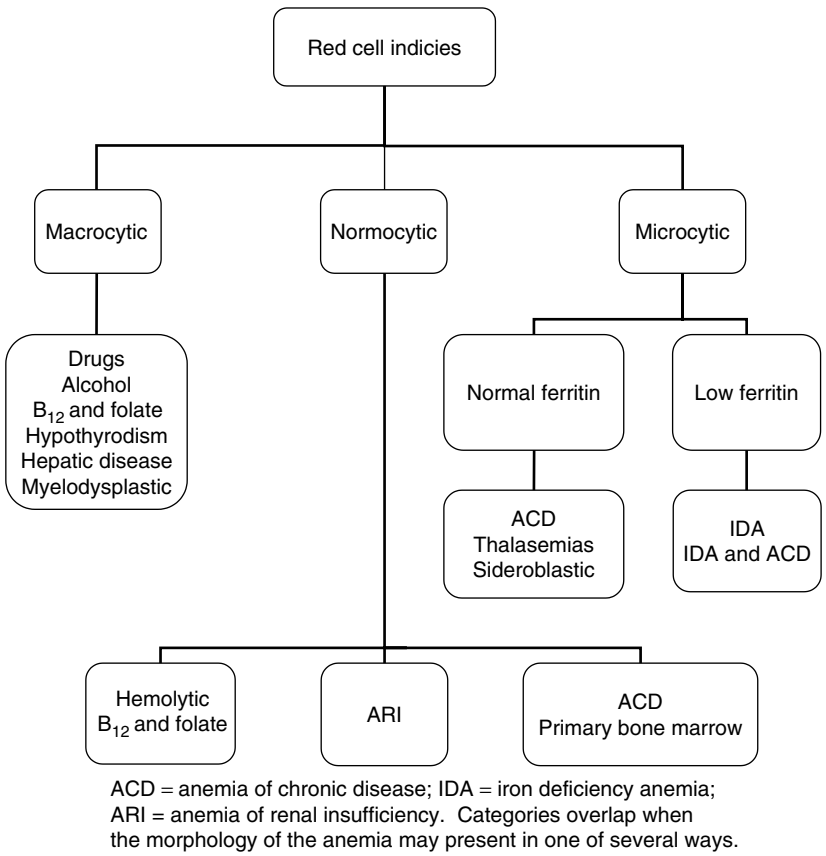

Figure 1 Algorithm for the diagnosis of anemia by red cell morphology. Categories overlap when the morphology of the anemia may present in one of several ways

these cases, soluble transferrin receptor may be useful in determining the diagnosis. Circulating soluble transferrin receptors is a relatively new tool in the diagnosis of anemia. The receptor assay is elevated in iron deficiency anemia even in the presence of chronic disease, but normal or only slightly raised in anemia of chronic disease. As ferritin concentrations are elevated in inflammation, liver disease, renal disease, cancer, and in some elderly women, soluble transferrin receptors can be of use in making the diagnosis of iron deficiency. Soluble transferrin receptor divided by the log of ferritin (<2.55) is the best method of differentiating anemia of chronic disease from anemia of chronic disease associated with iron deficiency anemia (Malope *et al.*, 2001). (see Table 2). However, there does not appear to be much advantage of these newer, more expensive methods over measuring total iron-binding capacity (Wians *et al.*, 2001).

Normocytic morphology is most often associated with anemia of chronic disease. Anemia of chronic disease is associated with the presence of renal insufficiency, cancer, congestive heart failure, hepatitis C, inflammation, diabetes, rheumatoid arthritis, osteoarthritis, hypertension, stroke, and chronic obstructive lung disease. In the studies of anemia of chronic disease, renal insufficiency accounts for about 27% of cases. Most of these patients have an erythropoietin deficiency. Figure 1 lists the anemia of renal insufficiency separately, since this diagnosis is the easiest to search for.

Anemia associated with chronic kidney disease is quite common. Approximately, 13.5 million adults have a creatinine clearance of 50 ml minute^{-1} or less, and about 800 000 adults have *chronic renal insufficiency–associated anemia*, defined as a hemoglobin concentration of $<11\,g\,dl^{-1}$ (Hsu *et al.*, 2002). In persons with chronic kidney disease, a statistically significant decrease in hemoglobin concentration was seen among men starting at a creatinine clearance of 70 ml minute^{-1} or less and among women starting at 50 ml minute^{-1} or less. At any given level of creatinine clearance, men had a larger decrease in hemoglobin concentration than women. Compared to subjects with a creatinine clearance of greater than 80 ml minute^{-1}, the decrease in hemoglobin concentration for subjects with a creatinine clearance of 20–30 ml minute^{-1} was $1.0\,g\,dl^{-1}$ in women and $1.4\,g\,dl^{-1}$ in men (Hsu *et al.*, 2002).

Anemia of chronic kidney disease is diagnosed by recognizing renal insufficiency in association with a low erythropoietin level. The Cockcroft–Gault equation is a usual calculation of estimated creatinine clearance (Cockcroft and Gault, 1976) and has been shown to be strongly correlated with more accurate measures of glomerular filtration rate (GFR) measured creatinine clearance (Lamb *et al.*, 2003).

If the serum creatinine is greater than $2\,mg\,dl^{-1}$, it is usually unnecessary to measure erythropoietin levels. However, older persons can have a declining glomerular filtration rate in the face of a relatively normal serum creatinine. This results from the loss of lean mass (sarcopenia) associated with aging or disease-related cachexia, reducing the source of serum creatinine. For example, an 85-year-old woman with a hemoglobin concentration of $10\,g\,dl^{-1}$ who weighs 55 kg and has a serum creatinine of $1.3\,mg\,dl^{-1}$ (normal range) will have a creatinine clearance calculated by the Cockcroft–Gault equation of 27.5 ml minute^{-1}. For this reason, a creatinine clearance should be calculated in all older persons with anemia to determine their renal status. The Cockcroft–Gault equation will demonstrate that the majority of older women with a creatinine of $1.2\,mg\,dl^{-1}$ or greater have severe renal impairment.

Primary bone marrow failure due to drug effects, alcoholism, radiation therapy, chemical exposure, and recent trauma or surgery, aplastic syndromes, and myelodysplastic syndrome may produce a normocytic morphology. Hemolytic anemias and, on occasion, nutritional anemia, may present with normocytic morphology and should be excluded.

Table 2 Comparison of anemia of chronic disease and iron deficiency anemia

	Iron deficiency anemia	Anemia of chronic disease
Mean corpuscular volume	Normal or decreased	Decreased or normal
Serum iron	Decreased	Decreased
Total iron-binding capacity	Increased	Normal to decreased
Serum ferritin	Decreased	Increased
Soluble transferrin receptor	Increased	Decreased

Hemolytic Anemia

In hemolytic anemia, increased cell destruction is suggested by an increased lactate dehydrogenase; increased hemoglobin catabolism is suggested by increased levels of indirect bilirubin; increased clearing of hemoglobin is suggested by decreased levels of haptoglobin; and bone marrow response is gauged by reticulocytosis. None of these tests are specific or able to distinguish among the various causes of hemolytic anemia. The causes of a hemolytic anemia can be classified into disorders of the structure or synthesis of hemoglobin, deficiencies of enzymes that provide the red cell with energy or protect it from chemical damage, and disorders of the red cell's membrane.

Defects in Hemoglobin Structure

Hemoglobinopathies, the inherited diseases of hemoglobin, are very common. H = hemoglobinopathies usually results from genetic alterations in the production of hemoglobin; for example, the sickle-cell mutation results in a single amino acid substitution in the β globin chain. Sickle-cell disease consists of the homozygous state for the sickle-cell gene (Hb SS) or a compound heterozygous state for the sickle-cell gene combined with either Hb C (a β chain variant) or β-thalassemia (Hb SC disease or sickle-cell β-thalassemia). Heterozygotes have one normal and one affected β chain gene and produce about 60% Hb A and 40% Hb S. Homozygotes produce mainly Hb S with small amounts of Hb F. Compound heterozygotes for Hb S and Hb C produce

almost equal amounts of each variant, whereas those who inherit the sickle-cell gene from one parent and β-thalassemia from the other make predominantly sickle hemoglobin. Sickle-cell anemia should be suspected in any patient with a hemolytic anemia. It can be confirmed by a sickle-cell test, although this does not distinguish between heterozygotes and homozygotes. A definitive diagnosis requires hemoglobin electrophoresis and the demonstration of the sickle-cell trait in both parents. The median life expectancy for men and women with homozygous sickle-cell anemia is 42 and 48 years respectively. In men and women who are heterozygous for Hb SC, mean life expectancy is 60 and 68 years respectively, while a few patients survive into their 70s (Platt *et al.*, 1994).

Defects in Hemoglobin Synthesis

The thalassemias are classified as α- or β-thalassemias, depending on which pair of globin chains is synthesized inefficiently. Both β and delta chain production are affected in rarer forms of thalassemias. Patients with the homozygote state for the β synthesis usually develop severe anemia in the first year of life. The Hb F level is always raised. Severe ineffective erythropoiesis results in erythroid marrow expansion to as much as 30 times the normal level and leads to skeletal changes and hepatosplenomegaly (Olivieri, 1999). Transfusion may result in normal growth and development. However, accumulation of iron may lead to damage to the myocardium, pancreas, and liver, and to infection and folic acid deficiency. Milder forms of β-thalassemia (thalassemia intermedia) can be associated with similar bone changes, anemia, leg ulcers, and delayed development in children. Heterozygote β-thalassemia persons are asymptomatic, with hypochromic microcytic red cells, a low mean corpuscular hemoglobin, low mean cell volume. The Hb A2 level is about twice normal. Homozygote persons for α-thalassemia (Hb Bart's) develop hydrops fetalis syndrome, characterized by the stillbirth of a severely edematous fetus in the second half of pregnancy. Hb H disease is associated with a moderately severe hemolytic anemia. Carrier states for α-thalassemia result in a mild hypochromic anemia with normal Hb A2 levels. Other anemias with an important inherited component include Fanconi's anemia (hypoplastic anemia with skeletal deformities), Blackfan–Diamond anemia (red cell aplasia), and several forms of congenital dyserythropoietic anemia.

Defects in Red Cell Enzymes

Red cells utilize two main metabolic pathways, either anaerobic metabolism of glucose or reduction of glutathione to protect against injurious oxidants. A large number of inherited enzyme defects have been described. Defects in the pyruvate kinase pathway can cause hemolytic anemia. Glucose-6-phosphate dehydrogenase deficiency involves a pathway that is critically important to prevent hemolysis. Precipitated hemoglobin may form a Heinz body, an erythrocyte inclusion that is detected by staining with crystal violet. Glucose-6-phosphate dehydrogenase deficiency is sex linked and affects males predominantly. It affects millions of people worldwide, mainly the same groups that are affected by the thalassemias. Neonatal jaundice, sensitivity to fava beans, and hemolytic responses to oxidant drugs are clues to glucose-6-phosphate dehydrogenase deficiency. Several drugs, including methylene blue, naphthalene, nitrofurantoin, phenazopyridine, primaquine, sulfonamides and sulfones, toluidine blue, and trinitrotoluene, have been associated with hemolytic anemia in persons with glucose-6-phosphate dehydrogenase deficiency (Steensma *et al.*, 2001).

Defects in the Red Cell Membrane

The red cell membrane is required to maintain the integrity of the cell. There are many inherited defects of the membrane proteins, some of which cause hemolytic anemia. Hereditary spherocytosis is due to a structural change that makes the cells more leaky and can be treated by splenectomy. Other inherited varieties of elliptical or oval red cells can produce chronic hemolysis and respond to splenectomy.

Accelerated Destruction of Red Cells

The diagnosis of autoimmune hemolysis is based on demonstrating that autoantibodies or complement components are bound to the red cells and are associated with a shortened red cell life span. Anemia results when the rate of red cell destruction exceeds the regenerative capacity of the bone marrow. The direct antiglobulin test was introduced by Coombs *et al.* in 1945 and remains the hallmark in laboratory diagnosis of autoimmune hemolytic anemia (Coombs *et al.*, 1945). The Coombs test demonstrates the presence of immunoglobulins or complement bound to the erythrocyte membrane. The antibodies can be classified into warm, cold, and mixed types, depending on the thermal characteristic of the autoantibodies (Sokol *et al.*, 1992). The diagnosis may be complicated when the hemolysis is associated with another type of anemia, hemorrhage, blood transfusions, or is minor (Sokol *et al.*, 1995). A large number of conditions have been associated with an autoimmune hemolytic anemia (see Table 3).

Aplastic Anemia

Aplastic anemia is a failure of the bone marrow. Erythrocytes, granulocytes, and platelets decrease to dangerously low levels. The pathophysiology of aplastic anemia is thought to be immune-mediated, with active destruction of blood-forming cells by lymphocytes. The aberrant immune response may be triggered by chemicals and drugs (see Table 4), viral

Table 3 Conditions associated with autoimmune hemolytic anemias

Warm antibody	Cold antibody
Chronic lymphocytic leukemia	Primary atypical pneumonia
Hodgkin's disease	Ebstein–Barr virus infection
Non-Hodgkin's lymphomas	Leprosy
Thymomas	
Multiple myeloma	
Waldenstrom's macroglobulinemia	
Systemic lupus erythematosus	
Scleroderma	
Rheumatoid arthritis	
Infectious disease/childhood viral disorders	
Hypogammaglobulinemia	
Dysglobulinemias	
Ulcerative colitis	
Ovarian dermoid cysts	
Immune deficiency syndromes	
Drug induced (α methyl dopa)	

Table 4 Drugs associated with aplastic anemia

Antiarthritics	Antithyroid drugs
Gold salts	Carbimazole
D-penicillamine	Methimazole
Colchicines	Propylthiouracil
Allopurinol	Diuretics
Antibiotics	Acetazolamide
Sulfonamides (excluding trimethoprim-sulfonamide)	Chlorothiazide
Anticonvulsants	Furosemide
Carbamazepine	Hypoglycemics
Hydantoins	Chlorpropamide
Flebamate	Tolbutamide
Antiarrhythmic	Nonsteroidal anti-inflammatory drugs
Quinidine	Butazones
Tocainamide	Indomethacin
Antihypertensive	Ibuprofen
Nifedipine	Psychotropic drugs
Antiplatetets	Chlordiazepoxide
Clopidogrel	Chlorpromazine
Ticlodipine	Other phenothiazines
Corticosteroids	

infections, or by endogenous antigens generated by genetically altered bone marrow cells. Anemia leads to fatigue, dyspnea, and cardiac symptoms, while thrombocytopenia leads to bruising and mucosal bleeding, and neutropenia leads to sharply increased susceptibility to infection (Young, 2002).

Aplastic anemia can be effectively treated by stem-cell transplantation or immunosuppressive therapy. Transplantation is curative but is best used for younger patients who have histocompatible sibling donors. Antithymocyte globulin and cyclosporine restore hematopoiesis in approximately two-thirds of patients. However, recovery of blood cell count is often incomplete, recurrent pancytopenia requires retreatment, and some patients develop late complications (especially myelodysplasia) (Myer and Oliva, 2002).

Paroxysmal nocturnal hemoglobinuria (PNH) is intimately related to aplastic anemia because many patients with bone marrow failure have an increased population of abnormal cells. These abnormal hematopoietic stem cells lack an entire class of distinctive cell-surface proteins, which may convey a selective advantage in resisting immune attack. PNH may be related to aplastic anemia and myelodysplasia. PNH cells have been identified in 42% of patients with aplastic anemia and 23% of those with myelodysplasia early in the disease process and before any treatment (Dunn *et al.*, 1999). Finding a nonimmune hemolysis with hemosiderinuria should lead to an investigation for PNH. PNH should be investigated in cases of aplastic anemia or a venous thrombosis. PNH is a rare disease with the annual incidence of only about 4 per million persons (Johnson and Hillmen, 2002).

MANAGEMENT

Anemia due to vitamin B_{12} or folate deficiency is treated by the replacement of the vitamin. Vitamin B_{12} can be replaced either by injections (1000 μg weekly for 1 month, then monthly thereafter), orally (1000 μg daily, which should not be given with food), or intranasally. Folate 1 mg should be used to treat folate deficiency and should be used during the first few weeks of vitamin B_{12} deficiency.

In persons with iron deficiency, the recommended treatment is iron sulfate 325 mg three times a day, providing 195 mg of elemental iron per day (Provan, 1999; Goddard *et al.*, 2000; Frewin *et al.*, 1997). The sulfate moiety can cause gastrointestinal distress, and if this occurs, iron in the form of gluconate or fumarate may be helpful. Some experts suggest that iron sulfate once a day may have a similar effect to three-times-a-day dosing if absorption is normal. The duration of iron therapy may be longer when once-a-day dosing is used. Whatever the chosen dose, a reticulocyte count should be obtained 1 week after starting iron. If there is not a robust reticulocyte response, intravenous iron should be considered. Iron therapy may be discontinued when the ferritin level is normalized (see Table 5).

Since the introduction of human recombinant erythropoietin in 1989, the treatment of anemia due to chronic disease has been revolutionized. A linear relationship between glomerular filtration rate and anemia has been demonstrated. In patients with chronic renal insufficiency, the evaluation of anemia should begin in women with a hemoglobin concentration of 11 g dl^{-1} or less, and in men with a hemoglobin concentration of 12 g dl^{-1} or less. Anemia can develop relatively early in the course of a chronic renal failure, and has been associated with a serum creatinine as low as 2.0 mg dl^{-1} (Hakim and Lazarus, 1988). Significant anemia

Table 5 Approach to the management of anemia

Diagnosis	Treatment
Iron deficiency	Ferrous sulphate 325 mg 1–3 times daily
Vitamin B_{12} deficiency	Vitamin B_{12} 1000 μg orally or intramuscularly
Folate deficiency	Folate 1 mg daily
Anemia of chronic kidney disease	Epoetin alfa 10 000 U weekly or darbepoetin alfa 60 mcg every 2 weeks.
Anemia of chronic disease	Treat underlying condition; consider epoetin alfa weekly or darbepoetin alfa every 2 weeks

has been noted when the calculated glomerular filtration rate is less than 20–35 ml minute^{-1} (Jacobs and Worwood, 1975; McGonigle *et al.*, 1985). In patients with an impaired renal function and a normochromic, normocytic anemia, it is rare for the serum erythropoietin level to be elevated. Therefore, measurement of erythropoietin levels in such patients is not likely to guide clinical decision making or therapy. While the majority of persons on dialysis receive erythropoietin, there are many persons who have chronic renal insufficiency who do not receive erythropoietin. This is particularly true among older persons.

As may be expected with increased blood volume, erythropoietin therapy increases blood pressure, necessitating close monitoring in patients with known cardiovascular disease. The hemoglobin level should not exceed 12 gm dl^{-1} in correcting anemia in renal insufficiency.

Erythropoietin has been shown to increase hemoglobin concentration in patients with anemia associated with surgical blood loss, cancer, chemotherapy, anemia associated with drug therapy for AIDS or hepatitis C virus, myelodysplastic disease, and the anemia of chronic disease, especially when associated with rheumatoid arthritis. Several conditions may result in an inadequate response to erythropoietin therapy, including coexisting iron, vitamin B_{12}, or folate deficiency, acute or chronic infections, inflammatory diseases, chronic blood loss, hemoglobinopathies, multiple myeloma, malnutrition, hemolysis, malignancy, hyperparathyroidism, and hypogonadism. Failure to respond to erythropoietin should trigger an evaluation for these conditions (Table 6).

Measurements of erythropoietin should be undertaken in patients with myelodysplastic syndrome, as those with concentration below 200 μg ml^{-1} often have an excellent response to treatment with erythropoietin together with granulocyte-colony stimulating factor.

Blood transfusions are regularly given to older persons who become symptomatic, drop their hemoglobin concentration below 8 g dl^{-1}, or who have an acute bleed. However, it is important to realize that despite adequate careful cross-matching of blood, complications are all too common. Transfusion reactions can lead to hemolysis and fever. Transfusions are often associated with circulatory overload. Since the original description of blood-born hepatitis A, numerous infections including AIDS have been transmitted to patients during blood transfusions. For these reasons, attempting to maintain hemoglobin concentration by other approaches is very important in the long-term care resident. Human recombinant erythropoietin administration can reduce blood transfusion requirements (Ania *et al.*, 1997).

Table 6 Potential causes for inadequate response to erythropoietin therapy

Iron/B_{12}/folate deficiency
Infection/inflammation (e.g. access infections, surgical inflammation, AIDS, systemic lupus erythematosus)
Chronic blood loss
Osteitis fibrosa
Hemoglobinopathies (e.g. α- and β thalassemias, sickle-cell anemia)
Multiple myeloma
Malnutrition
Hemolysis
Aluminum toxicity
Malignancy
Hyperparathyroidism
Hypogonadism
Other: Angiotensin-converting enzyme inhibitors (reported, but not verified)

SUMMARY

The positive clinical outcomes for treating anemia, such as improved quality of life, decreased hospitalization, and decreased mortality, demand that a hemoglobin concentration of less than 12 g dl^{-1} should be investigated and treated whenever possible. The differential diagnosis of anemia is complex, including inherited or acquired anemias that persist into older age. Chronic kidney disease and its associated anemia are very likely underdiagnosed in older persons. Erythropoietin should clearly be considered in all anemic older adults with chronic kidney disease whose serum creatinine is greater than 2 mg dl^{-1}. A calculated creatinine clearance should be done to identify residents with chronic renal failure whose creatinine may be less than 2 mg dl^{-1}. The availability of recombinant erythropoietin, and newer products with a longer half-life, make the goal of correcting anemia and improving patient outcomes a priority.

KEY POINTS

- Anemia has been associated with frailty, functional impairment, falls, and increased mortality.
- Positive clinical outcomes for treating anemia demand investigation and treatment whenever possible.
- The differential diagnosis of anemia is complex.
- Anemia associated with chronic kidney disease remains underdiagnosed in older persons.
- Newer treatment modalities facilitate the goal of correcting anemia and improving patient outcomes.

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38

Disorders of Hemostasis

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INTRODUCTION

Bleeding causes or contributes to the death of about 5% of the elderly population. This is primarily due to intracranial and subarachnoid hemorrhage, ruptured aortic aneurysm, and gastrointestinal bleeding from peptic ulcer and gastric or colonic malignancy. Bleeding due to primary disorders of hemostasis in the elderly is relatively rare. Severe congenital bleeding diatheses are usually diagnosed at a young age, with the majority of them now being treatable and carrying a normal life expectancy, while acquired disorders of hemostasis are an uncommon cause of death except as part of the syndrome of multiorgan failure. Most bleeding in the elderly is localized and the result of a specific underlying pathology, frequently malignancy. Bleeding disorders can be classified as being due to abnormalities of platelet number or function, disorders of the coagulation cascade, and disturbances of the vascular endothelium and connective tissues.

Thrombotic disorders are far more significant causes of morbidity and mortality in the elderly age-group. Arterial thrombosis and atheroma cause cardiovascular disease, cerebrovascular disease, and peripheral vascular disease. Likewise, venous thrombosis is primarily a disease of older age and is now recognized as being due to a combination of both circumstantial and underlying genetic factors. Aging itself results neither in any major or significant changes in the range of the common coagulation tests, such as the activated partial thromboplastin time (APTT), prothrombin time (PT), or thrombin time (TT) nor in the level of fibrinogen or other specific coagulation factors and inhibitors. Likewise, the platelet count does not alter with age. There is, however, convincing evidence from sensitive markers of coagulation activation that background turnover of the proteins is increased with age (Mari *et al.*, 1995). Although there are no major changes in hemostasis that occur with increasing age, diseases that may result in bleeding problems or thrombosis are more common and their consequences more serious in the elderly (Table 1).

DISORDERS OF PLATELET NUMBER

The normal platelet count is between 140 and 400×10^9/l. There is, however, some reserve, and hemostasis is normal with a platelet count of above 80×10^9/l, assuming normal platelet function. If the platelet count falls below this value, the bleeding time progressively prolongs but spontaneous hemorrhage, in particular, intracerebral hemorrhage, does not occur until the platelet count falls below 20×10^9/l. Platelet numbers can be decreased by three mechanisms: decreased production in the bone marrow, increased peripheral destruction, and splenic pooling in gross splenomegaly with hypersplenism. In addition, drugs should always be considered as a possible cause in any case of thrombocytopenia (Bick, 1993).

Decreased Platelet Production

A decreased platelet production can be due to any condition that causes infiltration and replacement or aplasia of the bone marrow, for example, aplastic anemia, leukemia, lymphoma, carcinoma and myelodysplasia, or deficiency of vitamin B_{12}, and folate in megaloblastic anemia.

Increased Peripheral Destruction

While in childhood, immune thrombocytopenic purpura (ITP) is usually an acute self-limiting condition, frequently precipitated by a viral infection, in adults, ITP often has an insidious onset without an obvious precipitant cause, and runs a chronic course over many months and years, occasionally being extremely refractory to treatment. ITP is due to the production of an autoantibody against platelets, usually directed against the platelet membrane-specific glycoproteins. The binding of the antibody to the platelet surface antigen results in the uptake of the platelet–antibody complex

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Table 1 Coagulation tests

Test	Test of	Causes of abnormality
APTT/KCCT	Intrinsic and common pathways	Factor VIII, IX, XI, XII, II, V or X deficiency, or inhibitor Lupus anticoagulant Heparin
PT	Extrinsic and common pathways	Factor VIII, II, V or X deficiency, or inhibitor Liver disease Warfarin
TT	Fibrinogen polymerization	A-hypo-dysfibrinogenemia Heparin Raised FDP
Fibrinogen	Fibrinogen quantity	A-hypo-dysfibrinogenemia
FDP/D-dimer	Fibrinolysis	Disseminated intravascular coagulation Venous thrombosis
Platelet count	Platelet number	Thrombocytopenia or thrombocytosis
Bleeding time	*In vitro* platelet function	Thrombocytopenia Functional platelet defect Aspirin

FDP, Fibrin degradation products; KCCT, Kaolin cephalin clotting time

by the reticuloendothelial system and premature destruction of the platelet. Destruction occurs primarily in the spleen and also in the liver and bone marrow, and platelet survival is decreased from the normal 7–10 days to only a few hours. Diagnosis is based on the finding of true thrombocytopenia, together with a normal bone marrow showing normal or increased numbers of megacaryocytes, the progenitor cells of platelets, and an absence of an alternative cause of excessive peripheral platelet destruction. A low platelet count from an automated blood cell analyzer should always be repeated and the blood film should be examined to exclude artefactual thrombocytopenia due either to the sample having clotted or to platelet clumping caused by the anticoagulant. The clotting screen should be normal. ITP in adults, unlike in childhood, seldom remits spontaneously. The initial treatment is with prednisolone, $1\,mg\,kg^{-1}$ daily. The condition is usually steroid responsive but frequently steroid dependent, and attempts to withdraw the steroids results in recurrence of thrombocytopenia. Often, the platelet count will stabilize at an acceptable level of above 50×10^9/l on no steroids or only a minimal dose, and in the absence of symptoms this is often well tolerated for many years. If there is no response to steroids or an unacceptably high dose is required to maintain a satisfactory platelet count, alternative therapies include intravenous immunoglobulin, $400\,mg\,kg^{-1}\,day^{-1}$ for 3–5 days, which usually raises the platelet count for around 3 weeks and sometimes results in a sustained remission, and splenectomy, which, while does not prevent autoantibody production, does prevent premature platelet destruction by the spleen. A splenectomy is successful in achieving complete remission in about 50–75% of cases progressing as far as surgery. Splenectomy should not, however, be undertaken lightly as it is not without hazard, particularly in the thrombocytopenic patient. In addition to the operative risks, there is the risk of subsequent overwhelming postsplenectomy sepsis: preoperative pneumococcal vaccination and postoperative penicillin prophylaxis should therefore be given. For those in whom a splenectomy is contraindicated or fails, immunosuppressive therapy with azathioprine or cyclophosphamide is sometimes effective. Danazol, vitamin C, interferon, and cyclosporin have all been tried with varying efficacy, as has extracorporeal absorption of the antibody with a protein A column. In difficult and refractory cases, none of these therapies is frequently or consistently successful (Warkentin and Kelton, 1994).

Increased Pooling of Platelets

Under normal circumstances, 25% of the peripheral platelet pool is sequestered within the spleen at any one time. With increasing and massive splenomegaly, this can increase to more than 90%, resulting in a peripheral platelet count falling even to 50×10^9/l. Bleeding, however, is rare as the platelets appear to be mobilized during hemostatic challenge (Karpatkin, 1983).

Thrombocytopenia due to Drugs

Drugs can cause thrombocytopenia by direct bone marrow suppression, for example, cytotoxic drugs, alcohol, and chloramphenicol, or by inducing an immune response – those most commonly being implicated are aspirin, paracetamol, antibacterial, anticonvulsants, diuretics, and other miscellaneous drugs such as tolbutamide, quinine, and quinidine. Heparin causes a characteristic syndrome of heparin-induced thrombocytopenia (HIT), which, unlike other drug-induced causes of thrombocytopenia, is associated not only with decreased platelet survival and thrombocytopenia but also with platelet activation and hence intravascular thrombosis. Consequently, this condition is associated with severe morbidity, due to severe venous or arterial thrombosis, and a mortality of around 30%. It is more common with unfractionated heparin than with low molecular weight heparin but can occur with either. Patients receiving heparin for both prophylactic and therapeutic indications should have their platelet counts regularly monitored to anticipate this serious complication. Treatment of suspected HIT involves immediate withdrawal of heparin and commencement of an alternative method of anticoagulation such as warfarin (Chong, 1995).

FUNCTIONAL PLATELET DEFECTS

By far, the most common platelet functional defect (Table 2) is that acquired following treatment with aspirin. Aspirin works by irreversibly acetylating the platelet enzyme prostaglandin synthase and thereby decreases platelet reactivity and aggregation for the platelet's entire lifespan. Aspirin prolongs the skin bleeding time. In recent years, aspirin has become established in the treatment of acute arterial thrombotic events, such as unstable angina and myocardial infarction, and in the secondary prophylaxis of myocardial infarction and transient ischemic attack and stroke. There is a trend toward decreasing the dose of aspirin, which not only decreases gastrointestinal toxicity but also results in the platelet being irreversibly acetylated by aspirin in the portal circulation; with low total dose, aspirin is then deacetylated within the liver, resulting in no systemic bioavailability of aspirin and thus in no inhibition of the beneficial effects of endothelial cell prostacyclin production. Other drugs that affect platelet function include nonsteroidal anti-inflammatory drugs, high doses of penicillin and cephalosporins, and some antidepressants and anesthetics. Abnormal platelet function can occur in any of the myeloproliferative disorders, namely, primary proliferative polycythemia, essential thrombocythemia, chronic myeloid leukemia, and myelofibrosis, leading to both bleeding and thrombosis. Bleeding is paradoxically more common with raised platelet counts, especially when greater than 1000×10^9/l.

Similarly, in myelodysplastic syndromes, in addition to the frequent thrombocytopenia, abnormal platelet function is common, and bleeding can cause severe morbidity, requiring platelet transfusion; bleeding and infection are the most common causes of death. Abnormalities of platelet function leading to a prolonged bleeding time frequently occur in uremia. This improves with dialysis, and can be specifically treated, if necessary, with both cryoprecipitate and desmopressin (DDAVP).

An acquired platelet function defect, due primarily to proteolytic degradation of platelet surface glycoproteins by plasma, occurs during extracorporeal circulation in cardiopulmonary bypass. It can be ameliorated by the use of the fibrinolytic inhibitor aprotinin, but may on occasion require platelet transfusion in addition.

Congenital functional platelet defects are extremely rare, with an incidence of less than one per million of the population. Deficiency of the platelet-specific glycoprotein Ib, which allows interaction with the von Willebrand factor, occurs in Bernard–Soulier syndrome, and deficiency of the platelet surface glycoprotein IIb/IIIa occurs in Glanzmann's thrombasthenia. Deficiency of platelet alpha and dense granules, which are usually released upon platelet aggregation and are involved in recruitment of large numbers of platelets into the platelet plug, are deficient in storage pool disease (Rao and Carvalho, 1994).

Table 2 Causes of acquired platelet functional defects due to drugs, especially aspirin

Myeloproliferative syndromes
Myelodysplasia
Uremia
Cardiopulmonary bypass

HEREDITARY COAGULATION DEFECTS

Severe deficiency (less than $0.01\,\mathrm{IU}^{-1}$ml) of factor VIII (hemophilia A) or factor IX (hemophilia B) will have been diagnosed at a young age, and management of these conditions is highly specialized and age independent. Spontaneous bleeding into muscles and joints is frequent and is managed by infusions of appropriate clotting factor concentrates (Figure 1). In addition, many of the older patients have severe complications of advanced hemophiliac arthropathy, and often hepatic impairment due to chronic infection with hepatitic viruses, especially hepatitis C virus. Hemophilia A and B both have sex-linked inheritance and occur in males. Mild (greater than $0.05\,\mathrm{IU}^{-1}$ml) and moderate ($0.01-0.05\,\mathrm{IU}^{-1}$ml) cases may have escaped diagnosis until a later age and will not present until they have a severe hemostatic challenge such as surgery, which can occur at any age. These patients will have a long APTT, and specific factor assays will reveal the diagnosis. They can usually be managed with desmopressin, a long-acting synthetic analog of vasopressin, the antidiuretic hormone, rather than with clotting factor concentrates, with the attendant saving on cost and reduced risk of viral transmission. Female carriers

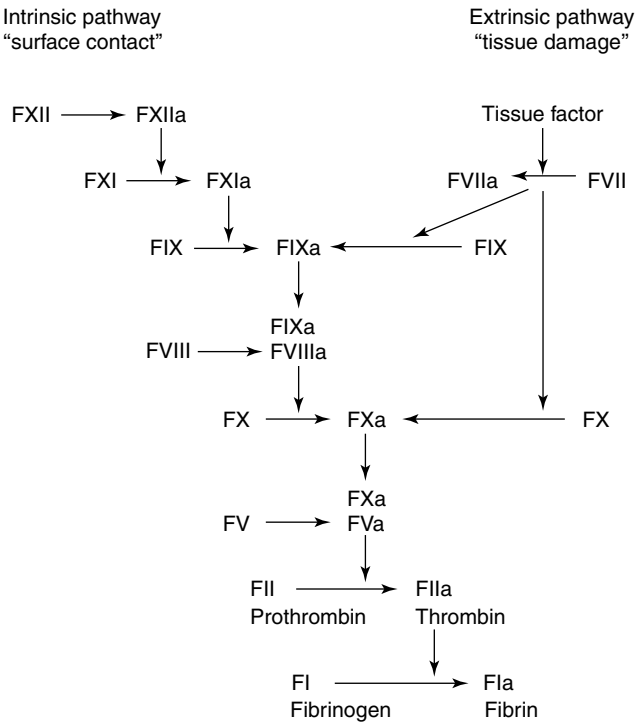

Figure 1 Coagulation cascade

of hemophilia A and B usually have around half the normal levels of the respective clotting factor, although, owing to the randomness of the lyonization effect (random inactivation of one X chromosome in all female cells), up to 30% of carriers will have factor VIII or factor IX levels sufficiently low to require treatment at times of surgery; conversely, many carriers have entirely normal levels of factor VIII and factor IX, and, therefore, carrier status cannot be determined accurately simply by measuring the appropriate factor levels but instead requires genetic analysis.

Von Willebrand's disease is extremely common, and has an incidence of up to 1% in the general population. It is autosomally dominantly inherited and, therefore, occurs in males and females equally. The majority of cases are mild; the condition is significantly underdiagnosed, and in milder cases, bleeding occurs with significant hemostatic challenges. Consequently, mild von Willebrand's disease can present and be diagnosed at any age. Von Willebrand's disease is due to a decreased concentration of the protein von Willebrand factor, which is important in mediating platelet adhesion to the subendothelium; von Willebrand factor also circulates noncovalently bound to coagulation factor VIII and so protects factor VIII from premature proteolytic degradation. Therefore, in von Willebrand's disease, diminished levels of the von Willebrand factor result in both a mild platelet defect and a mild defect of the coagulation cascade consequent upon the diminished amounts of factor VIII. Unlike in hemophilia, the skin bleeding time is increased and bleeding tends to be primarily mucocutaneous, with epistaxis, gum bleeding, gastrointestinal bleeding, and menorrhagia. Diagnosis and classification requires the determination of factor VIII concentration, the von Willebrand factor antigen, and the von Willebrand factor activity, by use of the ristocetin cofactor activity, and analysis of the von Willebrand factor multimer distribution. Mild type-I cases can usually be treated with desmopressin prior to significant hemostatic challenge, whereas the rarer, more severe forms of von Willebrand's disease usually require treatment with clotting factor concentrates, which should contain both factor VIII and the von Willebrand factor (Tuddenham, 1989).

ACQUIRED COAGULATION DEFECTS

Probably, the most commonly acquired coagulation defect (Table 3) in the elderly is iatrogenic, because of the use of the anticoagulants heparin and warfarin. Heparin is given parenterally and acts by potentiating the action of antithrombin to inhibit thrombin. It is a difficult drug to use, with a narrow therapeutic range, complicated pharmacokinetics, and significant interpatient variation in dose requirements. Insufficient heparin will result in thrombosis or extension of previously existing thrombosis, while excess treatment rapidly precipitates hemorrhage, which is potentially life threatening. Heparin infusion should be monitored by use of the APTT; the therapeutic range is a ratio of between 1.5 and 2 (Colvin and Barrowcliffe, 1993). Recently, low-molecular weight heparins have been introduced for both prophylaxis and treatment of venous thrombosis, and these have the significant advantages of a longer half-life, increased bioavailability, and more predictable pharmacokinetics and consequently can be given by once-daily subcutaneous injection without the need for monitoring, even in the doses required for treatment. Since low-molecular weight heparin has a greater effect on factor Xa than on thrombin (IIa), it cannot be monitored with the APTT but instead requires an antifactor Xa assay. However, in overdosage, even low-molecular weight heparin will prolong the APTT, and bleeding under these circumstances may require neutralization of the heparin with protamine sulfate (Barrowcliffe, 1995).

Table 3 Causes of acquired coagulation defects

heparin
Warfarin
Liver disease
Specific coagulation factor inhibitors
Disseminated intravascular coagulation
Paraproteins

Warfarin, likewise, is a drug with a narrow therapeutic range, complicated pharmacokinetics and multiple drug interactions, and significant hemorrhagic consequences if given in overdose. Warfarin also requires careful monitoring. There are well-established guidelines for the treatment of venous thrombosis, these being an international normalized ratio (INR) of 2–3 for uncomplicated thrombosis and 3–4 for recurrent and complicated thrombosis or in patients with the presence of artificial prosthetic heart valves or similar.

Liver disease is a common cause of an acquired coagulation disorder. In addition to being the site of synthesis of the majority of coagulation proteins, the liver is also extremely important in the clearance of activated clotting factors. In addition, liver disease is often also associated with dysfibrinogenemia, due to increased deposition of sialic acid residues on fibrinogen resulting in charge repulsion and failure to polymerize, and hypofibrinogenaemia, due to failure of synthesis. Furthermore, liver disease often causes portal hypertension and hypersplenism with consequent thrombocytopenia due to splenic pooling of platelets. The coagulation defect in liver disease first manifests as a prolongation of the PT and initially is due to decreased production of the active forms of the vitamin K–dependent clotting proteins, factors II, VII, IX, and X. Consequently, vitamin K may be of some use in correcting the coagulation defect in early liver disease. Vitamin K takes a minimum of 6 hours to work and its effect is maximal at 24 hours. In more advanced liver disease, there is a decreased production of all clotting factors and fibrinogen, except for factor VIII, and vitamin K is usually not effective (Joist, 1994). Disseminated intravascular coagulation is caused by a wide variety of triggering factors and mechanisms, and is discussed elsewhere.

Thrombotic thrombocytopenic purpura presents as a classic pentad of fever, thrombocytopenia, neurological and renal involvement, and a microangiopathic hemolytic anemia with red cell fragmentation. Although there remains controversy about the precise etiology of the condition, there

is undoubtedly diffuse and widespread intravascular platelet aggregation resulting in microvascular thrombosis. The coagulation tests, however, usually remain normal or only very mildly deranged, in contradistinction to the case in disseminated intravascular coagulation, where thrombocytopenia is accompanied by profound disturbances of coagulation. The treatment is with aggressive, large volume plasma exchange and plasma transfusion and will involve liaison with hematologists and renal physicians (Moake and Eisenstaedt, 1994).

Acquired factor VIII inhibitors are rare. They can occur spontaneously or in association with an underlying autoimmune or lymphoproliferative disorder. Their management involves both treatment of the active bleeding episode and subsequent efforts to remove or neutralize the antibody. The latter usually involves immunosuppression, although occasionally acquired inhibitors will resolve spontaneously. Treatment of bleeding episodes may require high doses of factor VIII, the use of porcine factor VIII, and the use of activated prothrombin complex concentrates or recombinant factor VIIa. In addition, intravenous immunoglobulin is often beneficial, and consultation with a hematologist with a special interest in this condition is extremely helpful (Ludlam *et al.*, 1994).

Paraproteinemias can affect coagulation either by nonspecific inhibition of fibrin polymerization by the paraprotein, which can occur in myeloma, Waldenström's macroglobulinemia, and other lymphoproliferative disorders, or by the paraprotein having specific activity against one or more of the proteins of the coagulation cascade. This is a relatively rare phenomenon, but activity against factor VIII, giving acquired hemophilia, and von Willebrand factor, giving acquired von Willebrand's disease, is recognized (Mannucci and Giangrande, 1994).

VASCULAR DISORDERS

In these disorders (Table 4), coagulation tests and platelet number and function are normal. The defect lies in the vascular endothelium and supporting tissues (Forbes, 1994). Senile purpura is relatively common and occurs on the extensor surfaces of the forearms and hands in particular. It is due to decreased amounts of collagen supporting the small blood vessels, which rupture with minor trauma or apparently spontaneously. The process is considerably accelerated by long-term treatment with corticosteroids. There is no specific treatment and, other than being cosmetically disturbing, it does not constitute a significant hemorrhagic diathesis. Hereditary hemorrhagic telangectasia is an autosomally dominantly inherited disease with multiple telangectasia of the lips, conjunctiva, and the oral cavity associated with telangectasia throughout the gastrointestinal tract and also with pulmonary arteriovenous malformations. The condition tends to become progressively more severe with age and frequently presents in later life, usually as chronic iron deficiency anemia. Troublesome gastrointestinal bleeding can usually be managed by iron supplementation but may require a chronic transfusion regimen. The fibrinolytic inhibitor, tranexamic acid, and estrogens have been used with some success. Owing to the widespread nature of the lesions, surgery is not usually a feasible treatment option (Guttmacher *et al.*, 1995). Scurvy (vitamin C deficiency) is associated with purpura and widespread bleeding, particularly from mucosal surfaces and subperiostally. It is due to both abnormal collagen synthesis and a defect in platelet function but is rare in the Western world, except in association with malnutrition and alcoholism. Amyloidosis may be primary or complicate paraproteinemias, collagen vascular disorders, and chronic infection. The deposition of amyloid protein in the blood vessels leads to fragility, and consequently purpura is common. Cases of a specific coagulation defect due to absorption of the coagulation factor X by the amyloid protein have occasionally been reported. Ehlers–Danlos syndrome, especially type IV with a deficiency of type-III collagen, results in structural weakness of major blood vessels with a tendency to rupture and consequent severe hemorrhage. Henoch–Schönlein purpura is rare in the elderly, being primarily a condition of childhood. It is an anaphylactoid purpura with cutaneous petechia and urticaria, associated with joint swelling, abdominal colic, and melena. Despite the purpura, which is usually a manifestation of severe thrombocytopenia, the platelet count remains normal in this condition. Precipitating drugs should be withdrawn; steroids give relief from the joint and abdominal symptoms.

Table 4 Hemorrhagic vascular defects

Senile purpura
Steroid purpura
Hereditary hemorrhagic telangiectasia
Gastrointestinal angiodysplasia
Ehlers–Danlos syndrome
Henoch–Schönlein purpura

THROMBOTIC DISORDERS

Although arterial thrombosis is a major cause of morbidity and mortality, its prevention is not possible at present; likewise, its pathophysiology is not well characterized. Smoking, hyperlipidemia, and a raised fibrinogen concentration are associated with accelerated atheroma, which accounts for the majority of arterial disease (*see* **Chapter 54, Peripheral Vascular Disease in Elderly Persons**). In addition, atrial fibrillation (*see* **Chapter 45, Arrhythmias in the Elderly**) and valvular cardiac defects are associated with arterial embolization, but a full understanding of arterial thrombosis does not exist at the present time (Packham and Kinlough-Rathbone, 1994).

The situation with venous thrombosis is somewhat different, and there have been rapid advances in the understanding, diagnosis, and management of venous thrombosis (*see* **Chapter 55, Venous Thromboembolism**) over the last few years. Venous thrombosis is primarily a disease of old age; until

Table 5 INR ranges in various conditions 1112

INR	Clinical state
2.0–2.5	Prophylaxis of deep vein thrombosis including surgery on high-risk patients
2.0–3.0	Treatment of deep vein thrombosis Pulmonary embolism Systemic embolism Prevention of venous thromboembolism in myocardial infarction Mitral stenosis with embolism Transient ischemic attacks Atrial fibrillation
3.0–4.5	Recurrent deep vein thrombosis and pulmonary embolism Arterial disease including myocardial infarction Mechanical prosthetic heart valves

recently, it was thought that in the majority of cases the cause was circumstantial, with predisposing factors being immobilization and surgery, particularly to the hip, knee, and pelvis, together with accessory factors such as obesity and malignancy. It has become clear, however, that in up to 50% of cases of venous thrombosis, there is an additional underlying genetic predisposition to thrombosis that becomes manifest under the above circumstances. The importance of thromboembolic prophylaxis of both surgical and medical patients at medium and high risk of developing thrombosis is increasingly being recognized and practised. Likewise, the need for objective diagnosis of venous thrombosis by ultrasound examination or venography in the lower limb, and ventilation–perfusion lung scanning and pulmonary angiography in cases of suspected pulmonary embolus, has become established. Objective validation of the diagnosis of venous thromboembolic disease should always precede the initiation of treatment. Treatment should initially be with heparin, either unfractionated or low-molecular weight heparin, and subsequently with oral warfarin. Warfarin in the elderly is not without hazards, there being an increased chance of drug interactions, and in general the dose required in elderly patients is somewhat lower than in younger patients. Furthermore, the risk of bleeding is increased both at high INRs and also at normal INRs because of the increased incidence of underlying pathology, such as peptic ulcer, gastrointestinal malignancy, and angiodysplasia. Consequently, it is important that recommended target ranges and duration of anticoagulation are adhered to and patients are not anticoagulated without good cause (Table 5) (British Society for Haematology, 1990).

THROMBOPHILIA

The proteins of the natural anticoagulant pathway act to limit and regulate thrombin generation. Deficiency of these proteins results in increased thrombin generation and consequently increased fibrin formation and venous thrombosis

Table 6 Thrombophilic conditions

Antithrombin – quantitative deficiency or qualitative dysfunction
Protein C – quantitative deficiency or qualitative dysfunction
Protein S – deficiency of total or free protein S
APCR resistance/factor V Leiden
Antiphospholipid syndrome (lupus anticoagulant)

(Table 6). Deficiencies of antithrombin, protein C, and protein S are rare but significant conditions do exist. They are autosomally dominantly inherited and only occur in the heterozygous form, the homozygous form being incompatible with life. These conditions usually present with venous thrombosis, which may be unusually widespread or occur at an unusual site, sometimes occurring spontaneously but often following a recognized predisposing factor. They may be recurrent and there is often a positive family history of venous thrombosis. Although patients may well present at a younger age, they can be diagnosed at any age, and certainly second or recurrent episodes of thrombosis will occur in the old age. The diagnosis of these conditions can be somewhat problematical as the concentrations of all these proteins fall during active thrombosis, and antithrombin levels fall during heparin therapy, while protein C and S levels fall during warfarin therapy. Consequently, patients should ideally be investigated when they have neither active thrombosis nor are on anticoagulants. The finding of a deficiency state should lead to family screening as other family members are at risk. In the absence of a first episode of thrombosis, management should consist of adequate thromboprophylaxis at times of increased risk, such as surgery and immobilization. After a first episode of thrombosis, reasonable management is to anticoagulate for 3–6 months with warfarin with a target range of 2–3; after recurrent thrombosis, lifelong anticoagulation should be considered, initially with a target range of 2–3 but increasing this to 3–4 should further episodes of thrombosis occur while patients are already anticoagulated (Meade, 1994).

A new thrombophilic defect of resistance to activated protein C (APCR) has recently been described. APCR is part of the natural anticoagulant pathway and usually acts to degrade activated factors V and VIII, thereby causing feedback inhibition of the coagulation cascade (Figure 2). Patients with APCR do not show the expected prolongation of the APTT following the addition of exogenous APCR, and consequently have a low-activated protein C ratio. It has been shown that the basis of this defect is a single base substitution at position 1691 of the factor V heavy chain, resulting in a substitution of the amino acid glutamine for an arginine residue. This abolishes an APCR cleavage site and results in a factor V molecule that can be activated by thrombin but can no longer be inactivated by APCR; consequently, there is enhanced and prolonged activation of the coagulation cascade, increased thrombin generation, and hence a predisposition to thrombosis. This condition can therefore be diagnosed both by a plasma assay and by genetic analysis of the factor V gene. The condition is autosomally dominantly

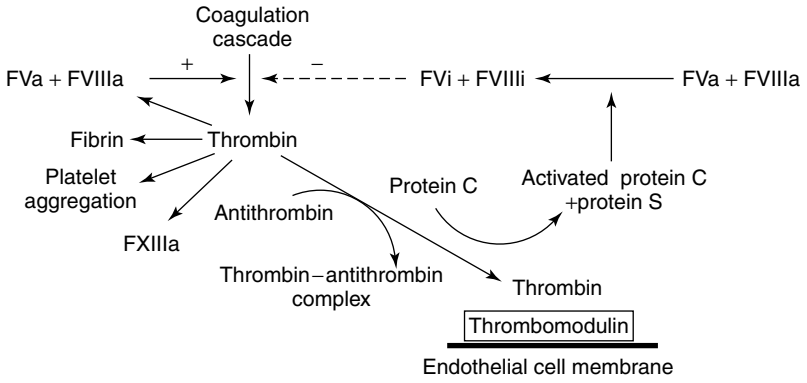

Figure 2 The natural anticoagulant pathway directly inhibits and negatively regulates the formation of thrombin by the coagulation cascade

inherited and is extremely common, occurring at an incidence of between 2 and 10% in the Caucasian population, although it appears to be rare or absent in non-Caucasian populations. Unlike the other thrombophilic conditions, individuals with both heterozygous and homozygous forms of this condition exist, and the lifelong incidence of thrombosis appears to be somewhat less than antithrombin, protein C and S deficiency. Indeed, a significant proportion of patients with this condition may never have a thrombotic event. The frequency with which it occurs within the Caucasian population suggests that in evolutionary terms it must have some, as yet obscure, evolutionary advantage, but with life expectancy increasing and surgery becoming more frequent nowadays, it is clear that this condition is a major predisposing factor contributing to venous thrombosis. Indeed, between 40 and 60% of patients having a first episode of thrombosis have this condition, a 12-fold increase over the incidence within the background population. Although still not fully validated, management should parallel the management of other hereditary thrombophilic conditions (Hillarp *et al.*, 1995).

Lupus Anticoagulant

The lupus anticoagulant is a laboratory diagnosis based on the finding of a prolonged APTT that is not due to a deficiency of a specific coagulation factor or a specific inhibitor of any coagulation factor, but to an autoantibody apparently directed against phospholipids, but in reality directed primarily against proteins that are intimately associated with phospholipids. Since the reactions of the coagulation cascade are phospholipid dependent, these antiphospholipid antibodies decrease the efficiency of the coagulation cascade and prolong the clotting time. The diagnosis can be confirmed using the dilute Russell viper venom test (DRVVT), in which the test is optimized so that phospholipid availability is rate limiting, and this accentuates the effect of antiphospholipid antibody. Confirmation is achieved by showing that the clotting time returns to normal when excess phospholipid (in the form of freeze-fractured platelets) is added to quench the antibodies and that the test is not corrected by the addition of normal plasma that contains only additional coagulation factors.

The name, lupus anticoagulant, is somewhat unfortunate. The lupus refers to systemic lupus erythematosus (SLE), and it was in patients with this condition that the phenomenon was first observed. However, it has subsequently become clear that the majority of patients do not have SLE. Likewise, although it appears to be anticoagulant *in vitro* by prolonging the activated partial thromboplastin time (ACCT), *in vivo* some lupus anticoagulants are associated with an acquired predisposition to thrombosis, and bleeding does not occur. Consequently, the finding of a lupus anticoagulant may be an indication for thromboprophylaxis or even anticoagulation.

The significance of the finding of a lupus anticoagulant can be very variable. Transiently positive tests frequently occur after infections and many drugs can precipitate these antibodies, as can chronic infection such as syphilis. In these circumstances, the antibody does not appear to be associated with an increased incidence of either arterial or venous thrombosis. In patients with an underlying collagen vascular disease, or in whom a primary antiphospholipid syndrome is diagnosed, there is an association between the finding of a positive test and recurrent arterial or venous thrombosis. The primary antiphospholipid syndrome consists of a positive lupus anticoagulant test and an association with livedo reticularis, thrombocytopenia, and recurrent miscarriages in females. The lupus anticoagulant can precipitate both arterial and venous thrombosis and, within an individual, the site of second and subsequent thrombosis tends to occur in the same system; these patients may require long-term anticoagulation. There is no evidence that the antibodies causing the prolongation of the APTT *in vitro* are those that cause thrombosis; indeed, they may be an epiphenomenon, as a wide range of autoantibodies are found in these conditions, including antibodies against cardiolipin, which can be IgG or IgM, and are detected by a solid phase enzyme-linked immunosorbent assay (ELISA) (Roubey, 1994).

KEY POINTS

- Bleeding can be due to disorders of the coagulation cascade, platelets or blood vessels.
- Bleeding disorders can be congenital or acquired, the latter being more common.
- Drugs are a common cause of bleeding disorders.
- Thrombin disorders, both arterial and venous, are common in the elderly.
- Recurrent, severe, or unusual episodes of venous thrombosis suggests thrombophilia.

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Disseminated Intravascular Coagulation

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INTRODUCTION

Disseminated intravascular coagulation (DIC) is a failure of hemostatic homeostasis (Figure 1). The hemostatic system comprises five components: the coagulation cascade, the fibrinolytic cascade, platelets, the natural anticoagulant pathway and vascular endothelial cells. It is a complex system which normally maintains blood fluidity when blood is confined within the intravascular vessels, but is able to trigger rapid and localized coagulation if vascular integrity is breached and tissue factor is exposed. In DIC there is unregulated and uncontrolled activation of the coagulation cascade and platelets resulting in generation of free intravascular platelet and fibrin thrombi resulting in vessel blockage. Simultaneously, there is activation of the fibrinolytic cascade generating plasmin, and consequently fibrin and fibrinogen degradation, together with depletion of a natural anticoagulant pathway which contribute to the systemic bleeding diathesis (Giles, 1994; Pareli *et al.*, 1976). DIC can have an acute onset with acute manifestations dominating the clinical picture, subacute where it arises as a complication of a predisposing condition, or occur in a chronic form, the manifestations of which are very different as is the diagnosis and management of this form of the condition.

PATHOPHYSIOLOGY

DIC is a pathophysiological syndrome characterized by common clinical manifestations and laboratory features. It is not a discrete pathological entity but a final common pathway for a variety of triggers and precipitating factors and can be initiated by a number of different mechanisms (Table 1). DIC is characterized by great variability between patients and as it is a dynamic condition that varies considerably over time, there is equally great temporal variation within individual patients. Consequently, it has been difficult to perform adequate randomized controlled trials in the management and treatment of DIC, although there have been several recent advances in its early diagnosis and treatment (Bick, 1993).

The primary triggers of DIC in the elderly are overwhelming sepsis and malignancy, particularly disseminated malignancy, massive trauma, and major surgery. ABO incompatible blood transfusions and snake bites are rarer but recognized causes. DIC may be precipitated by activation of the coagulation cascade following tissue factor exposure, for example, as in massive trauma and major surgery; activation of the fibrinolytic cascade, for example, the liberation of plasminogen activators by leukemic blasts in acute promyelocytic leukemia or carcinoma of the prostrate; intravascular platelet aggregation; endothelial cell activation, for example, by endotoxins in gram-negative sepsis and meningococcal septicemia or by direct proteolytic cleavage of circulating hemostatic proteins, as occurs in pancreatitis and with some snake venoms (Table 1). In addition to uncontrolled activation of the coagulation and platelet cascades, there is depletion of the natural inhibitors of coagulation and proteins of the natural anticoagulant pathway, namely antithrombin, protein C, and protein S. Depletion of these further enhances the microvascular thrombosis, and also leads to activation of the complement system, resulting in an inflammatory response and generation of vasoactive peptides, such as bradykinin. DIC also provokes a poorly characterized neuroendocrine response involving elevated catecholamines and glucocorticoids (Heeb *et al.*, 1989).

Clinically, DIC manifests as simultaneous bleeding and microvascular thrombosis leading to multiple organ dysfunction and is often associated with fever, hypotension, acidosis, hypoxia, and proteinuria. While bleeding is the most obvious and commonly recognized manifestation, death by exsanguination is rare due to the appropriate use of blood and platelet transfusions. The usual cause of death in DIC is multiorgan failure as a consequence of the microvascular thrombosis, which is not so clinically obvious. Treatment of multiorgan failure, which is a consequence of anoxia and ischemic necrosis of vital organs is far more difficult to treat satisfactorily (Marder *et al.*, 1994).

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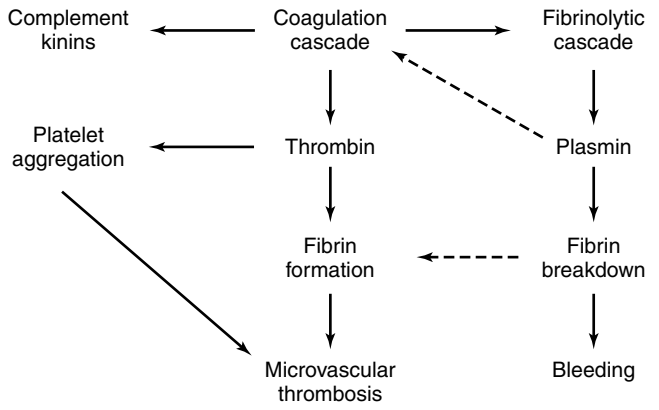

Figure 1 Mechanism of microvascular thrombosis and bleeding in DIC. Broken lines = inhibition

Table 1 Mechanisms and precipitating factors in DIC

Mechanism	Example
Coagulation cascade activation	Tissue factor exposure in trauma and extensive surgery
Fibrinolytic cascade activation	Plasminogen activators liberated in acute promyelocytic leukaemia
Intravascular platelet aggregation	Hemolytic uraemic syndrome, thrombotic thrombocytopenic purpura
Endothelial cell activation	Gram-negative sepsis, malignancy
Direct proteolytic cleavage of hemostatic proteins	Pancreatitis, snake venoms

The bleeding in DIC is multifactorial in origin as a result of depletion of fibrinogen and all coagulation factors as a consequence of consumption due to uncontrolled and excessive activation of the coagulation cascade, diminished platelet number due to consumption, and an additional or acquired platelet defect consequent to a proteolytic degradation of platelet surface glycoproteins and partial degranulation of α and dense platelet granules. Hyperfibrinolysis leads to elevated levels of fibrin and fibrinogen degradation products (FDP and D-dimers) which act as competitive inhibitors of fibrin polymerization. The uncontrolled generation of free plasmin degrades fibrin, fibrinogen, and coagulation factors, particularly factors V and VIII. Consequently, there is a systemic bleeding diathesis resulting in bleeding not only from local surgical incisions or traumatic wounds, but also generalized bruising, petechiae, purpura, together with bleeding from sites of venepuncture, arterial lines, drains, catheters, and from endotrachial tubes. There is also frequent gastrointestinal bleeding, hemoptysis, hematuria, and even intramuscular or intracerebral bleeding. Excessive bleeding from a single site, particularly following surgery, is usually more indicative of failure of local hemostasis than DIC and requires specific local measures. The microvascular thrombosis results in anoxic damage and ischemic infarction of vital organs, including lungs, kidneys, brain, pituitary, liver, adrenal, heart, and skin (Colman *et al.*, 1979).

DIAGNOSIS

The diagnosis of DIC is made in the presence of a predisposing cause, the clinical manifestations of systemic bleeding and multiorgan dysfunction, and from appropriate laboratory investigations (Table 2). The hemoglobin is usually reduced owing to intravascular red cell fragmentation resulting in a microangiopathic hemolytic anemia (MAHA) and there is profound thrombocytopenia. Coagulation times are abnormal with a prolongation of the activated partial thromboplastin time (APTT), prothrombin and thrombin time, and depletion of fibrinogen, all due to consumption. In addition, there is evidence of fibrinolytic activation and fibrin degradation with elevations of serum FDPs or plasma D-dimers. In addition to these rapid and readily available tests, recent studies have shown that waveform analysis of the coagulation profile on automated machines can have both diagnostic and prognostic significance and laboratory abnormalities can be included in a validated scoring system for DIC. In addition to consumption of the coagulation factors and prolongation of the clotting times, levels of natural anticoagulant pathway proteins, namely, antithrombin, protein C, and protein S, are also significantly reduced contributing to the microvascular thrombosis (Baker, 1989).

As DIC is a dynamic condition it is preferable to perform the simple clotting tests frequently, both before and after clinical interventions to judge their efficacy and the need for further blood product replacement therapy or interventions. For the role of thromboelastography, an endogenous thrombin potential in DIC remains to be clarified.

MANAGEMENT

The first principle of management of DIC should be toward resuscitation of the patient to achieve adequate oxygenation, blood pressure, circulation, and renal perfusion. Once resuscitation is complete then aggressive treatment of the underlying precipitating cause of the DIC should be addressed. Most frequently this is sepsis and aggressive broad-spectrum antibiotic therapy following the taking of appropriate microbiological samples is necessary. A few causes of disseminated malignancy, such as acute myelocytic leukemia and hormone responsive tests, and prostatic carcinoma, may also be amenable to treatment but the prognosis in DIC secondary to disseminated malignancy is usually poor, indeed mortality overall remains high at 25–75% in various theories.

Table 2 Laboratory diagnosis of DIC

Test	Result
APTT	Prolonged
PT	Prolonged
TT	Prolonged
Fibrinogen	Low, usually $<1\,g\,l^{-1}$
Platelets	Low, usually $<50 \times 10^9\,l^{-1}$
FDPs	Raised
D-dimer	Raised

TT, Thrombin Time.

There is considerable controversy about the place of blood product support in this condition. Clearly red cells and platelet support, together with plasma product support, is indicated in patients who are actively bleeding. In patients who are not actively bleeding, the use of transfused clotting factors and platelets serve only to make the microvascular thrombosis worse unless the underlying precipitating factors have been treated. However, once these issues have been addressed and if the patient is bleeding, it is appropriate to transfuse red cells to achieve a hemoglobin of above $10\,g\,l^{-1}$ or hematocrit above 30% to try and achieve a platelet count of $> \times 10^9$/l to correct the prothrombin time (PT) and APTT to no more than 10% more prolonged than the upper limit of normal and to increase the fibrinogen to $>1\,g\,l^{-1}$ through the appropriate use of red cells, platelets, fresh frozen plasma, and cryoprecipitate respectively (cryoprecipitate is particularly rich in fibrinogen). Following blood product intervention the clotting screen should be repeated to assess the response to therapy and the need for additional future therapy.

In DIC due to sepsis, there is now evidence that depletion of the natural anticoagulant pathway proteins, such as antithrombin, protein C, and protein S, contribute not only to microvascular thrombosis but also to the systemic inflammatory response and to a poorer prognosis. There is evidence in meningococcal meningitis that supplementation of depleted protein C improves outcome and recombinant human activated protein C is now licensed for use in severe sepsis with beneficial effects on mortality. The use of antithrombin concentrates is widespread in countries other than the United Kingdom but their efficacy has not yet been proven in an appropriate prospective randomized trial.

The use of heparin is even more controversial (Feinstein, 1982). There are no adequate controlled trials to support its use and while it would appear logical to use an anticoagulant in a condition where the major morbidity and mortality is due to thrombosis, the use of a systemic anticoagulant in patients either with active bleeding or at high risk of catastrophic bleeding is troublesome. Furthermore, there are considerable problems in determining the duration of treatment and monitoring of heparin therapy in the presence of severely prolonged clotting times and as heparin works by potentiating the activity of antithrombin, which is usually severely depleted in DIC, its efficacy is uncertain. Fibrinolytic therapy with tranexamic acid is contraindicated in DIC unless the trigger mechanism is hyperfibrinolysis, and the use of aprotinin, prostacyclin, and antiplatelet drugs remains controversial and unproven. There is evidence that human recombinant activated FVII may be useful in incontrollable hemorrhage.

CHRONIC DISSEMINATED INTRAVASCULAR COAGULATION

Chronic DIC manifests very differently from acute DIC. The cause is usually, but not exclusively, disseminated malignancy, which may be manifest but may often remain occult for weeks or months after the initial presentation. Patients usually present with bruising from thrombocytopenia and on further investigation are found to have in addition to thrombocytopenia, hypofibrinogenaemia, and elevated FDPs or D-dimers. Bleeding is a rare manifestation of this condition, although bruising is common, while thrombosis in the form of superficial thrombophlebitis and deep venous thrombosis is common. Furthermore, a sterile nonbacterial endocarditis is well recognized, which can result in presentation with arterial embolization (Sack *et al.*, 1977). Thus, the hallmarks of this condition are arterial and venous thrombosis rather than bleeding. The condition will usually resolve if the underlying cause can be successfully treated. If it cannot, the cautious application of anticoagulation rather than blood product support is the mainstay of treatment. Warfarin is notoriously difficult to use in this condition and low molecular weight heparin is the treatment of choice, both in terms of efficacy and improving overall outcome.

KEY POINTS

- DIC presents with hemorrhage, but it is the microvascular thrombosis that causes the multiorgan damage.
- DIC is commonly due to sepsis or disseminated malignancy.
- Diagnosis requires a blood count and a clotting screen.
- Treatment should address the underlying cause first, especially if sepsis, and only then may blood product support be indicated.
- Chronic DIC presents with thrombosis, rather than hemorrhage.

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Anticoagulants in the Elderly

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INTRODUCTION

Thromboembolism in the arterial and venous circulation is more frequent with increasing age. The elderly are also more likely to have conditions such as colonic neoplasms and peptic ulcers which make them more susceptible to bleeding with anticoagulant therapy. Because of age-related changes in cardiovascular and renal homeostasis and concomitant (often multiple) medical problems, they do not tolerate hemorrhage well. They are more sensitive to anticoagulants such as warfarin. It is less clear as to whether chronological age itself is a risk factor for anticoagulant-associated bleeding. This chapter will discuss the benefits/risks and methods to optimize anticoagulant therapy in the elderly.

THE ELDERLY ARE MORE PRONE TO THROMBOEMBOLISM

The elderly are more prone to arterial as well as venous thromboembolism, and thrombotic disease is the commonest cause of hospital admission, disability, and death in patients over 50 years of age in the developed world.

The incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) increases with increasing age. Between 65 and 69 years of age, annual incidence rates per 1000 for DVT and PE are 1.3 and 1.8 respectively, and rise inexorably to 2.8 and 3.1 in individuals aged between 85 and 89 years. Older men are more likely than women of similar age to develop PE. About 1.7% develop PE and 8% develop recurrent PE within one year of treatment for DVT (Kniffin *et al.*, 1994). The diagnosis of PE is often missed in elderly people and it is more often diagnosed only after death (Mangion, 1989).

In the arterial circulation, the risk of thrombosis and embolism also increases with increasing age. Thus, thrombotic and embolic strokes are more frequent with increasing age. One reason for this is that nonvalvular atrial fibrillation (AF) is much more common in the elderly and is associated with a fivefold increased risk of stroke (Wolf *et al.*, 1991). The prevalence of AF rises from 0.5% in the fifth decade of life to 8.8% in the eighth (Wolf *et al.*, 1991). Such individuals who do have an acute stroke are two- to threefold more likely to die than those with acute stroke who are in sinus rhythm (Lin *et al.*, 1996).

Over 100 years ago, Virchow identified three main factors for development of thrombosis. The first was reduction in blood flow which may be a factor in heart failure, a condition seen more frequently in the elderly. The second factor was changes in the vessel wall, which occurs with atherosclerosis and therefore with increasing age. Finally, changes in blood coagulability were cited by Virchow. Increases in clotting factor concentration in platelet and clotting factor activation and a decline in fibrinolytic activity are all seen in the elderly (Dodds *et al.*, 1975)

ANTICOAGULANT RESPONSE DIFFERS IN THE ELDERLY

Several studies have confirmed the original findings of Eccles that anticoagulant requirements decline with age (Eccles, 1975). In one study, Routledge and coworkers showed that warfarin requirements fell with increasing age so that patients aged less than 35 required a mean of 8.1 mg/day, more than twice as much to maintain the same International Normalized Ratio (INR) as in patients aged 75 years or over. The relationship between age and warfarin requirements was rather weak, however, indicating that other factors may be more important in determining warfarin dose than age itself (Routledge *et al.*, 1979a). These findings have been confirmed in a retrospective longitudinal study in 104 patients aged between 31 and 74 years when warfarin was started and followed for a median of 10 years. This suggests that the decline in dose is not related to a birth cohort effect but does occur in individuals as they grow older (Wynne

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et al., 1996). The average decline in dose (1.4% per year) in the study was very similar to the rate of decline observed in the much larger cross-sectional study discussed earlier (Routledge *et al.*, 1979a).

Similar decline in dose requirement with aging has also been reported with acenocoumarol. A study which included 1845 patients between 30 and 99 years showed progressive decline in acenocoumarol requirements from 30 to 80 years of age. The decline in dose was 2.7 mg/week/decade or 11.5% per decade (Cesar *et al.*, 2004).

The reason for the increased sensitivity to anticoagulants is still not fully known, although most studies indicate a pharmacodynamic sensitivity rather than any major change in the pharmacokinetics of warfarin (Shepherd *et al.*, 1977; Routledge *et al.*, 1979b). However, one study has reported an age-related decline in warfarin clearance (Mungall *et al.*, 1985).

THE ELDERLY ARE MORE PRONE TO HEMORRHAGE

The elderly are more prone to develop hemorrhage, even when not receiving anticoagulants. Life-threatening hemorrhage is most likely to occur in the gastrointestinal tract or intracranially. Although duodenal ulcer is commoner at younger ages, gastric ulcer and gastrointestinal bleeding due to nonsteroidal anti-inflammatory drugs are both commoner with increasing age. In addition, the mortality from gastrointestinal bleeding is higher in the elderly (Shetty and Woodhouse, 2003). Intracranial bleeding (intracerebral and subdural) in the absence of anticoagulant therapy is also more frequent in the elderly (Verstraete *et al.*, 1992).

The question most relevant to this discussion is whether chronological age is a factor associated with an increased risk of anticoagulant-associated bleeding. Several studies involving more than 2000 patients in total have failed to show that age was an independent risk factor for bleeding in the elderly (Verstraete *et al.*, 1992). It is therefore unlikely that a large effect of age was missed. In one of the largest of these studies (Sixty-Plus Reinfarction Study Research Group, 1982), the mean age of the patients was 67 years. Major extracranial bleeding was observed once in 25 treatment-years in the anticoagulant group, but no episode was fatal (28 vs 4 events). Malignancy or other specific pathology as the source of major bleeding was found in 40% of the cases and the use of anticoagulants in such patients was often associated with early diagnosis of a previously occult pathology which might otherwise have been missed until a much later stage. Minor extracranial bleeding (mostly skin hematoma, epistaxis, or subconjunctival bleeding) occurred in the Sixty-Plus Reinfarction Study about once in 9 years at risk in the anticoagulant group and once in 111.5 years of observation in the control group. There was no relationship between the incidence of bleeding and the patient's age or the duration of anticoagulant therapy.

No clear association was found between increasing age and the risk of minor or major bleeding in a combined retrospective and prospective cohort study involving 2376 patients (Fihn *et al.*, 1996). Patients aged 80 years or over were a possible exception, with a relative risk of bleeding of 4.6, but the confidence intervals (CIs) were wide (1.2–18.1). However, the intensity of anticoagulation and the deviation in the prothrombin time ratio were very much stronger predictors of risk of bleeding. A smaller retrospective cohort study of 261 patients (61% of whom were 65 years of age or older and 31% of whom were 75 years of age or older) has also examined age as a risk factor for anticoagulant-associated hemorrhage (Gitter *et al.*, 1995). Multivariate analysis indicated that age was not significantly associated with major hemorrhage, although the presence of malignant disease was associated with an increase in major bleeding.

Another combined retrospective and prospective cohort study, which included 323 patients over 80 years of age, found that the rate of major bleeding was 2.4 per 1000 patient-months on anticoagulants (Kagansky *et al.*, 2004). Functional impairments, cognitive and socioeconomic variables did not increase the risk of bleeding. The only significant predictive factors were insufficient education on oral anticoagulant therapy as perceived by the patient or the carer (odds ratio 8.83), polypharmacy (odds ratio 6.14) and INR values above the therapeutic range (odds ratio 1.08) on multivariate analysis.

A nested, prospective, case–control study which included 461 patients (200 men) aged 75 years or older (median age 79 years; age range 75–93 years), and 461 sex matched controls aged 70 years or younger (median age 61 years; age range 15–69 years), found that the rate of all bleeding events tended to be higher in the elderly, but this did not reach statistical significance (relative risk 1.44; 95% CI, 0.96–2.14; $p = 0.07$) (Palareti *et al.*, 2000). The incidence of bleeding increased with increasing INR (International Normalized Ratio, a standardized measure of the one-stage prothrombin time), and exponentially at INRs greater than 4.5. Fatal episodes of bleeding, which occurred in six patients and were all intracranial, were significantly higher in the elderly (relative risk, 6.4; 95% CI, 1.02–40.6 $p = 0.047$). In five of those patients the INR was 3.3 or more (range 3.3–5.9) at the time of the fatal bleed.

A further case–control study compared 170 patients (median age, 78 years) with nonvalvular AF who developed intracranial bleeding while on warfarin with 1020 matched controls (median age, 75 years) who were also receiving warfarin for nonvalvular AF but did not develop intracranial bleeding (Fang *et al.*, 2004). The risk of intracranial bleeding was found to be increased in patients aged 85 years or over (adjusted odds ratio, 2.5; 95% CI 1.3–4.7) and at INRs between 3.5 and 3.9 (adjusted odds ratio, 4.6; 95% CI, 2.3–9.4). The odds ratio for intracranial bleeding increased to 8.8 (95% CI 4.6–17) at INRs greater than 4 but INRs less than 2 were not associated with a decreased risk (adjusted odds ratio, 1.3; 95% CI, 0.8–2.2). The incidence of bleeding in the elderly has been shown to be higher in the first 90 days of anticoagulation both due to poor control of anticoagulation and to unmasking of an occult lesion (Palareti *et al.*, 2000).

The available evidence suggests that individuals over the age of 70 or 80 years are probably at a higher risk of intracranial bleeding. However, the incidence of this complication is still very low. Metanalysis of six AF trials of warfarin versus placebo, involving 2900 patients, showed an intracranial bleeding rate of 0.3% per year during anticoagulation and 0.1% per year in association with placebo (Hart *et al.*, 1999). Intracerebral hematomas account for 70% of intracranial bleeds associated with anticoagulation and are associated with a mortality rate of up to 60% (Hart *et al.*, 1995). Most of the remaining episodes are subdural hematomas which are less often fatal.

The elderly are more likely to be on multiple drugs which may interact with warfarin, resulting in higher INRs and thereby increasing the risk of intracranial bleeding. They are also more likely to have cerebrovascular disease, leukoaraiosis, and cerebral amyloid angiopathy which increase the risk of intracerebral bleeding. Poor mobility may predispose the elderly for recurrent falls which may increase the risk of both subdural and intracerebral bleeding.

An Outpatient Bleeding Risk Index has been shown to be successful in classifying patients into low, intermediate, and high-risk groups (Beyth *et al.*, 1998). The Index included four risk factors for major bleeding (attracting 1 point each in the index): age over 65 years, history of gastrointestinal bleeding, history of stroke, and one or more specific comorbid conditions (recent myocardial infarction, hematocrit of less than 30%, presence of diabetes mellitus, and serum creatinine of greater than 1.5 mg dl^{-1}). A score of zero indicated low risk, 1–2 was classified as medium risk, and a score of 3–4 was suggested to indicate high risk (23% in 3 months and 48% in 12 months). Although this may be a potentially useful tool in some circumstances, it automatically places all people aged over 65 years in the medium risk category which we believe is not always the case. It is important to recognize that underusage of anticoagulants should not be encouraged in elderly patients, since treatment has been shown to be highly effective in this group (Anon, 1994) (see the following text).

ANTICOAGULANTS ARE EFFECTIVE IN THE ELDERLY

Anticoagulants are as effective in the elderly patients as they are in younger ones, in the treatment of venous thromboembolism. Six studies of oral anticoagulation for the prevention of thromboembolic events in patients with nonvalvular AF, have shown a reduction in events in patients over a wide age range (Hart *et al.*, 1999). Adjusted-dose warfarin reduced stroke by 62% (95% CI, 48–72%). The absolute risk reduction for primary prevention was 2.7% per year and 8.4% per year for secondary prevention. The Danish Atrial Fibrillation, Aspirin, and Anticoagulant Therapy (AFASAK) Study included subjects with AF who were aged between 38 and 91 years, in whom anticoagulant therapy reduced the relative risk of stroke by 54% (Petersen *et al.*, 1989).

The Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) showed an 86% reduction in stroke in an elderly population (mean age 68 years) (The BAATAF Investigators, 1990). These studies have resulted in marked increase in the use of warfarin in the elderly.

THE RISK-BENEFIT EQUATION: HOW TO OPTIMIZE IT IN THE ELDERLY

The most important factors associated with risk of bleeding for patients on anticoagulants are: (1) degree of anticoagulation; (2) the presence of potential bleeding site; and (3) duration of anticoagulant therapy.

Degree of Anticoagulation

As discussed previously, several studies have reported a *log-linear* relationship between the degree of anticoagulation and the risk of bleeding (Horstkotte *et al.*, 1993; Figure 1). Thus, the bleeding risk rises threefold between INRs 2 and 3 and further threefold between 3 and 4 (Palareti *et al.*, 2000). Since a high INR is one of the most important factors determining the bleeding risk, dwarfing any possible age-related effects, it is essential that the lowest effective intensity of anticoagulation is maintained in the elderly.

In major studies of primary stroke prevention in nonvalvular AF, target INRs ranged from 1.5 to 4.5. There was no evidence that the most intensive anticoagulation reduced stroke risk more and it may well have increased bleeding

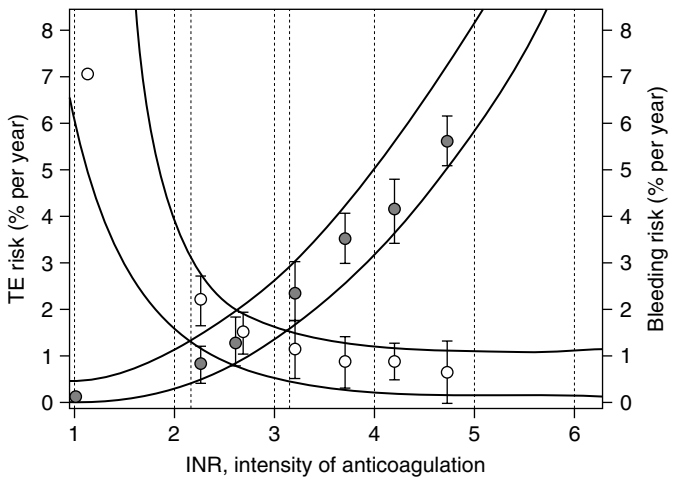

Figure 1 Relationship between intensity of anticoagulation and risk of thromboembolism (TE) and bleeding in 1865 patients receiving oral anticoagulants after insertion of St Jude prosthetic heart valves. The single open circle represents 12 patients who received only antiplatelet agents because of contraindications to warfarin therapy. INR = international normalization ratio (Reproduced by permission of The Journal of Heart Valve Disease)

risk. The higher intensities of anticoagulation used in the past may well have contributed to the reports of higher incidence of anticoagulation-related bleeding. The recommended ranges of anticoagulation for many indications have fallen over the recent years and this should improve the safety of anticoagulant therapy. A target INR of 2.5 is therefore generally recommended for treatment of venous thromboembolism besides primary and secondary stroke prevention in individuals with nonvalvular AF (British Society for Haematology, 1990). A higher intensity of anticoagulation may be needed under specific circumstances, such as prevention of thromboembolism in those with prosthetic heart valves, or those with recurrent thromboembolism.

PRESENCE OF POTENTIAL BLEEDING SITE

When bleeding occurs, it is usually from a pathological site, often in the bladder or bowel, or from an abnormal intracranial blood vessel. Even in apparently spontaneous bleeding (e.g. Into the skin), this may be related to the atrophic changes which occur with increasing age (Figure 2). As has been mentioned earlier, some episodes of hemorrhage may result in the discovery of potentially remediable (including malignant) lesions at an earlier stage than would otherwise have occurred. Certainly *all* patients who bleed should be investigated for underlying pathology, even if the bleeding episode occurred when the INR was excessive (Gitter *et al.*, 1995). Clinicians should also consider the possibility of occult bleeding in any patient with unexplained symptoms or signs while receiving warfarin. Alveolar hemorrhage may present with unexplained anemia or dyspnea, for example, (Papagiannis *et al.*, 1995). Retroperitoneal hemorrhage may also present diagnostic difficulties (Ivascu *et al.*, 2005).

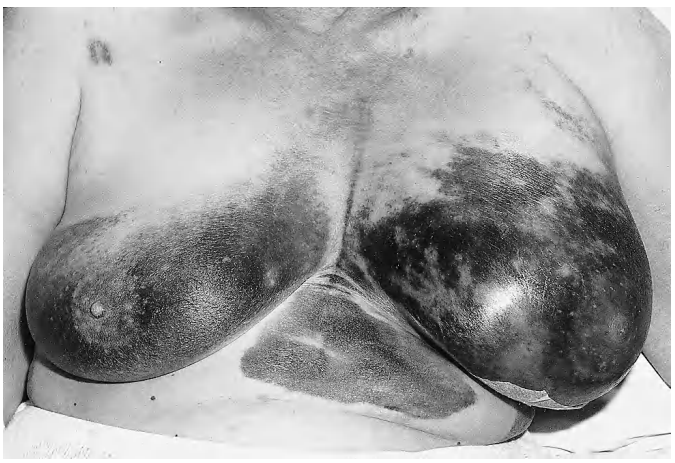

Figure 2 Severe bleeding into the breasts of a 70-year-old lady receiving warfarin after insertion of a prosthetic heart valve. More than 500 ml of blood was drained from the left breast and she was eventually controlled carefully between an INR of 2.5 and 3.0 without recurrence of bleeding

DURATION OF ANTICOAGULANT THERAPY

Many elderly patients are prescribed warfarin for stroke prevention in nonvalvular AF or to prevent thromboembolism from a prosthetic heart valve. Both these situations require long-term anticoagulation. A duration of 6 months is generally recommended for treatment of DVT and PE (British Society of Haematology, 1990). Long-term anticoagulation is also recommended in patients with recurrent DVT or PE. The decision about the duration of anticoagulation in a given patient will be dictated by the specific clinical circumstances in that particular individual, although the British Society of Haematology Guidelines are a helpful guide based on the available evidence.

The risk of bleeding continues as long as an individual is on anticoagulant therapy. As discussed earlier, the risk of bleeding is higher during the initial weeks and months of anticoagulation. One study, which included 712 patients with venous thromboembolism, found that the overall risk of serious hemorrhage was six per 1000 patient-months; all but nine such episodes occurred in the first month and none in the next 2 months (Research Committee of the British Thoracic Society, 1992). This early occurrence of significant proportion of major hemorrhage is supported by other studies (Palareti *et al.*, 2000). Therefore, close monitoring of elderly patients in the first month of anticoagulation is essential.

Perhaps, the most difficult time is during initiation of anticoagulants. Because of their sensitivity to warfarin, the elderly may be excessively anticoagulated at this time, particularly if standard rather than tailored induction doses are used. The original tailored regimen (Fennerty *et al.*, 1988) used a first dose of 10 mg, adjusted thereafter according to the INR, which was measured daily. Siguret *et al.* (2005) have since devised a regimen for patients aged over 70 years. This involved giving 4 mg daily for 3 successive days and was shown to be safe and accurate in elderly hospitalized patients.

CONCLUSIONS

Anticoagulants are now widely used in elderly patients. The view that they are lethal drugs in the elderly has been shown to be unjustified (Joglekar *et al.*, 1988). The introduction of INR, downward revision of therapeutic ranges and the production of guidelines for initiation and maintenance therapy have helped to improve the risk-benefit equation positively (Fennerty *et al.*, 1988). The use of computer-assisted anticoagulation and near-patient INR testing are likely to improve monitoring of anticoagulation even further (Shetty and Routledge, 1998). Education of patients and carers on important aspects of anticoagulant therapy is likely to improve the control of anticoagulation and compliance. A small study of compliance (nonadherence or concordance) found no decline in compliance in elderly ambulant patients (Kumar *et al.*, 1989). However, depression was related

to greater nonadherence at all ages in patients receiving warfarin after valve replacement (El-Gatit and Haw, 2003)

A careful analysis of risk versus benefit in every patient before commencing anticoagulant therapy is likely to minimize the incidence of serious complications. Most importantly, careful monitoring to maintain the lowest effective INR, to avoid dangerous drug interactions, and to detect and manage hemorrhagic complications promptly will further enhance the benefits of anticoagulants in the elderly.

KEY POINTS

- The elderly are more prone to venous and arterial thromboembolism.
- Aging is associated with increased sensitivity to anticoagulants.
- Intracranial hemorrhage is more likely to occur in individuals aged 75 years or over.
- The risk of all hemorrhage is greatest in the first month after commencement of anticoagulation, but nevertheless persists throughout the course of treatment.
- The risk of all hemorrhage increases disproportionately with increasing intensity of anticoagulation.
- Nevertheless, when they are used appropriately, anticoagulants are highly effective drugs in the elderly.

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41

Myelodysplasia

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INTRODUCTION

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by dysplasia, ineffective hematopoiesis, and potential risk of transformation into acute leukemia (Greenberg, 1983). These disorders are sporadic and arise *de novo* or may result following toxin, radiation, and chemotherapy exposure (Levine and Bloomfield, 1992). MDS primarily affects older patients, and has a median age of onset of 65 years, with an increased incidence with advancing age (Aul *et al.*, 1998). Disease onset prior to the sixth decade is uncommon, though not unheard of, especially with treatment-related or secondary MDS. As the demographics in developed countries have shifted toward older patient populations because of increased longevity and better quality of health care and more people are receiving intensive chemotherapy, it is likely that the prevalence of MDS will increase.

MDS may easily be overlooked in elderly patients. It can present simply as a chronic macrocytic anemia, and there may be a tendency to "leave well enough alone" in an older patient with multiple comorbidities. However, our understanding of MDS continues to improve. Better therapies are being developed for the treatment of these disorders. Thus, it is important to carefully evaluate any cytopenia in older patients.

Epidemiology and Clinical Presentation

The exact incidence of *de novo* MDS remains unclear, but appears to be greater than the incidence of acute myelogenous leukemia (AML) (Aul *et al.*, 1992). In one study, the annual incidence per 100 000 was estimated to be 15 for ages 60–69 but increased to 89 for those >80 years of age (Williamson *et al.*, 1994). The median age is approximately 65 years and has a slight male predominance (French Registry, 1987; Foucar *et al.*, 1985).

The incidence of therapy-related myelodysplasia is also increasing. Therapy-related MDS can result from prior exposure to ionizing radiation or chemotherapy. Prior exposure to alkylating agents is associated with the highest risk of MDS and has very distinct cytogenetic abnormalities, such as loss of the long arm of chromosomes 5 and/or 7. The risk for developing therapy-related MDS or AML has been described in long-term survivors of cancers treated with semustine (methyl-CCNU). The actuarial risk in patients treated for Hodgkin's disease is between 6 and 9% and 17% for patients treated for multiple myeloma. The risk of developing MDS increases with the use of regional radiation therapy following treatment for common cancers such as breast, small cell lung cancer, and testicular cancer. Topoisomerase II inhibitors such as epipodophyllotoxins and anthracyclines have also been associated with therapy-related AML, however usually without an MDS prodrome and commonly involve chromosomal abnormalities such as 11q23, 3q26, and 21q22 (Pedersen-Bjergaard and Philip, 1991).

The clinical presentation of MDS is varied. Symptoms, for the most part, are nonspecific and depend upon the number and severity of cytopenias present. Patients with anemia may have profound symptoms of dyspnea on exertion, fatigue, lethargy, malaise, dizziness, and even angina (Greenberg, 1983). Neutropenic patients may develop severe systemic infections, and infection represents a primary cause of death in many cases of MDS (Pomeroy *et al.*, 1991). Increased infection risk may be a result of neutrophil dysfunction based on impaired chemotaxis and/or microbial killing (Pomeroy *et al.*, 1991; Boogaerts *et al.*, 1983). However, T-cell function is thought to remain intact, and thus, patients with MDS less commonly develop viral or mycobacterial infections in the absence of treatment with immunosuppressive agents (Pomeroy *et al.*, 1991). Other symptoms may include easy bruising or bleeding, a common manifestation of thrombocytopenia and dysfunctional platelets.

The physical findings of MDS are likewise nonspecific and usually reflect underlying cytopenias if present.

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Of note, patients with chronic myelomonocytic may have splenomegaly, unlike patients with other subtypes of MDS.

DIAGNOSIS

Blood and Bone Marrow Examination

MDS is diagnosed in patients with one or more cytopenias and depends upon the finding of dysplastic features within the bone marrow. A peripheral blood smear is helpful in demonstrating a normocytic or a macrocytic anemia, but alone is insufficient for diagnosis. In order to make the diagnosis, a bone marrow aspirate and biopsy are required. An aspirate is necessary to evaluate morphology, quantitate the number of myeloblasts, as well as assess for cytogenetic abnormalities. A core bone marrow biopsy is used to assess the bone marrow cellularity, which is typically hypercellular and indicative of ineffective hematopoiesis in the setting of peripheral cytopenias.

The morphologic features of red-cell precursors in the bone marrow aspirate include megaloblastic (asynchronous maturation of the nucleus and cytoplasm) or binucleate or multinucleated cells. Ring sideroblasts may also be identified. These are red-cell precursors with iron-laden mitochondria, and are defined by the presence of five or more Prussian blue-staining iron granules encircling more than one-third of the nucleus in more that 15% of the erythroblasts. Erythroid hyperplasia may also be prominent and is associated with ineffective erythropoiesis (a hallmark of MDS), while pure red-cell aplasia or hypoplasia is rarely observed (Williamson *et al.*, 1991).

Abnormalities in the myeloid series can include a left-shift with a predominance of immature myeloid cells, hypogranulation, and hypolobulation of the nucleus in mature granulocytes. A classic finding is the presence of psuedo-Pelger-Huet cells, which are granulocytes with a bilobed nucleus in a *pince-nez* configuration. Most importantly, a typical feature in the bone marrow of MDS patients is the presence of myeloblasts. The proportion of myeloblasts has diagnostic as well as prognostic information (see the following text) and is important in differentiating AML from MDS.

The megakaryocytes may likewise be dysplastic and may have not only a quantitative but also a qualitative defect. Examination of the peripheral smear may reveal giant or agranular platelets. In the bone marrow, the megakaryocytes may be small and hypolobulated.

Dysplasia in the bone marrow is not sufficient to establish the diagnosis of myelodysplasia. Deficiencies of vitamin B_{12} and folate, hypothyroidism, viral infections such as Epstein-Barr virus (EBV) and the human immunodeficiency virus, and exposure to antibiotics and other chemicals such as ethanol, chemotherapy, and benzene can result in dysplasia. These other causes must be ruled out systematically by a careful history, physical, and laboratory examination.

Cytogenetics

A critical component of the bone marrow aspiration is the cytogenetic examination of the bone marrow, which may help not only to establish the diagnosis but also to yield important prognostic information (see following text). Roughly, 60% of patients with MDS have a normal karyotype, but the presence of a common cytogenetic abnormality may establish the diagnosis in difficult cases (Heaney and Golde, 1999). In addition, new cytogenetic abnormalities may document an evolution to a more clinically aggressive state (i.e. transformation to acute leukemia). The sensitivity of cytogenetic analysis has been greatly increased by the utilization of fluorescent *in situ* hybridization (FISH), which uses specific DNA probes to rapidly identify individual chromosomes in hundreds of cells and does not depend upon cell division. The drawback of this approach is that the analysis is restricted to already known and well-established cytogenetic abnormalities.

One series found that cytogenetic abnormalities were more common in the advanced stages of MDS of refractory anemia with excess blasts (RAEB) and refractory anemia with excess blasts in transformation (RAEB-T) compared to the less advanced MDS subtypes (Bernasconi *et al.*, 1994). The more common abnormalities are trisomy 8 as well as deletions of the long arms of chromosomes 5, 7, 11, 13, and 20. Complex karyoptypes, defined as three or more cytogenetic abnormalities, are a finding in 15% of cases, and confer a poor prognosis (Bernasconi *et al.*, 1994). A sole abnormality involving deletion of 5q is commonly seen in patients with refractory anemia, and represents a distinct clinical syndrome, the "5q- syndrome". This syndrome, seen most often in elderly women, is characterized by a prolonged clinical course, which does not typically progress to acute leukemia. The anemia is typically profound, but neutropenia is usually mild and platelets are typically elevated (Van den Berghe *et al.*, 1974; Boultwood *et al.*, 1994). Recurrent chromosomal translocations involving the platelet-derived growth factor receptor-B (PDGFR-B) have been identified in 5–10% of patients with chronic myelomonocytic leukemia (CMMoL) (Wlodarska *et al.*, 1995; Golub *et al.*, 1994). It must be understood that a normal karyotype does not exclude the diagnosis of MDS and is seen in approximately half of the cases of MDS.

Therapy-related MDS is also associated with specific chromosomal abnormalities. In particular, partial or complete loss of chromosomes 5 or 7 have been seen after exposure to alkylator therapy, while patients exposed to topoisomerase II inhibitors typically present with a monocytic leukemia without antecedent MDS, and typically have rearrangements of the mixed lineage leukemia gene located on 11q23 (Super *et al.*, 1993).

Pathogenesis

MDS is the result of a neoplastic transformation of the myeloid stem cell (Janssen *et al.*, 1989). The exact events that lead to transformation are still poorly understood, but

result in clonal hematopoiesis. Ineffective hematopoiesis is the hallmark of MDS and explains why patients will present with cytopenias, but have a hypercellular marrow. Kinetic studies using primary bone marrow samples from patients with MDS demonstrate a high rate of cell division, based on the incorporation of labeled thymidine into DNA (Raza *et al.*, 1997). Compounding this, the rate of apoptosis or programed cell death is also increased in MDS, which leads to a high rate of cell turnover but decreased production of mature hematopeoietic elements (Rajapaksa *et al.*, 1996; Mundle *et al.*, 1996). Interestingly, apoptosis is increased in early MDS, while in the later or more advanced stages of MDS, there is decreased apoptosis (Raza *et al.*, 1995; Shetty *et al.*, 1996). It is hypothesized that this may be part of the mechanism responsible for the transformation from MDS to AML.

In MDS, there is not only a quantitative defect in cells but also a qualitative defect in terminally differentiated cells. Studies have demonstrated decreased maturation of cells, as well as functional defects. Red-cell precursors in patients with MDS are less sensitive to the stimulus of erythropoietin (EPO); neutrophils have decreased microcidal activity; and platelets may also be functionally defective despite normal numbers (Greenberg, 1983; Hoefsloot *et al.*, 1997; Ruutu *et al.*, 1977; Russell *et al.*, 1979).

Classification

The current term MDS was adopted by the French, American and British (FAB) Cooperative Group in 1976 in their classification scheme of these disorders, but over this past century, many terms have been used to describe these syndromes including preleukemia, oligoleukemia, hematopoeietic dysplasia, and subacute or smoldering leukemia (Block *et al.*, 1953; Rheingold *et al.*, 1963; Saarni and Linman, 1973; Linman and Bagby, 1978; Dreyfus, 1976). Many classification schemes have been proposed in order to better subdivide and define the groups within these syndromes. In 1982, the FAB consensus conference devised five categories of myelodysplasia on the basis of morphologic criteria derived from bone marrow aspirates (Table 1). This classification scheme has improved the diagnosis of myelodysplasia and serves as a general predictor of prognosis. However, within the groups there still is a considerable variability in terms of overall survival, and transformation to acute leukemia. In general, patients with more bone marrow blasts (RAEB and RAEB-T) were noted to have a poorer prognosis with a decreased median survival and an increased risk of progression to AML, but 15% of patients with RA still progressed to AML (Sanz *et al.*, 1989).

The WHO classification was proposed as a modification of the FAB system (Harris *et al.*, 1999; see Table 2). Notably, the criteria for AML were lowered from 30% blasts in the bone marrow to 20% blasts, which eliminated the category of RAEB-T of the FAB classification. In addition, CMMoL has been removed from the MDS category and placed within the myeloproliferative disorders. A new category was also proposed, termed *refractory cytopenia with trilineage dysplasia* (RCTD), allowing patients with dysplasia on bone marrow aspirate but who present with an isolated cytopenia other than anemia to be classified as MDS.

Table 1 FAB classification of MDS

Type	Bone marrow blasts	Other features
RA	<5	<1% peripheral blood blasts, no Auer rods and no ringed sideroblasts
RARS	<5	<1% peripheral blood blasts, no Auer rods, and >15% ringed sideroblasts
RAEB	5–20	<5% peripheral blasts, no Auer rods, may have ringed sideroblasts
CMMoL	<20	<5% peripheral blasts, no Auer rods, >1000/mcl monocytes
RAEB-T	21–30	>5% peripheral blats, or Auer rods present

RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; CMMol, chronic myelomonocytic leukemia; RAEB-T, refractory anemia with excess blasts in transformation.

Prognosis

Several prognostic systems have been devised to better predict the outcome of individual patients. The most widely used

Table 2 WHO classification and criteria of MDS

Type	Peripheral blood	Bone marrow
RA	Anemia No blasts	Erythroid dysplasia only <5% blasts <15% ringed sideroblasts
RARS	Anemia No blasts	Erythroid dysplasia only <5% blasts >15% ringed sideroblasts
RCMD	Bi-or pan-cytopenia No/rare blasts No Auer rods Monocytes <1000/mcL	Dysplasia in >10% of cells in two or more myeloid cell lines No Auer rods <15% ringed sideroblasts <5% blasts
RAEB-1	Cytopenias <5% blasts No Auer rods	Unilineage or multilineage dysplasia 5–9% blasts No Auer rods
RAEB-2	Cytopenias 5–19% blasts Auer rods may be present	Unilineage or multilineage dysplasia 10–19% blasts Auer rods
MDS-U	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes No Auer rods <5% blasts
5q- syndrome	Anemia <5% blasts Platelets normal or increased	Normal to increased megakaryocytes with hypolobulated nuclei No Auer rods <5% blasts del (5q) only

RA, Refractory anemia; RARS, Refractory anemia with ringed sideroblasts; RCMD, Refractory cytopenia with multilineage dysplasia; RAEB-1, Refractory anemia with excess blasts-1; RAEB-2, Refractory anemia with excess blasts-2; MDS-U, MDS-unclassified.

Table 3 International Prognosis Scoring System (IPSS) in MDS

	Score				
Variable	0	0.5	1.0	1.5	2.0
% BM blasts	<5	5–10		11–20	21–30
Karyotype[a]	Good	Intermediate	Poor		
Cytopenias[b]	0/1	2/3			

Source: From Greenberg P. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997; **89, (6)**; 2079–2088. Copyright American Society of Hematology, used with permission.
[a]Karyotype definitions: Good: −Y, −5q, −20q, normal; Poor: chromosome 7 abnormalities, or complex karyotypes (3 or more abnormalities); Intermediate: All others. [b]Cytopenia definitions: Hemoglobin $<10\,g\,dl^{-1}$; Absolute neutrophil count <1800/μl, Platelet count <100 000/μl.

and accepted is the International Prognostic Scoring System, from the International Myelodysplastic Syndrome Risk Analysis Workshop (Greenberg *et al.*, 1997; see Table 3). In this analysis based on 800 patients, the important predictors for overall prognoses were cytogenetic abnormalities, the percentage of myeloblasts in the bone marrow, and the number of lineages that exhibited cytopenias. Favorable cytogenetics includes the loss of the Y, 5q, or 20q chromosomes or the presence of a normal karyotype. Adverse cytogenetic changes were those with three or more cytogenetic abnormalities or any abnormalities involving chromosome 7. Number scores are attributed to each variable, thus dividing patients into four categories on the basis of the sum of scores for each variable. The median survival for the categories were 5.7, 3.5, 1.2, and 0.4 years for the low, intermediate-1, intermediate-2, and high-risk groups, respectively (Greenberg *et al.*, 1997). The time for 25% of the patients in each of the four risk groups to evolve into acute leukemia was 9.4, 3.3, 1.1, and 0.2 years, respectively. This classification schema is a very useful prognostic information for patients and counseling regarding treatment options such as hematopeoietic stem cell transplantation.

Other factors that have been associated with prognosis include mutation or loss of heterozygosity of the tumor suppressor gene *p*53, CD34 positivity of bone marrow cells, increased expression of the Wilms' tumor gene (WT1), increased serum beta-2 microglobulin, mutation in the *FLT3* gene, and abnormal localization of immature precursors (Christiansen *et al.*, 2001; Shih *et al.*, 2004; Gatto *et al.*, 2003; Cilloni *et al.*, 2003; Verburgh *et al.*, 2003).

Treatment

The management of patients with MDS requires the consideration of several variables, including comorbidities, patient age, severity of cytopenias, as well as the fact that the older patient population in general do not tolerate or respond to conventional therapy. The treatment for MDS is divided into two categories, high and low intensity. High-intensity treatment in general requires hospitalization, and includes intensive chemotherapy and hematopoietic stem cell transplant. In contrast, low intensity is defined as treatments that can be performed as an outpatient, including hematopeoietic growth factors, differentiation agents, low-intensity chemotherapy, and transfusion support. Key factors in determining high- versus low-intensity treatment are a patient's age, performance status, as well as their IPSS score. High-intensity therapies are usually considered for patients <60 years old who have good performance status and who fall into the intermediate-2 or high-risk categories. High-intensity treatment may be considered for the patients >60 years old who have good performance status and who are in the higher risk categories, but generally patients >60 years of age are considered for low-intensity therapy. Patients >60 years of age in the low or intermediate-1 category are usually considered for supportive care or low-intensity therapy.

SUPPORTIVE CARE

Transfusion Support and Iron Overload

Central to the management of all patients with MDS is supportive care. Supportive care includes the treatment with antibiotics for infection and transfusion support for anemia and thrombocytopenia. In order to lessen isoimmunization, viral infections, and febrile transfusion reactions, leukoreduced and irradiated products are encouraged. In some cases, patients may receive well over 50 units of packed red blood cells. With each unit of blood containing 250 mg of iron, patients may develop iron overload. High levels of iron may lead to secondary hemachromatosis and its resultant hepatic, pancreatic, gonadal, and cardiac adverse effects (Kushner *et al.*, 2001). Iron chelation with deferoxamine (Davis and Porter, 2002) may be administered to these patients; however, this therapy is difficult. Deferoxamine only chelates roughly 25 mg of iron per day, must be administered subcutaneously, and can lead to chronic skin irritation and cataracts. Moreover, as many patients with MDS rarely live long enough to develop the complications of iron overload, orally available agents are being developed as an alternative to deferoxamine (Merson and Olivier, 2002).

In addition to requiring periodic red blood cell transfusions, some patients with more advanced MDS may have severe chronic thrombocytopenia with associated bleeding. This can be life-threatening if significant bleeding occurs in the brain or gastrointestinal tract. Platelet transfusions can be given, but should be given judiciously as many patients become alloimmunized and then fail to respond to subsequent platelet transfusions (TRAP, 1997). Similar to red blood cell transfusions, platelets should be irradiated (ICSGHEMS, 1998; TRAP, 1997).

Growth Factors

Hematopoietic growth factors, such as recombinant human granulocyte colony-stimulating factor (G-CSF), recombinant

human granulocyte-macrophage colony-stimulating factor (GM-CSF), and recombinant human EPO, are an important adjunct to supportive care of patients with MDS. Both G-CSF and GM-CSF result in an 80–90% increase in circulating neutrophils in phase II trials (Negrin *et al.*, 1990; Negrin *et al.*, 1989; Antin *et al.*, 1988; Ganser *et al.*, 1989). However, a phase III trial G-CSF in MDS did not demonstrate a survival benefit or a reduction in infections with their use (Greenberg *et al.*, 1993). Furthermore, the median survival of patients with RAEB receiving G-CSF was 10 months versus 21 months for those in the observation arm. Of note, the treatment arm had more high-risk and poor-prognosis patients according to the IPSS than the observation arm, which may in part explain this difference. At present, the myeloid growth factors should only be used as a single agent in a neutropenic patient with recurrent infections.

Recombinant EPO has also been used for the treatment of anemia in MDS. The serum EPO level is usually elevated in MDS patients, nonetheless, approximately 25% of patients with MDS respond to treatment with doses on the order of 40 000 units per week. EPO tends to have the greatest effect in patients with low transfusion requirements and low base-line serum EPO levels (Rose *et al.*, 1995; Hellstrom-Lindberg, 1995). Response to EPO may take time. In one study, response rates more than doubled from 12 to 26 weeks; thus, a long trail of the agent is generally required. The combination of EPO and G-CSF has been shown to increase the hematocrit and the number of circulating neutrophils, and the combination may be synergistic. A large randomized trial found that despite the improvement in hematologic parameters with combined growth factor support, there was no quality-of-life improvement or benefit compared to supportive care alone (Casadevall *et al.*, 2004). Thus, this strategy is not widely accepted.

Currently, there is no platelet growth factor clinically available. Thrombopoeitin is the endogenous hormone responsible for maintaining normal platelet counts. A pegylated derivative, megakaryocyte growth and development factor (MGDF), has been tested as an adjunct to supportive care in patients with AML induction therapy (Archimbaud *et al.*, 1999; Schiffer *et al.*, 2000). Its use did not decrease bleeding complications or reduce platelet transfusions in AML. Furthermore, when tested in healthy volunteers, it resulted in antiplatelet antibodies and thrombocytopenia, halting further development of this compound. Low doses of recombinant human interleukin-11, a thrombopoietic cytokine, have been tested in patients with MDS and bone marrow failure (Kurzrock *et al.*, 2001). Five of 11 evaluable patients with MDS had an increase of platelet counts with a median duration of 12–30 weeks. Side effects even at low doses included fluid retention, peripheral edema, conjunctival injection, and myalgias.

Pyridoxine, Androgens, Vitamins

The rationale for the use of pyridoxine in MDS is the potential improvement in ineffective erythropoiesis. Pyridoxine is a nontoxic cofactor required for heme biosynthesis, and is usually given for 3 months in patients with anemia from MDS, but responses are rare. There is no clear role for androgens, danzaol, or vitamins in the therapy of MDS.

Immunosuppressive Therapy

In the past, it was not uncommon to treat MDS patients with corticosteroids. Given the immunosuppression associated with the steroids, their routine use is not recommended, though they may result in transient improvement in cytopenias. There is evidence that patients with hypocellular bone marrows (i.e. hypocellular MDS) have an immune or T-cell-mediated process (Iwase *et al.*, 1995; Sugawara *et al.*, 1992; Smith and Smith, 1991). In these patients, treatment with horse or rabbit antithymocyte globulin, a treatment commonly used for aplastic anemia, has been found to be effective, with response rates upward of 50% (Molldrem *et al.*, 2002). Patients who typically respond are young, have low platelet counts and HLA-DR 15 histocompatibility antigen (Sauntharajah *et al.*, 2002). Although originally it was thought that only those with hypoplastic MDS would respond, it now seems clear that bone marrow hypoplasia is not a requirement for response (Killick *et al.*, 2003).

Differentiating Agents

Differentiating agents, such as phenylbutyrate, hexamethylene bisacetamide, and all-trans retinoic acid (ATRA) have been used with the rationale that these agents may promote cellular differentiation. ATRA used as a single agent has a response rate of only 10% (Visani *et al.*, 1995), while when used in combination with interferon alpha and G-CSF resulted in two complete responses in 17 patients with low-risk MDS (Hofmann *et al.*, 1999). Although phenylbutyrate (Gore *et al.*, 2002) and hexamethylene bisacetamide (Andreeff *et al.*, 1992) were associated with some responses, they were difficult to deliver, which hampered their further development in MDS.

The discovery that changes in DNA methylation and histone modifications are present and may play a pathogenic role in many cancers as well as MDS led to the use of small molecules that disrupt this process and hence promote hematopoietic maturation. Azacitidine (5-axaciticine, 5-aza, Vidaza) is a pyrimidine nucleoside analog of cytidine, whose mechanism of action is thought to be DNA hypomethylation in addition to a direct cytotoxic effect on the hematopoietic elements of the bone marrow. A phase III clinical trial comparing azacitidine to best supportive care in 191 patients with MDS demonstrated a 60% response rate in those patients who received azacitidine subcutaneously for 7 days every 28 days (Silverman *et al.*, 2002). The benefit of azacitidine was seen in all risk groups of MDS patients. Complete and partial response rates were 23% versus zero percent for the azacitidine and the supportive care arms, respectively.

The median time to leukemic transformation or death was 21 versus 13 months, respectively. In addition, there was a companion, quality-of-life analysis that demonstrated azacitidine to be superior to supportive care (Kornblith *et al.*, 2002). However, as crossover was allowed in this study, it is very difficult to draw conclusions regarding overall survival. Nonetheless, this regimen is well tolerated, and can be administered on an outpatient basis. Major side effects include nausea and vomiting, as well as myelosuppression. As of 2004, azacitidine is Food and Drug Administration (FDA) approved for use in MDS and is widely available.

A molecule chemically related to azacitidine, decitabine, also has promise as an agent for MDS. A phase II trial performed in Europe (Wijermans *et al.*, 2000) demonstrated that decitabine has significant activity in MDS. In this multicenter trial of 66 patients with MDS, decitabine was given at 15 mg/m2 IV over 4 hours every 8 hours for days 1, 2, and 3, with cycles repeating every 6 weeks. With this schedule, the overall response rate was 25, 48, and 64% for those in the intermediate-I, intermediate-II and high-risk groups, respectively. The median survival time from the start of treatment for the high-risk patients was 1.2 years, compared to an expected survival of 0.5 years. In addition, 31% of patients with abnormal pretreatment cytogenetics had major cytogenetic responses. Toxicity associated with this drug includes fever, infection, sepsis, neutropenia, anemia, and thrombocytopenia. A large phase III trial of decitabine versus best supportive care has been performed and preliminary results presented. In this North American trial of patients with advanced MDS, 89 received decitabine (Saba *et al.*, 2004). There was a 25% response rate, with 10% complete and 15% partial responses, 11% of patients had hematologic improvement, and median time to response was 100 days. Long-term follow-up for this trial is still needed, but decitabine appears to be a potent agent in the treatment of MDS. In an attempt to decrease the toxicity associated with this agent, an alternative schedule for prolonged exposure has been explored and had a demonstrated efficacy of 65% in patients with hematologic malignancies in a phase II trial (Issa *et al.*, 2004).

In addition to demethylating agents, compounds that inhibit histone deacetylase activity are potential therapeutic agents in MDS. These include depsipeptide, Subamrilic acetic acid (SAHA), and valproic acid, all of which are in various stages of clinical development (Klisovic *et al.*, 2003; Kuendgen *et al.*, 2004; Pilatrino *et al.*, 2005). Histone deacetylase inhibitors promote gene transcription by promoting acetylation of histones, which in turn helps "unravel" the DNA and promote transcription. *In vitro* valproic acid inhibits histone deacetylase activity and is synergistic with ATRA in inducing differentiation of primary leukemic cells. In a small study from Germany, 18 patients with MDS were treated with valproic acid (Kuendgen *et al.*, 2004). Responses were seen in eight patients (44%) treated with valproic alone, one of which was a partial remission. Median response duration was 4 months. Five patients were treated with valproic acid in combination with ATRA and none responded. However, four patients who initially responded to valproic acid alone and then relapsed were retreated with the combination of valproic acid and ATRA, and two had responses.

Thalidomide and Derivatives

In myelodysplasia, vascular endothelial growth factor is thought to play an important pathologic role. Thus, thalidomide, an antiangiogenic drug, was tested in a phase II trial for MDS at 100 mg escalating to 400 mg (Raza *et al.*, 2001). Of the 80 patients enrolled, 51 patients completed 12 weeks of therapy and of these 15 achieved red blood cell transfusion independence or a >50% decrease in transfusion requirements, but few responses were seen in platelets or white blood cells. Those who tended to respond have low-grade MDS. Furthermore, thalidomide is poorly tolerated secondary to side effects of constipation, somnolence, and peripheral neuropathy.

More potent thalidomide analogs are currently in clinical development. Perhaps one of the more promising agents in MDS is lenalidomide. In a recently published phase I trial in MDS patients (patients with transfusion-dependent anemia, not responsive to EPO, absolute neutropenia count >500 per cubic millimeter and platelet count >10 000 per cubic millimeter, and not treatment-related MDS), 56% of patients had a response; 20 patients achieved transfusion independence. The response was highest in patients with the clonal interstitial deletion involving chromosome 5q31.1 (5q). Nine of 12 patients with this chromosomal abnormality achieved a complete cytogenetic response (List *et al.*, 2005b). Phase II trials in patients with and without 5q- have been closed and preliminary results presented in abstract form (List *et al.*, 2005a). For the Phase II studies, patients had to have low or intermediate risk MDS, be transfusion dependent, have platelets >500 000 per cubic millimeter, and an absolute neutrophil count greater than 500 per cubic milliliter. One hundred and forty-eight patients with 5q- were enrolled and transfusion independence was achieved in 64% of patients (defined as >56 days without a red blood cell transfusion in addition to a 1 gm per deciliter increase in hemoglobin). Pathologic complete remission was documented in 31 of 110 evaluable patients, and even after a median follow-up of 9.3 months, the median duration of response has not yet been achieved. Nine patients progressed and 12 had disease complications including neutropenia. The most common adverse events were neutropenia and thrombocytopenia in approximately 35% of patients, which necessitated an interruption of dose or dose decrease. Thus, lenamolimide is a very promising agent in low-risk MDS, though its use in high-risk MDS is uncertain.

Farnesyl Transferase Inhibitors

Farnesyl transferase inhibitors are another potential therapeutic agent for patients with MDS. These agents may target the Ras MAP-kinase pathways by inhibiting the farnesylation of signal transduction proteins including ras and

others. Transforming ras mutations are frequently found in MDS as well as in other cancers (Neubauer *et al.*, 1994). There are several farnesyl transferase inhibitors in various stages of clinical development, to be used alone as well as with other agents. A phase II trial of R115777 (Zarnestra; Johnson and Johnson Pharmaceutical Research and Development, Raritan, NJ) dosed at 600 mg twice daily in 28 patients with all subtypes of MDS demonstrated a modest effect, with two complete remissions and one partial remission. However, the dose was poorly tolerated with side effects of myelosuppression, neurotoxicity, and rash, requiring a dose reduction or discontinuation in 11 of 27 patients. Of note, all of the responses occurred in patients who were dose reduced to 300 mg twice daily (Kurzrock *et al.*, 2004).

Intensive Therapy

Induction Chemotherapy. For the most part, intensive and aggressive antileukemic chemotherapy as is used for AML has not been as effective when used in patients with MDS. In a retrospective study from the MD Anderson Cancer Center, outcomes with AML induction regimens was compared with those treated for AML, RAEB, and RAEB-T (Estey *et al.*, 1997). This study demonstrated that patients with MDS (RAEB or RAEB-T) did equally as poorly or as well as those with AML after controlling for age and cytogenetics (Estey *et al.*, 1997). No data is available regarding the benefit of postremission consolidation with high-dose ara-C in these patients, as older adults with AML do not benefit from this intensive approach as do younger adults with *de novo* AML (Stone *et al.*, 2001; Mayer *et al.*, 1994). The lack of benefit for intensive chemotherapy in these patients is due to the decreased capacity to tolerate intensive chemotherapy. Furthermore, the stem cell defect in MDS occurs in a very early or proximal stem cell, which is more likely to be resistant to chemotherapy due to the overexpression of the multidrug resistance p-glycoprotein (MDR-1). This protein acts to confer resistance to chemotherapy. Several studies using modulators of MDR-1 plus standard induction regiments for AML have been done in patients with advanced MDS or AML from MDS in order to circumvent this mode of resistance. In one study, quinine was used as an MDR modulator in combination with mitoxantrone and cytarabine, which resulted in a 52% complete response rate in those patients who expressed the p-glycoprotein compared to 18% for those patients who did not receive the quinine (Wattel *et al.*, 1998). In another study using PSC833, no difference was seen in remission rates or overall survival between those who did and did not receive the MDR modulator (Greenberg *et al.*, 2004).

Hematopoietic Stem Cell Transplantation

Because the defect in MDS occurs in an early hematopoietic precursor, allogeneic transplant represents a potentially curative option. Many studies have suggested that low-risk MDS as well as those with high-risk disease experience a long-term disease-free survival from a matched related donor allogeneic transplant (Sierra *et al.*, 2002; Nevill *et al.*, 1998; Appelbaum and Anderson, 1998). Unfortunately, many patients do not have this option of treatment either because of age, comorbidity, or lack of a sibling donor. The use of nonmyeloablative or reduced intensity conditioning in older patients is growing. This treatment modality seeks to maximize the immune effect of graft versus leukemia while minimizing the toxicity associated with ablative conditioning regimens. Nonmyeloablative transplantation has a low short-term mortality rate in patients with MDS up to age 70–75, however, the long-term data on efficacy are still immature (Alyea *et al.*, 2005).

KEY POINTS

- MDS is diagnosed in patients with one or more cytopenias and depends upon the finding of dysplastic features within the bone marrow.
- The bone marrow biopsy provides important diagnostic as well as prognostic information in the quantification of blasts and cytogenetic profile, which make up a significant part of the International Prognosis Scoring System (IPSS).
- 60% of patients with MDS will have a normal karyotype.
- The WHO classification scheme has redefined the FAB category of RAEB-t (>20% blasts) as AML.
- Therapy is risk adapted based on age, comorbidities and IPSS score.

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Management of Leukemia in the Elderly

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INTRODUCTION

Acute leukemias are clonal disorders of the hemopoietic (acute myeloblastic leukemia, AML) or lymphopoietic (acute lymphoblastic leukemia, ALL) system, leading to accumulation of immature cells in the bone marrow and in the peripheral blood and depletion of normal blood elements. The incidence of both AML and ALL increase with aging (Lichtman and Rowe, 2004; PUi *et al.*, 2004). Though these disorders are relatively rare and are commonly managed by a specialist in neoplastic diseases, the geriatrician may play a central role in the diagnosis, in the selection of patients who may benefit from aggressive treatment, and in the administration of supportive care. This chapter provides a frame of reference for clinical decisions in elderly patients with acute leukemias.

ACUTE MYELOBLASTIC LEUKEMIA

The discussion of AML in the elderly is linked to the discussion of myelodysplastic syndromes (MDS) (Langston *et al.*, 2004), a number of preleukemic conditions that appear to be involved in more than 50% of cases of AML in patients aged 60 and older.

Biology of AML and MDS

A brief review of hemopoiesis may help understand pathologic manifestations and current treatment strategies of AML and MDS. Hemopoiesis is a hierarchical process that leads to the formation of mature blood elements from a pluripotent hemopoietic stem cell (PHSC) (Balducci, 2003) (Figure 1). From the PHSC, early hemopoietic progenitors, committed to the myeloid (colony forming unit-colony, CFU-C), the erythroid (burst forming unit-erythroid, BFU-e) and the megakaryocytic series are derived and from these the differentiated precursors of the circulating blood elements originate. The PHSC may become committed to different hemopoietic lines and has a large self-replicative potential, and low proliferation rate. The early progenitors may differentiate only into one line and have more limited self-replicative potential and higher proliferation rate than the PHSC. Differentiated precursors have high proliferative rate and very limited self-replication. PHSC and committed progenitors are indistinguishable from lymphocytes at light microscopy. Their existence may be demonstrated by special culture techniques or by flow cytometry. Commitment, differentiation, and maturation are modulated by a number of cytokines, including the granulocyte colony-stimulating factor (G-CSF) and erythropoietin (epo), and require an intact stroma able to home the stem cells and the progenitors and to turn off and on the production of hemopoietic cytokines.

In AML, a clone of hemopoietic cells loses the ability of maturing while acquiring increased proliferation. As a result of this combination of events, the neoplastic clone of cells undergoes a continuous expansion at the expense of normal hemopoiesis. The final result is increased concentration of immature cells (blasts) in the bone marrow and in the circulation, and deficit of normal blood elements. Increased concentration of blasts in the circulation may lead to obstruction of small blood vessels (leukostasis) resulting in bleeding and ischemia, while reduced concentration of neutrophils, red blood cells, and platelets is responsible for increased risk of infections, hypoxia, and hemorrhages, respectively.

More than half of the cases of AML in individuals over 60 show evidence of abnormal maturation of more than one cell line, suggesting that they are preceded or accompanied by MDS. In MDS, the predominant hemopoietic defect is an arrest of normal maturation, with accumulation of abnormal (dysplastic) hemopoietic precursors in the bone marrow.

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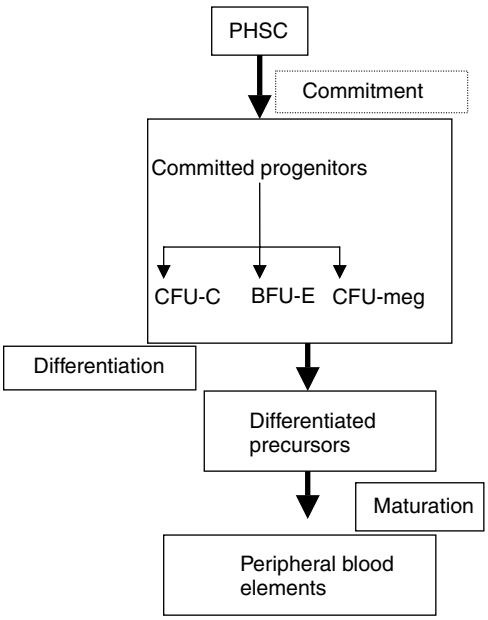

Figure 1 A summary view of hemopoiesis

The main pathologic manifestations of MDS are those of pancytopenia.

The main treatment strategy for the management of AML is the destruction of the neoplastic clone with cytotoxic chemotherapy, and for MDS, the induction of normal maturation of dysplastic precursors, which may be obtainable with hemopoietic cytokines, angiogenesis inhibitors, and DNA methyl-transferase inhibitors. The distinction between AML and MDS is not airtight, especially in older individuals. For some forms of AML (hypoplastic AML) in which dysplastic changes predominate, the best treatment may consist of transfusion of blood elements and hemopoietic cytokines, rather than cytotoxic chemotherapy.

The destruction of the neoplastic clone by cytotoxic chemotherapy may be complete if the neoplastic changes have occurred in the committed progenitors. As long as the PHSC is not affected, it is possible to eliminate the sick hemopoietic branch and expect restoration of normal hemopoiesis. When the PHSC itself is involved by neoplastic changes, however, the treatment is rarely successful, as the root itself of the hemopoietic tree is sick. This unfortunately is the situation in MDS and in the majority of AML occurring in individuals over 60.

AML: Clinical Presentation and Prognosis

The most common clinical manifestations of AML are caused by pancytopenia and may include fatigue, dyspnea on exercise and at rest, infections due to staphylococcus, gram-negative organism, and certain fungi such as candida, aspergillus, and mucor, whose incidence is more common in the presence of neutropenia. Manifestations of leukostasis are rare and may include confusion, dyspnea, and coronary ischemia.

Table 1 WHO classification of acute myeloid leukemias

Acute myeloid leukemia with recurrent genetic abnormalities
Acute myeloid leukemia with t(8;21) (q22;q22)
Acute myeloid leukemia with abnormal bone marrow eosinophils and inv(16) (p13;q22) or t(16;16) (p13;q22)
Acute promyelocytic leukemia (APL) with t (15;17) (q22;q12)
Acute myeloid leukemia with 11q23 abnormalities
Acute myelogenous leukemia with multilineage dysplasia
Acute myelogenous leukemia following MDS or myeloproliferative disorders (MPD);
Acute myeloid leukemia without antecedent MDS/MPD, but with dysplasia in at least 50% of cells in 2 or more lineages
Acute myeloid leukemia and MDS, therapy related
Related to alkylating agents
Related to topoisomerase II inhibitors (anthracyclines, etoposide)
Acute myelogenous leukemia not otherwise categorized

The diagnosis is established by examination of the bone marrow: by definition of the WHO, the diagnosis of AML is established when the percentage of blasts in the bone marrow is 20% or higher (Vardiman *et al.*, 2002; Winton and Langston, 2004). Generally, the bone marrow of patients with AML is hyperplastic, but in a small number of cases it is hypoplastic. Hypoplastic AML has a more indolent course and reduced sensitivity to chemotherapy (Nagai *et al.*, 1996). The management of choice is support with transfusion of blood elements (Baudard *et al.*, 1999).

In 1974, a panel of general experts had proposed a morphological classification of AML, that has prognostic value. Though it is still used, this classification has been all but superseded by the new classification proposed by the WHO, that takes into account cytogenetic findings and the presence of multilineage dysplasia, which indicates involvement of the PHSC and poorer prognosis (Table 1). Cytogenetic is the single most important prognostic factor. The AML with recurrent genetic abnormalities have the best prognosis with a 5-year survival higher than 50% with cytotoxic chemotherapy. Unfortunately, the prevalence of poor cytogenetic patterns, associated with myelodysplasia, increases with the age of the patient (Lichtman and Rowe, 2004). Other important information is obtained from flow cytometry. The expression of the CD-34 marker indicates a very immature neoplastic cell, whereas the CD-56 indicates multidrug resistance. The expression of the CD-33 marker indicates that AML may be susceptible to gemtuzumab ozogamicin (mylotarg) (Giles *et al.*, 2003). Cytogenetics and flow cytometry should be routinely performed in patients with AML.

Treatment

The mainstay treatment of acute myelogenous leukemia is cytotoxic chemotherapy, which involves two major steps: remission induction and postremission treatment (Lichtman and Rowe, 2004; Winton and Langston, 2004). Remission induction is generally obtained by combination of an anthracycline and cytarabine, aimed to produce marrow aplasia,

followed in approximately three to four weeks by regeneration of a new marrow. By definition, remission involves normal peripheral blood counts and less than 5% blasts in the bone marrow. The risk of infections and bleeding is highest during remission induction; as many as 30% of older individuals may die of these complications prior to obtaining a complete remission. Postremission treatment is necessary to prevent relapse, and includes consolidation with cytarabine in high doses. The need of postconsolidation treatment is controversial: in individuals younger than 60, with a related donor, allogeneic stem cell transplant is recommended, though the benefits of this approach has never been conclusively demonstrated. Other authors advocate the use of prolonged, low dose treatment, called *maintenance* (Lichtman and Rowe, 2004). Older individuals have reduced tolerance for cytarabine in high doses due to high incidence of cerebellar toxicity (Cova and Balducci, 2004). The inability to deliver cytarabine in full doses may be responsible for the poorer outcome in individuals over 60 (Mayer *et al.*, 1994).

A special case is represented by AML with 15–17 translocation or acute promyelocytic leukemia (APL). This form of AML has certain unique characteristics that include the following.

- ATRA (all-trans-retinoic acid) should be part of the treatment, as this agent in combination with chemotherapy was shown to improve the duration of remission and the possibilities of cure.
- Cytarabine is not necessary for remission induction or consolidation.
- Marrow aplasia is not necessary to obtain a complete remission.
- Patient who relapse may be sensitive to treatment with arsenic trioxide.
- More than 50% of patients can be cured.
- Disseminated intravascular coagulation (DIC) may be part of the clinical presentation.

The diagnosis of APL warrants an attempt to treatment in virtually all patients unless they are actively dying of another disease. If the patient appears too frail to receive chemotherapy, remission induction with ATRA may be attempted (Winton and Langston, 2004).

The majority of patients with AML who obtain a remission, especially older patients, will experience a recurrence after a period that may last between six months and two years.

Treatment options include:

- Reinduction with the same treatment regimen.
- Induction with different treatment regimens, including mitoxantrone and etoposide or topotecan.
- Reinduction with mylotarg, a monoclonal antibody directed to the CD-33 antigen and bound to ricin toxin. Mylotarg has been associated with a 20–30% response rate. It should be noticed, however, that this compound is associated with substantial myelotoxicity, as the CD-33 antigen is expressed in the majority of the hemopoietic lines. In addition, mylotarg is associated with increased risk of deep vein thrombosis (Giles *et al.*, 2003).
- New treatment options are explored in older patients with AML. These include the use of a farnesyl transferase inhibitor (FTI) (Lancet and Karp, 2003), which may induce a response with minimal myelotoxicity, the use of mylotarg for remission induction (Giles *et al.*, 2003), and the use of drugs that may reverse the resistance to chemotherapy, such as cyclosporine and its derivatives (Baer *et al.*, 2002). Of these strategies, the FTI appears as the most promising.

Supportive care plays an important role in the management of older patients in AML especially in the period of time that precedes the regeneration of new bone marrow after induction of aplasia. General principles of supportive care include:

- Myelopoietic growth factors (GM-CSF and G-CSF) appear to reduce the duration of neutropenia and the risk and severity of neutropenic infections after remission induction and consolidation. Most authors would recommend the use of these compounds (Rowe and Liesveld, 1997).
- Prophylactic platelets transfusions are indicated when the platelet counts drops below 10 000/μl, to prevent spontaneous intracranial hemorrhages. When refractoriness to random platelet transfusion develops, transfusion of crossmatched and eventually of HLA matched platelets is indicated. Platelet refractoriness is defined as failure to increase the platelet counts of more than 5000/μl 1 hour after transfusion (Tummouth and Friedman, 2003).
- Red blood cell transfusions are indicated when the hemoglobin drops below 8 gm dl^{-1} (10 gm dl^{-1} in patients with coronary artery disease) or when the patient has dyspnea at rest and the hemoglobin level is lower than 12 gm dl^{-1} (Petrides, 2003).
- Proper management of infections may be life saving. Upon development of temperature $>100.6\,^{\circ}F$, patients should be hospitalized, cultures from the blood, sputum, urine, and throat obtained and broad-spectrum antibiotic coverage instituted immediately to cover gram-negative intestinal organisms, pseudomonas aeruginosa, and staphylococcus aureus. If fever persists after 48 hours and no pathogen is isolated, fungal and viral coverage should also be instituted (Green, 2004).
- All patients with AML receiving cytotoxic chemotherapy should also receive prophylaxis against hyperuricemia with allopurinol and urine alkalinization. In patients at high risk of hyperuricemia due to elevated blast counts in the peripheral blood or in the bone marrow, pretreatment with uricase is indicated (Holdsworth and Nguyen, 2003).

The decision to institute treatment with cytotoxic chemotherapy is based on different considerations that include the following:

- Because of compromise in general conditions and poor prognosis AML, the prognosis is poorer for older patients

than for the younger ones. Only 10% of acute leukemics receiving induction treatment were found alive one year after treatment institution (Litchman and Rowe, 2004). The benefits and risks of treatment should be assessed based on the patient's general conditions and on the expected course of AML.

- Patients with good prognosis cytogenetics stand a chance of being cured and at least an attempt to treatment is recommended. In the presence of cardiovascular morbidity that prevents the use of anthracyclines, cytarabine as a single agent is a reasonable option.
- Patients whose blast count is increasing rapidly are at high risk of dying of leukostasis and an attempt to lower their white blood cell counts is reasonable. The initial manifestations of leukostasis may be seen for a blast count $\geq 50\,000/\mu l$ and are common for a count $> 100\,000/\mu l$. Leukostasis may be temporarily prevented with leukapheresis, high doses of hydroxiurea and intermittent administration of cytarabine at intermediate doses ($500\,mg\,m^{-2}$ of body surface areas).
- Patients with hypoplastic AML benefit most from supportive care of transfusion of blood products. In some conditions, especially when dysplasia is present, a trial of erythropoietin and myelopoietic growth factors may be beneficial.

Diagnosis and Treatment of MDS

The WHO has provided a new classification of MDS (Table 2) according to clinical findings and prognosis (Langston *et al.*, 2004; Howe *et al.*, 2004). According to the percentage of blasts in the bone marrow, MDS are considered low and high grade. Of the low grade, MDS with isolated del 5q, RA, and refractory anemia with ringed syderoblasts (RARS) have the best prognosis, the lowest risk or leukemic transformation, and the more prolonged survival. Refractory anemia with excess blasts 1 (RAEB-1) presents with 5–10% blasts and Refractory anemia with excess blasts 2 (RAEB-2) with 10–20% blasts in the bone marrow.

Table 2 WHO classification of MDS

Low-grade myelodysplasia (<5% blasts in the bone marrow)	Refractory Anemia (RA) Refractory Cytopenia with Multilineage Dysplasia (RCMD); Myelodysplastic syndrome, unclassified (MDS-U) MDS with isolated del (5q) Refractory anemia with ringed syderoblasts (RARS) Refractory cytopenia with multilineage dysplasia and ringed syderoblasts (RCMD-RS)
High-grade myelodysplasia (5–20% blasts in the bone marrow)	Refractory anemia with excess blasts 1 (RAEB-1) Refractory anemia with excess blasts 2 (RAEB-2)

The initial manifestations of MDS are related to pancytopenia and include dyspnea, infections, and bleeding. In the majority of cases, MDS are asymptomatic at presentation and are recognized because complete blood counts obtained for unrelated reasons reveal anemia or pancytopenia.

The diagnosis of MDS is confirmed by the presence of typical cytogenetic abnormalities in the bone marrow and of dysplastic changes in the hemopoietic precursors. The presence of ringed syderoblasts supports the diagnosis of RARS or Refractory cytopenia with multilineage dysplasia and ringed syderoblasts (RCMD-RS). Ringed syderoblasts result from the accumulation of iron in the mitochondria and are due to a deficit in the production of the heme ring of hemoglobin, which is synthesized in the mitochondria. As the mitochondria surround the nucleus, the accumulation of iron in these organelles appears as a blue ring around the nucleus, with blue-Prussian stain. Cytogenetics is abnormal in less than 50% of cases, however, and ring syderoblasts are found in less than 5% of cases of MDS. Most often, MDS is a diagnosis of exclusion. The anemia may be normo or macrocytic and is always hypoproliferative (i.e. with low reticulocyte count). Important differential diagnosis include B12 deficiency, that is present in at least 5% of individuals aged 60 and older and is due to decreased absorption of food B12 from gastric achloridria and reduced secretion of proteolytic enzymes (Balducci, 2003), and this condition is completely reversible by B12 supplementation.

The diagnostic workup includes examination of the bone marrow, with cytogenetics. In the majority of cases (approximately 80%) the marrow is hyperplastic. In the presence of hypoplastic marrow, a diagnosis of aplastic anemia should be entertained, a condition that may be ameliorated with the combination of antithymocite globulines (ATG) and cyclosporine (Bennett, 2003).

Cytogenetics is essential for the prognosis of MDS. The presence of 5q- abnormality is diagnostic of a very indolent form of anemia, with low risk of leukemic transformation, whereas multiple cytogenetic abnormalities purport high risk of leukemia and shortened survival. Other important prognostic elements include percentage of blast in the bone marrow and number of hemopoietic lines involved. The International Prognostic Scoring System (IPSS) combines these prognostic parameters into a single prognostic score, predictive of survival and leukemic transformation (Table 3) (Greenberg *et al.*, 1997).

Treatment of MDS

The only potentially curative treatment of MDS at present is allogeneic bone marrow transplantation, an option not available to individuals aged 60 and older. Other forms of treatment that have shown some efficacy include hemopoietic growth factors, angiogenesis inhibitors, and DNA methyltransferase inhibitors.

Of the hemopoietic growth factors, erythropoietin and darbepoietin have improved the anemia and reduced the need

Table 3 International Prognostic Scoring System (IPSS) for MDS

A. Scoring system				
Score	0	0.5	1	1.5
Bone marrow blasts	<5%	5–10%	–	10–20%
Karyotype	Good (normal, -Y;5q-)	Intermediate	Poor (≥abnormalities; chromosome 7 abnormalities)	–
cytopenias	0–1	2–3	B.	C.

B. Prognostic groups based on IPSS			
Total score	Risk group	Median survival (years)	Median time 25% evolution to AML (years)
0	Low	5.7	9.4
0.5–1	Intermediate	3.5	3.3
1–2	High	1.2	1.1

of red blood cell transfusions in 20–30% of cases. These agents seem to be particularly effective in low-grade MDS and when the levels of endogenous erythropoietin are less than 500 mU ml^{-1} (Langston *et al.*, 2004). The addition of G-CSF may double the response to erythropoietic agents, especially in patients with ringed sideroblasts. The evidence that G-CSF and GM-CSF may reduce the risk of neutropenic infections in MDS is inconclusive, but these compounds may be helpful in individual cases.

Of the inhibitors of angiogenesis, thalidomide, and the experimental agent CC5013 (Revimid) have shown activity in improving peripheral blood counts, especially in low-grade MDS (Dredge *et al.*, 2003). In a recent presentation at the American Society of Clinical Oncology, Revemid was reported superior to placeboin causing hematologic and cytogenetic remission in patients with low risk MDS. (List A *et al.*, 2005.)

Methyl-transferase inhibitors include the nucleoside analogues 5-azacytidine (5-AZA) and decitabine, both of which have shown activity in single arm studies. In a randomized controlled study comparing 5-AZA and supportive care in 191 patients, 5-AZA produced a 60% response rate (vs. 5% in the control group) prolonged the median survival (18 vs. 11 months) and the median time to leukemic progression (21 vs. 13 months). To note, 77% of patients had high-grade MDS (Silverman *et al.*, 2002).

Promising experimental agents include arsenic trioxide, farnesyl transferase inhibitors, and receptor tyrosine kinase inhibitors.

Treatment recommendations may be so summarized:

- In patients with low-grade MDS in need of blood transfusions, erythropoietic growth factors, erythropoietic growth factors in combination with G-CSF and thalidomide may be used in this sequence. If all these forms of treatment fail, a trial of DNA methyl-transferase inhibitors may be considered.
- In patients with high grade MDS, methyl-transferase inhibitors should be considered as front-line treatment, and if these fail, experimental treatment may be considered. Angiogenesis inhibitors represent a lesser toxicity option for these patients.
- The majority of patients with MDS is at risk of iron overload from multiple blood transfusions. This complication may be minimized by concomitant administration of a chelating agent (desferoxiamine).

ACUTE LYMPHOID LEUKEMIAS

The classification of ALL involves B and T cell ALL, and among these two major groups several subgroups are identified according to the degree of maturation of the neoplastic lymphopoietic precursors (PUi *et al.*, 2004). As in the case of AML, cytogenetics represents the most powerful prognostic indicator. Of interest, specific genetic abnormalities are associated with specific sensitivity or lack thereof to chemotherapy and may be used to direct the treatment in individual patients (PUi *et al.*, 2004). For example, hyperdiploidy is associated with increased sensitivity to methotrexate, while t (9,22) with sensitivity to imatinib (Tomas *et al.*, 2004).

Though the prevalence of negative prognostic factors increases with age, about 40% of adults with ALL are free of disease at 5 years.

The clinical presentation of ALL is similar to that of AML and is related to pancytopenia, while leukostasis is less common.

The mainstay treatment is chemotherapy and the case of B cell ALL involves generally four drugs: steroids, l-asparaginase, anthracyclines, and vincristine. The best results have been obtained with multidrug combinations of chemotherapy, including cytarabine and methotrexate, and intrathecal chemotherapy for the prevention of meningeal leukemia (PUi *et al.*, 2004). In most forms of ALL, prolonged maintenance treatment appears beneficial.

The management of older individuals with ALL should be based on individual life expectancy and treatment tolerance, and on the aggressiveness of the disease. As general principles:

- in patients with life expectancy of 1–2 years and smoldering ALL, supportive care only with transfusion of blood products is reasonable;

- in patients with limited life expectancy and more aggressive disease it is reasonable to use a combination of steroids, vincristine, and an anthracycline to induce a remission and to treat the patient as needed;
- it is reasonable to recommend standard multidrug treatment in patients with more prolonged life expectancy, including central nervous system (CNS) prophylaxis, in the attempt to induce a prolonged remission.

CONCLUSIONS

The incidence of AML increases with age. The prognosis of this condition is generally worse with age due to increased prevalence of resistance to chemotherapy, poor cytogenetics, and to poorer tolerance of cytotoxic chemotherapy. In a small percentage of patients, the treatment may be curative or lead to prolonged survival: these include individuals with favorable cytogenetics or with the M3 subtype of AML. In the other individuals, cytotoxic chemotherapy is associated with significant morbidity and mortality and should be used mainly for palliative purposes, in patients who are symptomatic from rapidly increasing white blood cell counts. Hypoplastic AML has generally an indolent course and may be managed with blood transfusion and occasionally hemopoietic growth factors.

AML in older individuals is preceded by myelodysplasia in about 60% of cases; until recently the treatment of MDS was supportive. New drugs including methylation inhibitors (5-azacytidine) and angiogenesis inhibitors (thalidomide) may delay the progression of MDS and prolong the survival of these patients.

KEY POINTS

- AML in elderly individuals has high prevalence of unfavorable characteristics and is preceded by MDS in 60% of cases.
- Treatment of AML may be curative in older individuals in presence of favorable cytogenetics (t8,22;i16; t15,17) or in presence of M3. In all other cases, the main benefit of chemotherapy appear palliative.
- New promising drugs in AML in the elderly include mylotarg, a monoclona antibody bound to the ricin toxin, and farnesyl transferase inhibitors.
- MDS is several-fold more common than AML in older individuals. Management of MDS in addition to transfusion of blood products or hemopoietic growth factors may include methylation and angiogenesis inhibitors.
- ALL is rare in older individuals: the management is the same as in younger patients, but the prognosis is poorer.

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PART III

Medicine in Old Age

Section 4

Cardiovascular Disease and Health

Principles and Practice of Geriatric Medicine, 4th Edition. Edited by M.S. John Pathy, Alan J. Sinclair and John E. Morley.
 ISBN 0-470-09055-3

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Epidemiology of Heart Disease

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INTRODUCTION

Until recently, much cardiological expertise and effort has been directed toward middle-aged males not dissimilar in social class and origin to their clinical investigators. Unfortunately, as in middle age, heart disease is also a leading cause of death in late life. Heart disease in older adults is not, however, like that in younger adults, excepting that it occurs in older people. Risk factor profiles are different, as is disease presentation, response to prevention and response to treatment. The interaction with other comorbidities is often of great clinical importance. In this chapter, we shall highlight a number of these differences, with two of the chief being that heart disease in late life is increasingly a women's health issue, and that heart disease and the condition of frailty are intricately linked. Indeed, age itself is not as important as other factors, such as comorbidities and level of function.

The number of very old people worldwide is increasing, as is their relative proportion in the general population. With this increase comes an increase in the absolute number of people with chronic diseases. The Western world is experiencing a somewhat slow and orderly transition from a population with primarily acute diseases to one with primarily chronic diseases. The developing world is going through this transition much more quickly, and will soon be in the unenviable position of having a large population of older adults with chronic diseases, while also experiencing a burden of acute diseases similar to the current state. Throughout the following discussion, the reader must remember that, whatever the situation in the developed world, it is direr in the developing world.

ISCHEMIC HEART DISEASE (*see* Chapter 46, Ischemic Heart Disease in Elderly Persons)

Incidence and Outcomes

Ischemic heart disease is a leading cause of death worldwide. Although mortality rates and incidence rates are decreasing, the absolute burden of the disease is increasing, as more people live to later ages. The oldest women are not yet experiencing a decline in their rates of death (Table 1). Because of their increasing numbers, the absolute number of deaths among the oldest-old is increasing. In Canada, the absolute number of admissions to hospital for myocardial infarction increased by 13% between 1994 and 1999, but increased by over 50% for those 90 and older.

Older adults are more likely to die after myocardial infarction, both short and long term, compared with younger adults, with those over 85 having mortality rates close to one-third on the day of the event, with 1-year mortality also being approximately one-third (Rasmussen *et al.*, 2004). This compares with rates of approximately 15% and less than 5% in patients younger than 65. Mortality rates with myocardial infarction have decreased dramatically over the past two decades, with, for example, the rates of 1-year mortality in Danish men aged 35–64 dropping from 8 to 3%. Older men have not experienced the same benefit, with the rate in Danish men 85 years and older being stagnant at 36 versus 35%. In Denmark and Sweden, older women have slightly lower mortality rates than older men, and their rates have been decreasing over time. Women aged 65–74 have higher mortality rates than men of the same age (Rasmussen *et al.*, 2004). In Olmsted County in the United States, the incidence of myocardial infarction and other indicators of coronary artery disease is decreasing in men and younger people, but increasing in women and older people (Figure 1) (Arciero *et al.*, 2004).

RISK FACTORS

INTERHEART, a landmark cardiovascular study, was published in 2004. Much of the following discussion will flow from it. INTERHEART was a large case-control study of myocardial infarction conducted worldwide (Yusuf *et al.*, 2004). One potential weakness, when considering our aims, is that subjects were mostly recruited from coronary care units.

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Table 1 Mortality associated with myocardial infarction in Canada, by age, male

	1989		1995		1999	
	Rate[a]	Number	Rate[a]	Number	Rate[a]	Number
90+	2260	509	2106	601	2036	661
85–89	1873	1090	1593	1138	1542	1331
80–84	1472	1924	1181	1968	1023	1817
75–79	1039	2491	793	2145	657	2137
70–74	734	2476	484	2037	404	1807
65–69	463	2213	311	1636	262	1442
60–64	298	1678	207	1233	154	935

Mortality associated with myocardial infarction in Canada, by age, female

	1989		1995		1999	
	Rate[a]	Number	Rate[a]	Number	Rate[a]	Number
90+	1652	1046	1564	1272	1575	1478
85–89	1266	1524	1136	1723	1019	1837
80–84	897	1999	718	2020	597	1794
75–79	553	1906	427	1672	348	1614
70–74	325	1421	224	1207	170	926
65–69	170	976	128	753	97	581
60–64	91	558	66	408	48	303

[a]crude rate/100 000.
Source: Disease Surveillance On-Line, Government of Canada.

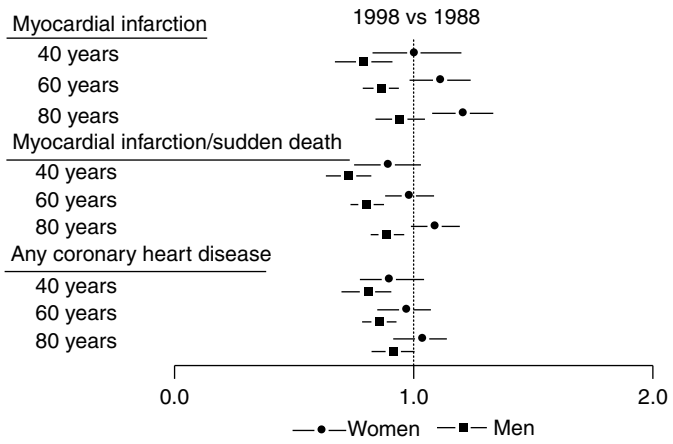


Figure 1 Change in incidence of heart disease by sex and age (Reprinted from *American Journal of Medicine*, V117, Arciero TJ *et al.*, Temporal Trends in the incidence of coronary disease, pp 228–33, Copyright 2004, with permission from Excerpta Medica, Inc.)

The oldest and most frail patients with acute myocardial infarction often never reach these units, being cared for in general units, or perhaps even at home. This study also shows that almost all of the population's attributable risk for heart disease, worldwide, in men and women, can be explained by the traditional modifiable risk factors. Risk factors in old age are outlined in Table 2.

Age

Age is often cited as an important risk factor for many conditions, and certainly for heart disease, the incidence and mortality rises with age. Simply saying that age is a risk factor for a condition is intellectually lazy, and not always helpful. In various analyses, age is often used as a shorthand for many unmeasured exposures, and the importance of age often diminishes in more fully specified models.

Table 2 Clinical risk factors for ischemic heart disease in late life

Strong	Weak
Age	Alcohol
Smoking	Psychosocial distress
Diabetes mellitus	Being a caregiver
Hypertension	Orthostatic hypotension
	Exercise
	Diet (lack of fruits/vegetables/fiber)
	Cholesterol

Another feature of age that must always be considered is whether the condition is aging-related or age related. Aging-related means that the condition becomes more common with age, and so is likely related to wear-and-tear, or degeneration. Age related, on the other hand, means that specific conditions are most common in specific age ranges. This implies that there is something about the changes occurring at that period in one's life that increases the risk of that condition. With regard to heart disease, the most obvious age-related disease is congenital heart disease, but other conditions, such as rheumatic heart disease, are also age related. Some cardiac diseases currently considered to be aging-related may in the future be discovered to be age related. A similar situation occurs with Alzheimer's disease, where it seems that the risk associated with apolipoprotein E does not inexorably increase with age, but rather decreases after the 9th decade.

Finally, age is a limited indicator of one's health and physical condition. Investigators from the Canadian Study of Health and Aging compared measures of chronological age with biological age, and found that biological age was a much better predictor of outcomes than chronological age (Mitnitski *et al.*, 2002).

Having said all this, age is universally recognized as a risk for heart disease. In the INTERHEART study, most of the following risk factors were still important in the older subjects, though the magnitude of associated risk was less than in younger subjects (Yusuf *et al.*, 2004).

Blood Pressure (*see* Chapter 48, Hypertension)

Hypertension continues to be a major risk factor in late life, there being seemingly no threshold beneath which blood pressure is "safe" (Lewington *et al.*, 2002). Although some studies suggest that the effect is attenuated in late life, the population burden is high, as the prevalence of hypertension increases dramatically with age. Potential treatment benefits, both individually and as a society, are much greater for older adults (Wong *et al.*, 2003). The presence of hypertension may lose some of its negative effect in late life (Abbott *et al.*, 2002; Casiglia *et al.*, 2002), though this is not a consistent finding (Yusuf *et al.*, 2004).

Hypertension is common in old age, with 60–70% of people over the age of 65 having hypertension, about two-thirds of this is isolated systolic hypertension (Fagard, 2002), which is particularly common among older women. The reporting of the difference between the systolic and diastolic pressure, the pulse pressure, is becoming a popular method of assessing systolic hypertension. The evidence on which to base treatment decisions has not, however, been developed with pulse pressure in mind.

In an old and frail nursing home population (mean age 86, 35% 2-year death rate), no blood pressure value, (systolic, diastolic, mean arterial pressure, or pulse pressure) was related to cardiovascular events over 2 years of follow-up (Askari *et al.*, 2004). The authors also looked at change in blood pressure and death, and again found no relation, which argues against heterogeneity from a preterminal decline as a confounder in their analysis. Blood pressure may lose its importance among the very frail. Orthostatic hypotension, common in frail older adults, may also increase the risk of myocardial infarction (Luukinen *et al.*, 2004).

Finally, some studies suggest that low blood pressure may increase mortality in older adults (Farnett *et al.*, 1991), and others suggest that antihypertensives may be associated with falls (Cumming *et al.*, 1991). Although these findings relate more to comorbidities, and most antihypertensives are safe (Boutitie *et al.*, 2002; Greenberg, 2003, Leipzig *et al.*, 1999), they scare many clinicians off treating hypertension in older adults. Isolated systolic hypertension itself may be an explanation for a diastolic J-curve (Kannel *et al.*, 2004). Perhaps considering biological age, and the degree of frailty, could help clinicians make more rational and defensible decisions.

Cholesterol (*see* Chapter 53, Pathogenesis of Atherosclerosis)

The data on lipids is still somewhat controversial, with some epidemiological studies suggesting that lipids are not risk factors in older subjects (Simons *et al.*, 2001). Longitudinal data from the Framingham study shows elevated cholesterol to still be a major risk factor among men over the age of 80, though not among women at that age (Figure 2) (Lloyd-Jones *et al.*, 2003). Other longitudinal data agree with this (Abbott *et al.*, 2002). Certainly, lower lipids in early life are protective against late-life disease (Strandberg *et al.*, 2004). Even in very functionally impaired nursing home residents, elevated low-density cholesterol is associated with cardiovascular disease (Suryadevara *et al.*, 2003). It will likely take randomized controlled trials in very elderly subjects to clarify this issue.

Some of the controversy may relate to the increased risk of mortality with low lipid levels in frail older adults. This may well be an early biochemical sign of a terminal decline, and should not be allowed to muddy the waters of the relationship between elevated cholesterol and heart disease (Onder *et al.*, 2003; Hu *et al.*, 2003).

Figure 2 Effect of cholesterol on risk of heart disease at age 80. Bottom line total cholesterol <200, middle 200–239, top >240. LR20 = lifetime risk of 20% (Reproduced by permission from Lloyd-Jones DM *et al.*, Lifetime risks of coronary heart disease by cholesterol at selected ages, Archives of Internal Medicine, **163**, pp 1966–72, Copyright 2003, American Medical Association. All rights reserved)

Diabetes

Twenty-year follow-up of women from the Nurses' Health Study in the United States found that diabetes was a major risk factor for fatal cardiac disease and for all-cause mortality, independent of other risk factors (Hu *et al.*, 2001). Diabetes retains its negative effects in late life (Abbott *et al.*, 2002). The INTERHEART study found diabetes to be a risk at all ages, in every part of the world, and to a greater extent in women (Yusuf *et al.*, 2004).

Smoking (*see* Chapter 14, Smoking in the Elderly)

Smoking continues to be a risk factor in late life (Abbott *et al.*, 2002; Yusuf *et al.*, 2004). The population-attributable risk is less in women, reflecting the lower prevalence of smoking in today's elderly women compared to elderly men. With teenage girls taking up smoking much more enthusiastically than their male peers, this situation may reverse in the future. Older smokers may be more likely to stop, to set an example for younger members of the family. Much of the last few decades' reduction in heart disease mortality can be attributed to reductions in smoking (Unal *et al.*, 2004).

Alcohol (*see* Chapter 15, Alcohol Use and Abuse)

As has been well publicized, to the delight of many, moderate alcohol use may protect against ischemic heart disease (Wells *et al.*, 2004). In the INTERHEART study, its effect was weak compared to other modifiable risk factors, but more pronounced in women (Yusuf *et al.*, 2004). Alcohol use was one of the factors in that study that did not have consistent effects by region, not being beneficial in the Middle East, South Asia, or South America. A Danish longitudinal study

found that changes in alcohol consumption were reflected by the expected changes in risk (Gronbaek *et al.*, 2004), though other studies have not found this result (Wannamethee and Shaper, 2002). The effect of alcohol may be reduced in the oldest-old (Abbott *et al.*, 2002).

Exercise

Degree of physical activity may be more protective in women than men (Yusuf *et al.*, 2004). Some work suggests that the effect of exercise may diminish with age (Abbott *et al.*, 2002). Regardless of this, any physical activity is better than none (Lee *et al.*, 2003a), and even the frailest and sickest of patients can exercise (Mallery *et al.*, 2003).

Obesity and Diet

The effect of current obesity may be reversed in the oldest-old, with the heaviest subjects having the lowest risk (Figure 3) (Abbott *et al.*, 2002). This may be due to other conditions or frailty affecting the lighter subjects. Even in the INTERHEART study, where the population was relatively young, abdominal obesity was not a risk factor for women over the age of 65. Other factors, such as waist circumference, may be more important than body mass index (Kanaya *et al.*, 2003). Diet is also protective, with fruits, vegetables, and fiber, all exerting positive effects (Yusuf *et al.*, 2004; Mozaffarian *et al.*, 2003). Fat intake may not be harmful in old age (Jakobsen *et al.*, 2004).

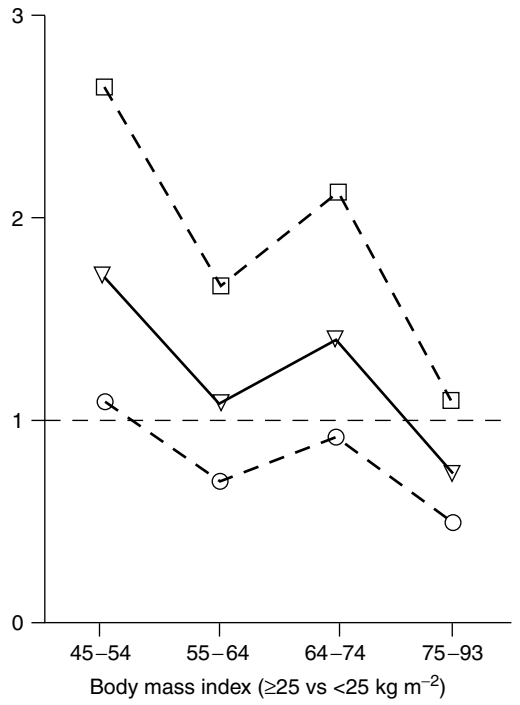


Figure 3 Effect of body mass index and age on 6-year percent incidence of coronary heart disease. + = 75–93, □ = 65–74, ↓= 55–64, ∇ = 45–54 (Reprinted from *Annals of Epidemiology*, V12, Abbott RD *et al.*, Age related changes in risk factor effects on the incidence of coronary heart disease, pp 173–81, Copyright 2002, with permission from Elsevier)

Hormones

Although estrogen and its replacement has long been of interest in the prevention of heart disease in women, more recent epidemiological evidence does not support this (Lawlor *et al.*, 2002). Certainly, the treatment trials seem to have laid this question to rest (Rossouw *et al.*, 2002), (Anderson *et al.*, 2004). With the loss of interest in estrogen, researchers are turning to the possible effects of testosterone and its supplementation (Liu *et al.*, 2003).

Genetics

The genetics of heart disease is becoming a focus of attention. The first gene identified for a family with an autosomal dominant pattern of coronary artery disease is MEF2A (myocyte enhancer factor-2) (Wang *et al.*, 2003). Most of the members of this family presented with disease in middle age. A number of possible susceptibility genes have been identified, many acting on either lipid metabolism or platelet activation (Novelli *et al.*, 2003). It is difficult to know if genetics will be relevant to coronary artery disease in late life.

Of particular interest is the epsilon 4 allele of apolipoprotein E (Song *et al.*, 2004); it is associated with coronary artery disease, but more interestingly is also considered a "frailty" gene, in that those carrying this allele tend to have worse overall survival than those who do not. This allele is also the strongest known genetic susceptibility factor for late-onset Alzheimer's disease.

Some genetic variants may be protective against heart disease. In a population of centenarians, they and their offspring were more likely to have a beneficial allele of the cholesteryl ester transfer protein than control subjects (Barzilai *et al.*, 2003). The associated phenotype included larger lipid particles and less hypertension and cardiovascular disease.

Other Factors

As demonstrated by the INTERHEART study, psychosocial risk factors, such as general or financial stress, increase the risk of myocardial infarction, worldwide, in men and women, and in young and old patients (Rosengren *et al.*, 2004). What has been termed *social capital* is a popular concept in epidemiology, and probably related to heart disease (Shen *et al.*, 2001). Social capital is made up of factors like community involvement, friendliness, and degree of volunteerism. Some authors criticize the whole concept as being imprecise and difficult to understand with regard to what is being measured. As aging is not confined to the aged, many epidemiologists are taking a life-course approach (Ben-Shlomo and Kuh, 2002) to the risk of heart disease, and in

general have found that early-life experiences are related to heart disease, though less strongly than late-life experiences. For example, this effect was found in a Swedish study of socioeconomic effects on heart disease in women, and in the Alameda County Study in the United States (Wamala *et al.*, 2001; Beebe-Dimmer *et al.*, 2004). Being a caregiver may also be a risk factor (Lee *et al.*, 2003b).

Multiple Risk Factors

There are a number of composite risk factor scores available, of which perhaps the best known is that derived from the Framingham data (Anderson *et al.*, 1991). Unfortunately, the risk scores do not seem to work as well as might be hoped (Lloyd-Jones *et al.*, 2004). Regardless of this, one's probability of developing heart disease does increase with a greater number of risk factors (Yusuf *et al.*, 2004).

"SILENT" MYOCARDIAL INFARCTION

The so-called silent myocardial infarction, diagnosed on a routine electrocardiogram, is common in older adults (Aronow, 2003); these patients are at a similar risk of new coronary events as patients with clinical myocardial infarction, and so should be investigated and treated to the same standard. It may well be that their infarction had an atypical presentation (or, as Professor Roy Fox would say, the patient is screaming but the physician is deaf). In the Bronx Aging Study, 390 subjects aged 75–85 were followed for 8 years (Nadelmann *et al.*, 1990). Those with a history of myocardial infarction without electrocardiographic evidence (8%, electrocardiographically silent infarction), and those with electrocardiographic evidence without a clinical history (6%, silent infarction) had just as poor a prognosis as those with both a clinical history and electrocardiographic evidence (4%).

CONGESTIVE HEART FAILURE

Some writers suggest that an epidemic of congestive heart failure is coming. It is the third most common cause of admission to hospital in Canada (in terms of the number of patients affected), only slightly behind myocardial infarction and pneumonia (Tsuyuki *et al.*, 2003). Such an epidemic is approaching the developing world as well (Cubillos-Garzon *et al.*, 2004).

The vast majority of patients seen for congestive heart failure is aged 65 and over. In Nova Scotia, the rate of admission for congestive heart failure is 7/100 000 for people less than 50, compared to 3600/100 000 for those aged 80 to 89 (Howlett *et al.*, 2003); over half of the female patients were over 80. These older women are less likely to have left ventricular systolic dysfunction than their male counterparts. An Italian registry reported similar results, except that their population was younger (Pulignano *et al.*, 2002). This may reflect the source of their sample, which was specialist clinics. Their older patients were more likely to be female, have more severe disease, and normal left ventricular systolic function. They were also more likely to have atrial fibrillation. Mortality was also higher, being 26% at 1 year in those 75 and older compared with 14% in those less than 70.

Mortality rates in heart failure are much higher in older adults compared to younger ones, and similar in the oldest-old men and women. In Canada, mortality rates are approximately 12.5/100 admissions for heart failure in patients 75 and over, compared to approximately 3/100 admissions in those 50–64 (Lee *et al.*, 2004). Although mortality rates have been decreasing in heart failure overall, this improvement is mostly seen in men and younger adults (Roger *et al.*, 2004). Table 3 outlines crude mortality rates and the number of deaths in Canada, illustrating the impact on older women, and the improvement in men of all ages. In older adults, survival is better for those with diastolic dysfunction compared to those with systolic dysfunction (Figure 4) (Kerzner *et al.*, 2003). In Nova Scotia, 10% of patients admitted to hospital with congestive heart failure are discharged to a nursing home (Howlett *et al.*, 2003).

Common risks for congestive heart failure in older adults include ischemic heart disease, hypertension, diabetes and smoking, with hypertension being somewhat more common in women and ischemic heart disease somewhat more common in men (Howlett *et al.*, 2003; He *et al.*, 2001). The effect of alcohol is confusing, as its moderate use may protect against congestive heart failure, yet predispose to having systolic dysfunction if heart failure is present (Abramson *et al.*, 2001; Walsh *et al.*, 2002; Thomas *et al.*, 2002).

Table 3 Mortality associated with congestive heart failure in Canada, by age, male

	1989		1995		1999	
	Rate[a]	Number	Rate[a]	Number	Rate[a]	Number
90+	1190	268	1289	368	1158	376
85–89	481	280	512	366	468	404
80–84	257	336	252	420	215	383
75–79	115	276	110	300	95	311
70–74	48	164	49	207	38	174
65–69	25	123	22	119	17	98
60–64	11	64	7	45	6	40

Mortality associated with congestive heart failure in Canada, by age, female

	1989		1995		1999	
	Rate[a]	Number	Rate[a]	Number	Rate[a]	Number
90+	1067	676	1165	947	1100	1032
85–89	402	485	459	697	379	684
80–84	182	407	170	480	144	435
75–79	79	273	66	259	55	258
70–74	29	129	25	138	24	135
65–69	12	73	12	72	9	54
60–64	5	32	5	32	3	20

[a]crude rate/100 000.
Source: Disease Surveillance On-Line, Government of Canada.

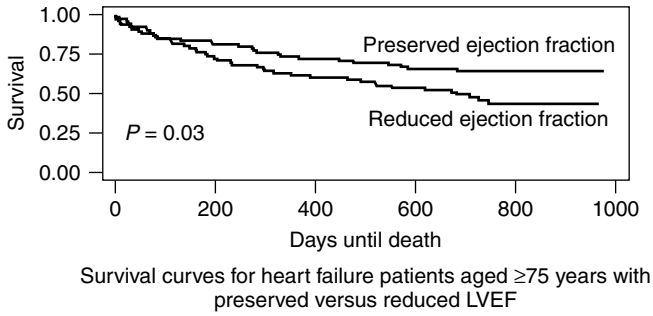


Figure 4 Survival in patients over the age of 75 with congestive heart failure and reduced or preserved ejection fraction (Reprinted from *American Heart Journal*, V146, Kerzner R, Predictors of mortality in younger and older patients with heart failure and preserved or reduced left ventricular ejection fraction, pp 286–90, Copyright 2003, with permission from Elsevier)

Systolic Versus Diastolic Heart Failure

It is important to distinguish between diastolic and systolic heart failure (or perhaps using the more precise terminology, heart failure with preserved or reduced left ventricular ejection fraction) (Hogg *et al.*, 2004). The causes of these two forms of heart failure differ, and they differ in various parts of the world (Table 4). Diastolic dysfunction tends to be a disease of older women, with hypertension being a leading cause (Kerzner *et al.*, 2003; Ahmed *et al.*, 2003). Systolic dysfunction tends to be a disease of men, often with a history of ischemic heart disease. A survey in Hong Kong found ischemic heart disease to be the most frequent cause of systolic heart failure, while rheumatic heart disease was the most common cause of diastolic heart failure (Erk, 2004), In this study, the mean age of those with diastolic dysfunction was younger than in those with systolic dysfunction. African-Americans may be at a higher risk for systolic failure, which does not seem to be solely attributable to differences in care and prevention (Yancy, 2001). Mortality may be lower for those with preserved systolic function (Hogg *et al.*, 2004). Patients with diastolic heart failure can be difficult to diagnose, as they often lack some of the expected findings, such as a positive chest X ray (Ahmed *et al.*, 2003).

OTHER CARDIOVASCULAR DISEASES

Sudden Death

The incidence of sudden death increases with age, but not as swiftly as death in general, making it a proportionately less important cause of death in older adults (Krahn *et al.*, 2004). The incidence in the general population is 1/1000, but in those 80 and older is 8.5/1000 (Straus *et al.*, 2004) and it is more common in men. The precise cause is often difficult to identify, but in an autopsy series of unexpected deaths in the community of people aged 85 and older, heart disease accounted for three quarters of the deaths, with the vast majority of these being caused by acute infarction (Berzlanovich *et al.*, 2003). The most common cause of death after cardiac disease was pulmonary embolism. Sudden cardiac death is also an issue in the developing world (Rotimi *et al.*, 2004).

Table 4 Risk factors for diastolic or systolic heart failure

Diastolic	Systolic
Female	Male
Older age	Younger age
Hypertension	African-American
Left ventricular hypertrophy	Ischemic heart disease

Arrhythmia

Atrial fibrillation (*see* **Chapter 45, Arrhythmias in the Elderly**) is by far the most common arrhythmia, and the number of people affected is increasing. Most people with atrial fibrillation are elderly (Ruigomez *et al.*, 2002). Between 1996 and 2001, the number of admissions to US hospitals for treatment of atrial fibrillation increased by 34% (Figure 5) (Khairallah *et al.*, 2004). Affected women outnumber men in late life, but the men are more likely to die in hospital, and more likely to be discharged to a nursing home. Through the 1980s and 1990s, the mortality associated with atrial fibrillation increased by 5% annually (Wattigney *et al.*, 2002).

Rheumatic Heart Disease

Rheumatic heart disease continues to be an issue in the developing world, though it is declining in the developed world (Logminiene *et al.*, 2004). The frequency of diseases such as rheumatic fever in the developing world, in conjunction with their aging population, may lead to what is being referred

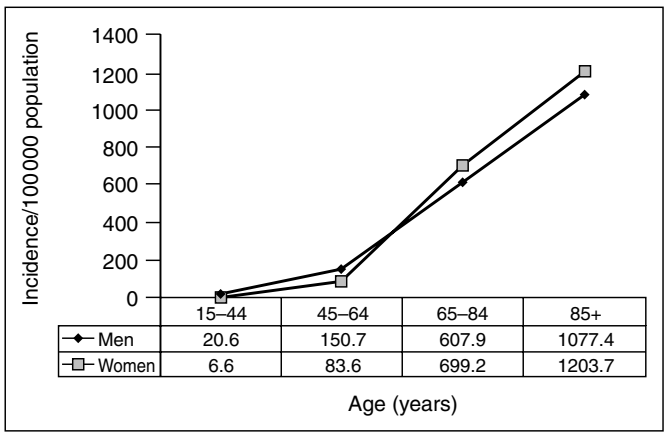


Figure 5 Incidence of atrial fibrillation by age and sex (Reprinted from *American Journal of Cardiology*, V94, Khairahhal F *et al.*, Epidemiology and determinants of outcome of admissions for atrial fibrillation in the United States from 1996 to 2001, pp 500–4, Copyright 2004, with permission from Excerpta Medica)

to as a coming, costly epidemic of chronic heart disease in the developing world (Cubillos-Garzon *et al.*, 2004). With an increasingly mobile world population, and a resurgence of rheumatic fever in the developed world, cases of rheumatic heart disease will be encountered by geriatricians of the future.

Congenital Heart Disease

With the advent of ready access to echocardiography, congenital heart disease is being discovered in ever-older adults. The most frequent clinically relevant abnormality is a bicuspid aortic valve, with an incidence of 13.5/1000 live births (Hoffman and Kaplan, 2002). It often leads to stenosis requiring intervention. With effective early treatment, patients with congenital heart disease will soon be presenting to geriatricians.

Infective Endocarditis

The incidence of infective endocarditis increases with age, peaking in the early 70s in both men and women, with men being more frequently affected (Hoen *et al.*, 2002). Older adults with endocarditis have different characteristics from younger patients. An Italian/French study found that patients over 70 were more likely to have pacemakers involved, and more likely to have a presumed gastrointestinal or urinary source, compared to younger patients (Di Salvo *et al.*, 2003). The organisms causing endocarditis also differed, with more streptococcus bovis and less staphylococcus aureus in older adults. In-hospital mortality was also higher (17% in older adults vs approximately 10% in others), though it was lower than that in earlier studies.

The data on the number of older adults who would require antibiotic prophylaxis to prevent infective endocarditis with particular interventions are scarce, but an echocardiographic survey suggests that 50% of people 60 years and older and 60% of those 80 years and older require prophylaxis according to current guidelines (Croft *et al.*, 2004). Whether this is actually necessary and effective is unknown.

CARDIOVASCULAR DISEASE AND FRAILTY

Frailty has many meanings to many people (Hogan *et al.*, 2003). When using this term, we mean multiple interacting factors; biomedical, psychological, social and environmental, which interact to make an individual vulnerable to poor outcomes, and is often associated with the geriatric giants such as falls and immobility. Heart disease is an important contributor to frailty in older adults, and is the leading cause of death in frail nursing home residents (Aronow, 2000). Frailty also interacts with heart disease in the sense that frail adults have worse outcomes than non-frail adults (Lien *et al.*, 2002).

A Finnish study found that although the prevalence of ischemic heart disease is falling in younger adults, it is increasing in older ones, likely reflecting more effective treatments (Kattainen *et al.*, 2004a). Disability rates among older adults with cardiovascular disease, particularly women, is also increasing. After adjustment for other comorbidities, cardiovascular disease is an important contributor to disability, with population-attributable fractions of 20% for myocardial infarction and 18% for heart failure in Finnish women, and 13.5 and 4.3% respectively in Finnish men, aged 65–74 (Kattainen *et al.*, 2004b). Hypertension without other manifestations of vascular disease was not associated with disability in either sex. Among British women, coronary artery disease is, after arthritis, the chronic disease chiefly associated with decreased mobility (Adamson *et al.*, 2004). Favorable cardiovascular disease risk factor profiles in middle age are associated with better function and quality of life in late life (Daviglus *et al.*, 2003).

In the Cardiovascular Health Study, the inverse of frailty, successful aging was studied (Newman *et al.*, 2003). They defined this as remaining free of major illnesses, and maintaining both physical and cognitive function. They investigated the relationship of successful aging to subclinical cardiovascular disease, defined by findings on electrocardiogram, carotid ultrasound, and ankle-arm blood pressure measurements. After following approximately 3000 subjects for 8 years, 48% remained successfully aged. The likelihood of doing so was related to both age and subclinical vascular disease, with men also being at a slightly higher risk (Figure 6). A number of modifiable risk factors, such as smoking and lack of exercise, were associated with unsuccessful aging.

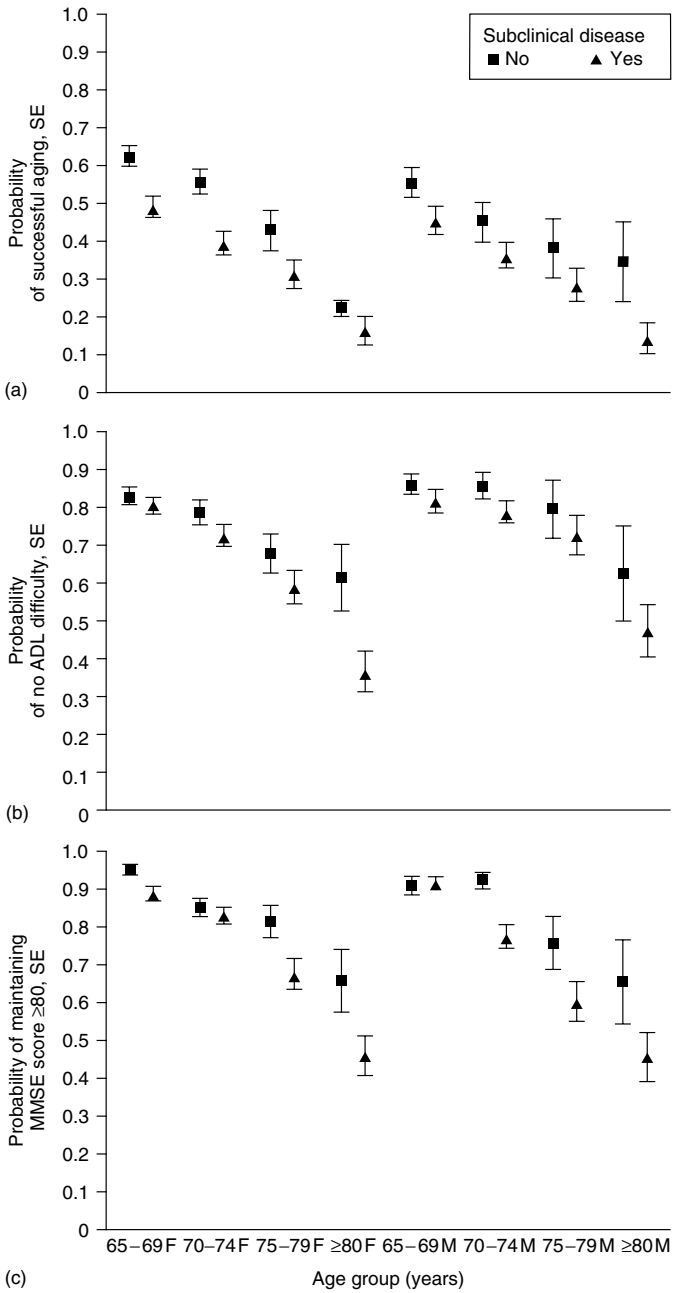
The relationship between cardiovascular disease and frailty is unclear, however. A longitudinal Dutch study found no relationship between baseline or incident cardiac disease and decline in physical function, after adjustment for other comorbidities, most importantly chronic lung disease, stroke, diabetes mellitus, and arthritis (Kriegsman *et al.*, 2004).

CARDIOVASCULAR DISEASE AND DEMENTIA

Vascular dementia shares many risk factors and characteristics with cardiovascular disease (Hebert *et al.*, 2000). Of greater interest are the links between vascular disease and Alzheimer's disease, which also shares risk factors with heart disease (Tyas *et al.*, 2003). Some authors go so far as to suggest that Alzheimer's disease is a manifestation of cerebrovascular disease (de la Torre, 2002). Finally, as with frailty, the presence of dementia adversely affects the outcomes of cardiac disease (Sloan *et al.*, 2004).

PREVENTION

Prevention runs along a continuum of the disease, from asymptomatic through to severely impaired (Figure 7). Data



Probabilities of successful aging (a), no difficulty in activities of daily living (ADL) (b), and maintaining Mini-Mental State Examination (MMSE) score of 80 or higher (c), by sex, age group, and subclinical disease status. F indicates female; M, male. Bars indicate SEs.

Figure 6 Probability of markers of frailty by subclinical cardiovascular disease, by age and sex. ADL = Activities of Daily Living, MMSE = MiniMental State Exam (Reproduced by permission from Newman AB *et al.*, Successful aging, Archives of Internal Medicine, **163**, pp 2315–22, Copyright 2003, American Medical Association. All rights reserved)

from the United States suggest that both primary and secondary prevention of ischemic heart disease has been successful, in that both the incidence of the disease and its case-fatality ratio are decreasing (Ergin *et al.*, 2004). The oldest-old may not be benefiting to the same extent, suggesting that our prevention maneuvers should be refocused. The data on frailty and cardiovascular disease suggests that frailty may also be preventable (Newman *et al.*, 2003), so not smoking and taking exercise may do away with the "sans teeth... sans everything" of Shakespeare (1623).

Secondary

Clinicians generally do a poor job of prevention in older adults. People aged 85 and older are less likely to receive some classes of drugs after a myocardial infarction than people 65–84, with the classes with the largest differences being beta-blockers and statins (Pilote *et al.*, 2004). Beta-blockers are perhaps understandable, given likely comorbidities. Although the underuse of statins is defensible, given the lack of evidence in this age-group, decisions about therapy should, in our view, not be made on age alone, but rather on the individual's likelihood of benefit and their degree of frailty. If the regulators of the pharmaceutical industry required all manufacturers to test their products on all adults, these situations would not be seen. Older patients with congestive heart failure are less likely to receive beneficial medications such as angiotensin converting enzyme inhibitors, beta-blockers, and anticoagulants (Pulignano *et al.*, 2002). Even an intervention as simple as smoking cessation, with proven efficacy at all ages, is often not suggested (Maguire *et al.*, 2000).

An issue in secondary prevention that is most troublesome is the use of warfarin for stroke prophylaxis in atrial fibrillation. Despite its efficacy, its use is often discouraged in older adults, because of fears regarding falls and other complications (Man-Son-Hing and Laupacis, 2003). One calculation suggested that a patient would need to fall 295 times yearly to outweigh the benefit of warfarin.

Tertiary

There is good evidence that comprehensive outpatient management programs improve outcomes in congestive heart failure. Such programs should be encouraged. Cardiac rehabilitation, for those with ischemic heart disease, is also beneficial and probably underutilized.

CONCLUSION

We have outlined the importance of heart disease in elderly people. Heart disease in older adults differs from that in younger adults, in presentation, prognosis, and pathology. The preponderance of women is the most obvious difference; geriatric cardiology (and geriatrics in general) can almost be considered a women's health discipline. We also hope that, with the advent of the discipline of geriatric cardiology and of interest in elderly patients, the principles and practice of the treatment and prevention of heart disease in the elderly will progress rapidly.

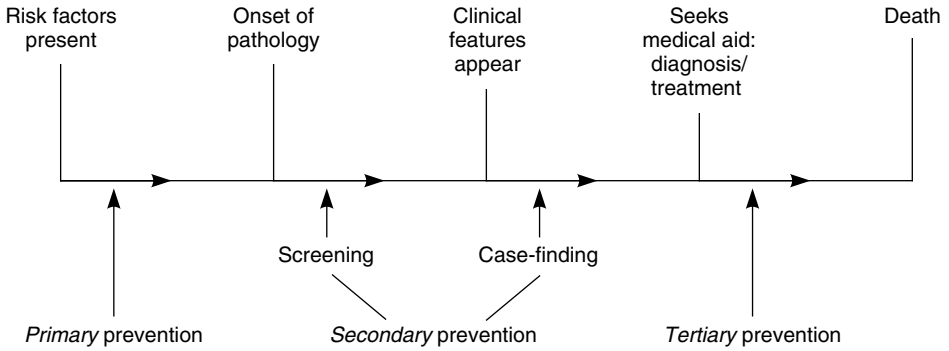


Figure 7 Prevention (Reproduced from Powell, (1994) by permission of John Wiley & Sons Ltd.)

KEY POINTS

- With an increasing number of older people, the number of people presenting with heart disease is increasing.
- The prevalence of congestive heart failure rivals that of ischemic heart disease in older people.
- The proportion of women with heart disease is much greater in older adults than in younger adults.
- Although many traditional risk factors for heart disease are also risk factors in older adults (e.g. smoking), others (e.g. overweight) appear to be less important.
- Preventive maneuvers are important at all ages.

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44

Cardiac Aging and Systemic Disorders

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INTRODUCTION

It is difficult to define a chronological age above which people should be defined as "elderly". Aging is a heterogeneous process and, therefore, deterioration in function of organ systems often does not match well with chronological age. "Healthy" or "intrinsic" aging is associated with gradual decline in organ function and homeostatic reserve, but usually by itself does not cause symptoms under normal circumstances, or in usual daily activities. However, healthy aging does result in a reduced threshold for clinical expression of many diseases that are more common in the older population. Aging also can modify the risk factors, clinical manifestations, and prognosis of disease.

There are particular changes in cardiovascular structure and function with intrinsic aging. Knowledge of these is essential for the accurate interpretation of the effect of disease in older people. However, it should be remembered that it is often difficult to disentangle intrinsic aging from disease. This chapter aims firstly to summarize effects of healthy aging on cardiac function. The potential effects of age-associated cardiac changes on the manifestation of various systemic (noncardiac) diseases are then considered.

INTRINSIC CARDIAC AGING AND CLINICAL SIGNIFICANCE

Even with healthy aging, the cardiovascular system undergoes major changes. The elasticity and compliance of the aorta and large arteries is reduced with resultant higher systolic arterial pressure, increased impedance to left ventricular ejection and subsequent left ventricular hypertrophy and interstitial fibrosis (Vaitkevicius *et al.*, 1993; Chen *et al.*, 1998). The left ventricle becomes stiffer leading to impaired diastolic filling, increasing the risk of diastolic heart failure (Gardin *et al.*, 1998). However, some of these changes are not solely due to intrinsic aging, but are influenced by powerful environmental factors. For example, the increase in systolic blood pressure with aging is largely absent in rural Africans, but becomes manifest when such subjects move to an urban environment.

Aging is associated with reduction in the number and sensitivity of beta-adrenoreceptors in the sinoatrial node, leading to a decrease in both intrinsic and maximal sinus rate. During exercise, the appropriate increase in heart rate is also attenuated, and the older heart relies on dilatation and increased stroke volume to increase cardiac output (working on the physiological principles of the Starling curve). This compensatory response is effective at submaximal workloads; however, it has limits and maximum cardiac output is reduced in the older heart.

Fibrosis and increased stiffness of cardiac structures also influences cardiac reserve. Aging is also associated with hypertrophy and increased stiffness of the myocardium. This results in impaired left ventricular filling during diastole, with increased reliance on atrial contraction to fill the ventricle. Fibrosis of the conducting system increases the risk of bundle branch and complete heart block (Shirani *et al.*, 1995). Aging is also associated (see Figure 1) with thickening of heart valves with calcification and fibrosis. As a result, a minor degree of valvular dysfunction such as aortic incompetence (visualized on Doppler echocardiography) is usual in older people. Many older people with an aortic systolic murmur have aortic sclerosis with disturbed flow across the valve, but no significant pressure gradient. This was considered to be a benign condition in the elderly, but is now recognized to be associated with significant increased cardiovascular and total mortality (Otto *et al.*, 1999).

Amyloid deposition is usual in the aging heart; however, adverse clinical consequences are rarely seen. Deposits are laid down intracellularly in the myocardium, and in the walls of small coronary arteries. In postmortem studies of older people amyloid deposits in the heart have been found in 80–100% of cases (Kushwaha *et al.*, 1997; Kawamamura *et al.*, 1995). Although most elderly patients do not have symptoms from cardiac amyloid, some will develop

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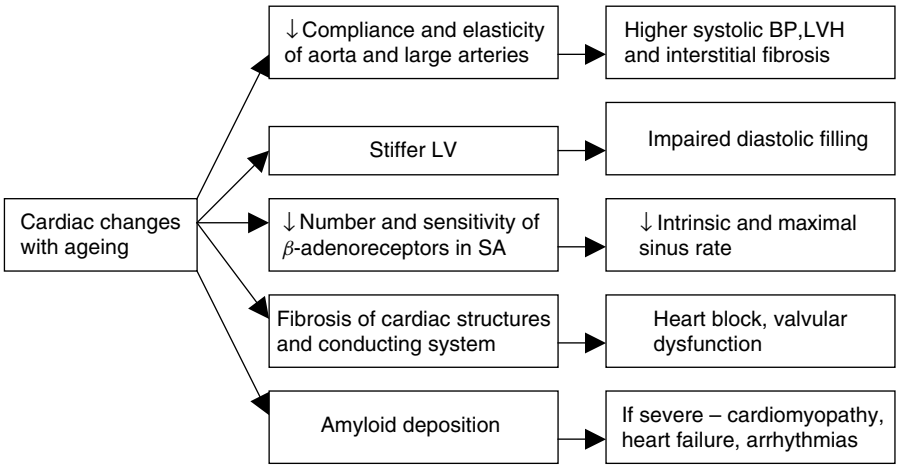

Figure 1 Changes in cardiovascular system with healthy aging

extensive deposits resulting in amyloid cardiomyopathy. It can be a cause of, or contributor to, heart failure and cardiac arrhythmias (including atrial standstill) in the elderly (Kyle *et al.*, 1996). Amyloid cardiomyopathy is rarely suspected in life (Gertz and Kyle, 1989). The electrocardiograph may show low voltage complexes. On echocardiography, the myocardium has a bright "speckling" appearance with other features of a restrictive physiology. In advanced cases virtually every cardiac structure can be infiltrated. Multisystem involvement is common, however, this rarely results in any clinically significant dysfunction of other organs.

The incidence and prevalence of ischemic heart disease increases dramatically with rising age (Cupples and D'Agostino, 1987; Armstrong and Feigenbaum, 2001). In the developed world up to 30% of the over 65s have symptoms of ischemic heart disease with angina or previous acute myocardial infarction. However it has been estimated that a further 30% have clinically significant but covert disease in which typical symptoms of angina pectoris are not present. Aging is associated with impaired perception of ischemic cardiac pain; on exercise there is a delay from onset of myocardial ischemia to symptoms of angina in older people. When symptoms occur they may be vague or nonspecific, such as acute confusion or a fall with acute myocardial infarction, or lethargy and reduced physical capacity with exercise-induced myocardial ischemia. Therefore, ischemic heart disease is a common cause of reduced cardiac homeostatic reserve in older people, and in the event of a stressor such as systemic illness adverse clinical consequences such as heart failure or cardiac arrhythmias can occur. The presentation, diagnosis, and treatment of coronary artery disease in older people is discussed in detail in **Chapter 46, Ischemic Heart Disease in Elderly Persons**.

SYSTEMIC DISEASE AND CARDIAC MANIFESTATIONS IN OLDER PATIENTS

The reduction in cardiac homeostatic reserve associated with intrinsic aging, and the high prevalence of underlying cardiac disease (particularly ischemic heart disease) greatly increases the risk of cardiac dysfunction (particularly heart failure and arrhythmias) with noncardiac disease in older people.

Cardiac Manifestations of Noncardiac Disease

The Brain

Acute strokes in older people, including infarction and subarachnoid or intracranial hemorrhage are more likely to be associated with cardiac rhythm or conduction disturbances and disorders of repolarization resembling acute myocardial infarction. Increased troponin is seen in approximately 20% of patients with acute stroke. It has been hypothesized that this is usually due to myocytolysis, a nonspecific response to stress and activation of the sympathoadrenal system and elevated glucocorticoids (Gardin *et al.*, 1998; Samuels, 1984) although some patients will have underlying coronary thrombosis and classical acute myocardial infarction. Electrocardiographic changes and troponin elevations can occur after acute stroke in the absence of significant coronary heart disease. However, elevated troponin may still be a useful prognostic marker in the setting of acute stroke, as it is associated with increased mortality and increased risk of poor outcome including the need for long-term institutional care in survivors.

Congestive heart failure (CHF) and cardiac arrhythmias (particularly chronic atrial fibrillation) are recognized risk factors for cognitive decline and dementia in elderly people. Activated coagulation causing low-grade cerebral ischemic damage is one likely mechanism. There is evidence of increased thrombin generation and fibrin turnover in subjects with atrial fibrillation who develop dementia compared to those whose cognitive function remains intact (Barber *et al.*, 2004). Observational data suggests that anticoagulation with warfarin protects against development of dementia in atrial fibrillation. Another potential mechanism is low blood pressure and reduced cerebral perfusion. Cognitive impairment has been correlated with the degree of left

ventricular dysfunction and systolic blood pressures below 130 mmHg (Pullicino and Hart, 2001).

A degree of cognitive dysfunction occurs in most patients after cardiac surgery including coronary artery bypass grafting (Diegeler *et al.*, 2000). Older patients with preexisting small vessel cerebral ischemia are at particular risk. Low blood pressure during surgery and small cerebral embolic events are thought to be the main contributors.

The Respiratory System

Cardiac failure and atrial fibrillation are common complications of serious respiratory illness in older people. Chronic obstructive pulmonary disease and reduced lung function (FEV1, forced expiratory volume) are independent risk factors for atrial fibrillation. Respiratory infections including influenza and respiratory syncytial virus are associated with increased risk of hospitalization for heart failure and sudden death (Yap *et al.*, 2004). Potential mechanisms include infection-induced rises in cytokines that have negative cardiac inotropic effects.

Gastrointestinal System

Age is an independent risk factor for circulatory collapse and death after acute gastrointestinal hemorrhage. This is likely to be due to reduced homeostatic cardiac reserve.

Helicobacter pylori infection in the young is associated with raised fibrinogen levels and ischemic heart disease. However, no link has been confirmed with ischemic heart disease in elderly subjects; claims that helicobacter eradication therapy decreases fibrinogen levels in coronary heart disease are likely to be confounded by regression to the mean (Yusuf and Mishra, 2002).

In the past, gastrointestinal angiodysplasia has been thought to be associated with aortic incompetence. However, more recent case-control studies have not supported any link between these conditions.

Renal System

Deterioration in renal and cardiac function often occurs together in older people. Renal impairment in older people is associated with increased risk of ischemic cardiovascular disease (*see* **Chapter 46, Ischemic Heart Disease in Elderly Persons**). The risk is inversely related to glomerular filtration rate and is significantly increased by the time serum creatinine is elevated (Schillaci *et al.*, 2001). This association is partly due to common etiologies, including risk factors for vascular disease such as hypertension or diabetes mellitus causing ischemic damage to kidneys and heart. In addition, impaired ability to excrete salt and water in renal failure may lead to fluid overload and cardiac failure, and in heart failure there is reduced cardiac output and a fall in renal perfusion which may lead to decline in renal function.

In severe heart failure, it is often difficult to obtain a balance between adequate diuresis and control of heart failure, without causing hypotension and a reduction in circulating plasma volume and an associated decrease in renal perfusion and glomerular filtration rate. When elderly patients with chronic heart failure do develop impaired renal function with elevated creatinine, this is an adverse prognostic factor for hospitalization and for death.

Osteoporosis and Vascular Calcification

Osteoporosis in older people is associated with vascular calcification, primarily involving the intimal arterial layer. This vascular calcification arises in atherosclerotic blood vessels and heart valves (particularly the aortic valve). Oxidized lipids are a major risk factor, promoting mineralization of vascular cells while inhibiting mineralization of bone cells. It is present in most subjects over the age of 65 years, and is more frequent in diabetes mellitus and end-stage renal disease.

It has been suggested that lipid lowering therapy with statins (HMG CoA, 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors) may reduce the risk of osteoporotic fractures, as well as prevent ischemic vascular events in older people (Whitney *et al.*, 2004), although at present there are no randomized controlled trial data to support this.

Endocrine Abnormalities and the Cardiovascular System

Growth Hormone

Acromegaly is associated with cardiac enlargement and hypertension (*see* **Chapter 18, Smart Homes**). Chronic overproduction of growth hormone also impairs carbohydrate metabolism and leads to a state of hyperinsulinemia and insulin resistance. These factors lead to an increased risk of atherosclerosis. Elderly people with acromegaly are more likely to develop acromegalic cardiomyopathy with cardiac enlargement and chronic heart failure that is often refractory to treatment.

Thyroid Dysfunction

Hyperthyroidism is common in older people, with cardiovascular manifestations dominating the clinical presentation; palpitations, dyspnea, sinus tachycardia, arrhythmias, and systolic hypertension are common features. Heart failure is particularly likely if preexisting heart disease is present. The risk of atrial fibrillation is increased in older patients; it may be paroxysmal or chronic. Even subclinical hyperthyroidism in the elderly is reported to be three times more likely to cause atrial fibrillation and it has been suggested these patients should be actively treated with antithyroid drugs, beta-blockers, and radioactive iodine as appropriate (Sarwin *et al.*, 1994). In the absence of underlying heart disease, atrial fibrillation may revert to sinus rhythm when a euthyroid state is achieved. However, in older patients or when atrial fibrillation has been present for a long duration, the rate of reversion

is lower (Klein and Ojama, 2001). Cardiovascular complications are the main cause of death even after treatment of hyperthyroidism (Franklyn *et al.*, 1998).

Hypothyroidism also has important cardiac manifestations in older people. Bradycardia, nonpitting edema, pericardial effusion, and CHF are all recognized as complications. The electrocardiograph may show low voltage complexes. Even a mild degree of chronic thyroid hormone deficiency (subclinical hypothyroidism) can affect the cardiovascular system. Exertional dyspnea and easy fatigability are common complaints, resulting from a combination of systolic and diastolic dysfunction on effort (Biondi and Klein, 2004). Endothelial dysfunction may increase the risk of hypertension and arterial thrombotic events. Diastolic hypertension tends to predominate, and is due to increased systemic vascular resistance. There is an increased risk of atherosclerosis in these patients, due to hypertension and an atherogenic lipid profile. However, due to a decreased metabolic demand on the myocardium and low physical activity levels, symptoms of angina may not be present even in the presence of significant coronary artery disease.

Many of these cardiac manifestations of hypothyroidism reverse with thyroxine replacement therapy. However, extra caution has to be exercised in the elderly while initiating treatment to avoid precipitating acute myocardial infarction and heart failure, as they are likely to have underlying ischemic heart disease. The initial dose of thyroxine should be about 25% of the anticipated replacement dose, increased in a stepwise fashion at 6–8 weeks intervals (Crowley *et al.*, 1997).

Diabetes Mellitus (see Chapter 122, Type 2 Diabetes Mellitus in Senior Citizens)

A low (high?) index of suspicion is necessary for the detection of myocardial ischemia in the elderly with diabetes as the presentation is more likely to be silent or atypical, particularly in females. The reported incidence of arteriosclerotic coronary heart disease in elderly type 2 diabetics is likely to be an underestimate as most studies have excluded the elderly with renal dysfunction, ischemia, and other comorbidities (Ioanitoaia *et al.*, 2001). Elderly diabetics are likely to have multivessel coronary artery disease (often unsuitable for percutaneous revascularization procedures or coronary artery bypass grafting), and have an increased risk of CHF. In addition, diabetic cardiomyopathy, associated with small vessel disease has been described (Uusitupa *et al.*, 1990).

Systemic Infections and the Heart

A variety of systemic infections have been suggested to increase the risk of ischemic heart disease. Candidates have included specific organisms such as chlamydia and helicobacter pylori, and chronic sepsis associated with periodontal disease. Suggested mechanisms have included chronic inflammation with elevated C-reactive protein, increased oxidized lipids, and raised fibrinogen levels, all of which are associated with atherosclerosis (Chrischilles *et al.*, 1992).

Nutrition and Cardiovascular System in the Elderly

Symptomatic heart failure, especially in the elderly, can affect food intake, leading to malnourishment. Cardiac cachexia in patients with CHF is associated with higher mortality independent of the severity of CHF (Bourdel-Marchasson and Emeriau, 2001). Besides presenting with significantly more comorbidity, patients with low body mass index are at higher risk of postoperative complications following cardiac surgery (Potapov *et al.*, 2003).

Conclusions

Cardiac manifestations of systemic disease are very common in older people. Healthy aging is associated with a reduction in cardiac homeostatic reserve, increasing the risk of cardiac arrhythmias and heart failure with many noncardiac illnesses. In addition clinically significant ischemic heart disease is present in the majority of the over 65s in the developed world, further reducing cardiac reserve. Ischemic heart disease is linked to dysfunction in numerous other organ systems; the classic scenario of multiple pathologies in an older person often includes cardiac dysfunction. Optimal management of the older patient requires that these multiple interacting contributors to symptoms or functional decline are identified, and key modifiable contributors prevented or treated.

KEY POINTS

- Aging is associated with a marked reduction in cardiac homeostatic reserve due to a combination of intrinsic aging, and a high prevalence of underlying cardiac disease (particularly ischemic heart disease).
- This reduced homeostatic reserve greatly increases the risk of cardiac dysfunction (including heart failure and arrhythmias) with noncardiac disease in older people.
- Cardiac dysfunction in older people also places other organ systems at risk. Examples include increase risk of dementia with both atrial fibrillation and chronic heart failure.
- Frequently, there is a complex interaction between different organ systems. For example, deterioration in renal and cardiac function often occurs together in older people.
- Optimal management of the older patient requires that these multiple interacting contributors to symptoms or functional decline are recognized, and key modifiable contributors prevented or treated.

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Arrhythmias in the Elderly

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ARRHYTHMIAS IN THE ELDERLY

The population is aging and, as the heart ages, pathophysiological changes occur that predispose to numerous rhythm disturbances. Prognostic improvements made in the management of heart disease have further increased the burden by prolonging exposure to conditions that promote the development of arrhythmias. Arrhythmias are associated with a substantial risk of morbidity and mortality, and the management of arrhythmias in the elderly presents important challenges. Clinical presentation can vary from one extreme (asymptomatic incidental finding) to the other (acute hemodynamic collapse) and includes a myriad of nonspecific symptoms common to many disorders. There is a widening range of treatment options and plans must be individualized as there is a vast scope amongst the elderly for comorbidity, polypharmacy, impaired cognition, poor exercise tolerance, and other factors that modify the risk benefit ratio. This chapter will review arrhythmias common in the elderly and their management.

The Elderly Heart

Aging of the heart is associated with the deposition of amyloid in the atrial myocardium, a gradual loss of the specialized pacemaker myocytes of the sinoatrial (SA) node, and the deposition of collagen and fibrous tissue in the specialized ventricular conduction tissue. These aging processes are associated with a pathological outcome in some patients. For instance, loss of SA node pacemaker cells contributes to the development of sick sinus syndrome. This process is augmented by pathological changes secondary to cardiovascular disease such as hypertension and coronary atherosclerosis, both of which increase in incidence with age. In reviewing 12-lead and 24-hour electrocardiogram (ECG) survey findings in the elderly, it can be difficult to distinguish between whether purely aging or pathological processes are responsible.

12-Lead ECG Surveys

Findings of a prolonged PR interval, left axis deviation and bundle branch block (BBB) are more common in the elderly. First-degree heart block, as a lone finding in an asymptomatic patient, is not associated with an adverse prognosis. Left axis deviation is associated with cardiovascular disease but in the absence of clinical disease does not carry a worse prognosis. An increase in left ventricular hypertrophy and left BBB with age correspond to the increased incidence of cardiovascular disease and clearly are associated with an increased mortality. Right BBB is more common than left in the elderly, but has no prognostic impact *per se*.

24-Hour Ambulatory ECG Surveys

In the absence of medication, a sustained bradycardia is not a normal finding in the elderly. However, elderly subjects do show a significant reduction in 24-hour heart rate variability (Umetani *et al.*, 1998). A survey of 500 asymptomatic individuals aged 50 to 80 years (Spodick *et al.*, 1992) found no association between heart rate and age, and a study of 1372 individuals aged 65 years and older (Manolio *et al.*, 1994) found no association between bradycardia and age. Various studies have shown a small decline in mean heart rate with age (Camm *et al.*, 1994) but even in healthy subjects aged 80 to 99 years, mean heart rate is still >70 bpm (Umetani *et al.*, 1998). A persistent and significant bradycardia should alert the clinician to the possibility of sinus node disease. There is a low incidence of sinus arrhythmia in the elderly, but ectopic activity is considerably increased. Specific brady- and tachyarrhythmias will be discussed individually below.

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SYMPTOMATIC BRADYCARDIAS

Cardiac impulses originate in the SA node, propagate through the atria and are normally conducted to the ventricles via the atrioventricular (AV) node and Bundle of His. Bradycardias can result from abnormalities at any level: dysfunction of SA node automaticity or conduction disturbances within the AV node or Bundle of His. These will be discussed individually below. Bundle branch or fascicular blocks may prolong ventricular depolarization (QRS complex width) or cause electrical axis deviation, but will not result in a bradycardia unless conduction through all fascicles is interrupted, equivalent to complete AV block. The autonomic nervous system regulates sinus node automaticity and AV nodal conduction. The balance of parasympathetic and sympathetic tone is subject to influence from a host of extrinsic factors: physiological (e.g. sleep (*see* **Chapter 63, Sleep Disorders in Elderly People**)), pathological (e.g. hypothyroidism (*see* **Chapter 120, Thyroid Disorders**)), and iatrogenic (e.g. medication). The causes of a bradycardia are summarized in Table 1.

Presentation

Episodes of bradycardia are common in all age groups. However, a sustained bradycardia is not a normal finding in the elderly and as discussed above, implies pathology. The presence or absence of symptoms is principally determined by the heart's ability to compensate for a bradycardia. Cardiac output is the product of heart rate and left ventricular stroke volume. If the latter cannot increase sufficiently to match demand and peripheral and/or cerebral perfusion falls, this will result in symptoms. These vary from understated symptoms such as lack of concentration, fatigue, poor memory, dizziness, and myalgia to more pressing concerns of syncope and heart failure. Patients with paroxysmal tachycardias may experience palpitations or ischemic symptoms.

Table 1 Causes of a bradycardia

System	Cause
Cardiovascular	Ischemia/Infarction Infiltrative disorders (e.g. sarcoid, amyloid, hemochromatosis) Inflammatory disorders (e.g. SLE, rheumatoid)
Respiratory	Obstructive sleep apnea
Medication	β-blockers (including topical conjunctival administration) Antiarrhythmics (e.g. digoxin, amiodarone) Antihypertensives (e.g. calcium channel antagonists) Parasympathomimetic (e.g. atropine)
Iatrogenic	Valve replacement Catheter/Surgical ablation Correction of congenital heart disease
Endocrine	Hypokalemia Hyperkalemia Hypothyroidism
Neurological	Raised intracranial pressure Increased vagal tone (e.g. micturition, defecation, coughing) Carotid sinus hypersensitivity
Infectious disease	Infective endocarditis Lyme disease Chagas disease
Miscellaneous	Hypothermia Metastatic disease

SLE, systemic lupus erythematosus.

Assessment

Documentation of a bradycardia (rhythm strip, 12-lead ECG or 24-hour tape) is not sufficient. The symptoms described above are all nonspecific and differential diagnoses are extensive, especially in the elderly. It is essential to establish a correlation between the patient's symptoms and the occurrence of bradycardia; otherwise treatment of the arrhythmia may be successful but the patient will be disappointed with the results. In addition, pacemaker insertion is not without risks and as with any implanted device, infection can be particularly devastating. History, examination, and investigations should be targeted at confirming the presence of arrhythmia and association with symptoms, excluding reversible risk factors (such as medication, hypothyroidism, and sleep apnea) and to differentiate physiology from pathology.

Sinus Node Dysfunction (Sick Sinus Syndrome)

The term syndrome confers the impression of a constellation of findings and this is precisely what happens in sinus node dysfunction. ECG recordings can consist of sinus bradycardia, SA block and periods of sinus arrest, particularly occurring after paroxysms of atrial tachyarrhythmias (tachy-brady syndrome). Dysfunction may progress to the stage that no sinus beats occur and atrial fibrillation (AF) occurs. Mortality is unaffected by sinus node dysfunction (Brignole, 2002) and survival is influenced by associated pathology such as ischemic heart disease.

Indications for pacing (Gregoratos *et al.*, 2002):

- Sinus node dysfunction with documented symptomatic bradycardia or where bradycardia is the result of necessary medication, such as in the treatment of tachyarrhythmias (class I recommendation).
- Sinus node dysfunction and heart rate <40 bpm, where an association between symptoms consistent with bradycardia and the presence of bradycardia has not been clearly established (class IIa recommendation).

Atrioventricular Block

First-degree Heart Block

The PR interval (time from onset of P wave to onset of QRS complex) corresponds to the time from initiation of

atrial depolarization, conduction through the atria and to the bundle branch system via the AV node and Bundle of His. A prolonged PR interval (>0.2 seconds) with preservation of 1 : 1 AV conduction is termed *first-degree heart block*. Moderate prolongation of the PR interval in this fashion is a benign condition (Mymin *et al.*, 1986) but PR intervals >0.3 seconds can be symptomatic (Serge Barold, 1996).

Indications for pacing (Gregoratos *et al.*, 2002):

- First-degree heart block associated with symptoms of a delay in AV synchronous contraction (class IIa recommendation).
- First-degree heart block in association with symptomatic left ventricular (LV) dysfunction where pacing will result in a hemodynamic improvement (class IIb recommendation).

Second-degree Heart Block

This is an intermittent failure of atrial depolarization to result in ventricular depolarization and this tends to occur in various patterns. Mobitz type I second-degree heart block (Wenckebach) is present when there is progressive lengthening of the PR interval with each beat until an atrial depolarization is not conducted, resulting in a dropped beat. The PR interval resets and the cycle resumes. Mobitz type II second-degree heart block occurs when atrial depolarizations are intermittently blocked without preceding progressive PR interval prolongation. AV conduction occurring in a 2 : 1 fashion (or higher) represents another pattern of second-degree heart block, but is not classified as type I or II. If block of two or more consecutive P waves occurs, this is termed *advanced second-degree heart block* (see Figure 1).

Indications for pacing (Gregoratos *et al.*, 2002):

- Any form of second-degree heart block associated with symptomatic bradycardia (class I recommendation).
- Type II second-degree heart block with a wide QRS complex (class I recommendation).
- Advanced second-degree heart block with either documented asystole lasting greater than or equal to 3.0 seconds or any escape rhythm of rate <40 bpm in an awake patient (class I recommendation).
- Asymptomatic type II second-degree heart block with narrow QRS complex (class IIa recommendation).

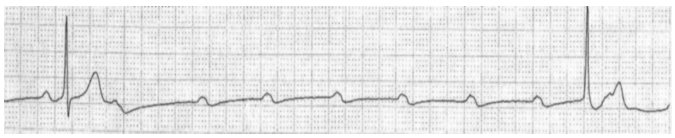

Figure 1 Rhythm strip showing advanced second-degree heart block

Third-degree Heart Block (Complete Heart Block)

Complete heart block is a complete block of conduction between the atria and ventricles resulting in regular atrial activity and the presence of an independent escape rhythm. This is generally ventricular in origin with a wide QRS complex and rate of approximately 30–40 bpm. Nodal escape rhythms imply the anatomical level of block is higher within the AV node itself, rather than the Bundle of His. The lower the origin of the escape rhythm, the less specialized and hence less reliable the conduction tissue.

Indications for pacing (Gregoratos *et al.*, 2002):

- Third-degree heart block with one of the following features: symptomatic bradycardia; documented asystole greater than or equal to 3.0 seconds; or any escape rhythm of rate less than 40 bpm in an awake patient (class I recommendation).
- Asymptomatic third-degree heart block, especially in the context of LV dysfunction or cardiomegaly (class IIa recommendation).

Choice of Pacemaker

Once the decision to implant a pacemaker has been made, consideration should be given to the appropriate pacemaker mode. The choice is between ventricular pacing (VVI/R) and more physiological dual chamber pacing (DDD/R) where AV synchrony is maintained. Physiological pacing may improve hemodynamics, but dual chamber systems are more expensive and require two leads instead of one. Hence, implantation can be technically more challenging and there is a greater potential for late complications. A series of large prospective, randomized trials have recently compared ventricular and physiological systems (DDD/R or AAI/R) for sinus node dysfunction and AV block (see Table 2 for a summary of these trials).

None of these trials demonstrated a difference in mortality between ventricular and physiological pacing systems. However, a statistically significant reduction in the development of AF was found in the Mode Selection Trial (MOST) and both Canadian Trial Of Physiologic Pacing (CTOPP) trials. Therefore, elderly patients with sinus node dysfunction who require pacing should receive atrial or dual chamber system (whether atrial is better than dual chamber pacing is under investigation). Subgroup analysis of the CTOPP trial revealed that those patients who were pacemaker dependant were more likely to benefit from physiological pacing (Tang *et al.*, 2001). Given these findings, physiological pacing should be considered for those likely to be pacemaker dependant. There is no evidence for a benefit of dual chamber pacing over simple ventricular pacing for AV block in the elderly. Therefore, VVI pacemaker is all that is required for pacing AV block.

Complications of Pacemaker Implantation

Complications can occur during implantation and include pneumothorax, lead dislodgement, and failure to sense or

Table 2 Characteristics of trials comparing ventricular and physiological pacing

Trial	*n*	Age (years)	Indication	Follow-up (years)	Results
CTOPP	2568	73	SND or AVB	3.1	No significant difference in stroke, cardiovascular death, or hospitalization for heart failure Annual rate of AF significantly lower in physiologic group, but higher perioperative complication rate
CTOPP (long term)	2568	73	SND or AVB	6	No significant difference in cardiovascular death, stroke, or total mortality Persistent significantly lower rate of AF in physiologic group
MOST	2010	74 (median)	SND	2.8	No significant difference in death, nonfatal stroke or hospitalization for heart failure Incidence of AF significantly lower in physiologic group
PASE	407	76	SND or AVB	2.5	No significant difference in stroke, stroke or all-cause mortality, stroke, death, or hospitalization for heart failure No significant difference in the development of AF
UKPACE	2021	80	AVB	4.6	No significant difference in all-cause mortality No significant difference in 2° end-points of AF or heart failure

CTOPP: Canadian Trial Of Physiologic Pacing (Connolly, 2000c); CTOPP (long term), Canadian Trial Of Physiologic Pacing long-term follow-up (Kerr *et al.*, 2004); MOST: Mode Selection Trial (Lamas *et al.*, 2002); PASE: pacemaker selection in the elderly (Lamas *et al.*, 1998); UKPACE: United Kingdom Pacing and Cardiovascular Events; SND:sinus node dysfunction; AVB: atrioventricular block.

capture. Postprocedure complications of wound hematoma and infection can develop within days and device erosion, lead fracture, or dislodgement occurs later. In a recent series, early complications (within two weeks of implantation) occurred in 6.7% of patients and late complications in 7.2% of patients (Kiviniemi *et al.*, 1999). The majority of these patients required an invasive correction of the complication. Despite the reduction in size of the modern pacemaker, special considerations have to be made for elderly patients. Devices are generally implanted subclavicularly between the skin and the pectoral muscle, but skeletal deformities resulting from osteoarthritis or osteoporosis of the shoulder, spine, or pectoral region may occasionally prevent this. In addition, wound healing and device erosion through the skin is more likely to occur with cachexia and thinning skin. In such patients, the pacemaker may be better positioned under the pectoral muscle. Clearly as with any procedure, a risk benefit assessment has to be made on an individual basis.

ATRIAL TACHYARRHYTHMIAS

Atrial Ectopic Beats

These are a common finding in the elderly and if especially frequent can result in a pulse that could be confused for AF. No specific treatment is required; however, if symptomatic, patients generally respond to β-blocker therapy.

Atrial Tachycardia

Short bursts of atrial tachycardia are common in the elderly. In many cases, no symptoms are associated and no treatment may be needed. Sometimes the atrial tachycardia triggers AF and then treatment of the tachycardia may be necessary.

Multifocal Atrial Tachycardia (MAT)

Another common atrial arrhythmia in the elderly, multifocal atrial tachycardia (MAT) is characterized by the appearance of diverse P wave morphologies as complexes originate from different foci within the atria. This can result in irregular R–R intervals and hence clinically mimic AF. There is an association with chronic airways disease and drug toxicity (digoxin, theophyllines, and tricyclic antidepressants). Treatment should be aimed at the underlying cause.

Atrial Flutter

Atrial flutter and AF are two ends of the same spectrum. Whereas the atria are activated in a chaotic manner in AF, atrial flutter consists of organized atrial activation seen on the ECG as a regular saw-tooth pattern of flutter waves with a rate of approximately 250–350 bpm (see Figure 2). A physiological 2 : 1 AV block frequently occurs and atrial flutter should always be suspected with a ventricular rate of 150 bpm. In the elderly 4 : 1, 8 : 1, and other AV ratios may also be seen. Vagal maneuvers or intravenous adenosine can temporarily increase the AV block making flutter waves more visible and they have a tendency to be more apparent in the inferior leads (II, III, and AVF). Atrial flutter commonly occurs in patients with AF and vice versa. Antiarrhythmic medication prescribed for AF can convert the AF into atrial flutter. Management of the two conditions is essentially similar and although the stroke risk associated with atrial flutter may not be as great, there is still a substantial risk (Biblo *et al.*, 2001) and the high likelihood of coexistent AF indicates the use of anticoagulation.

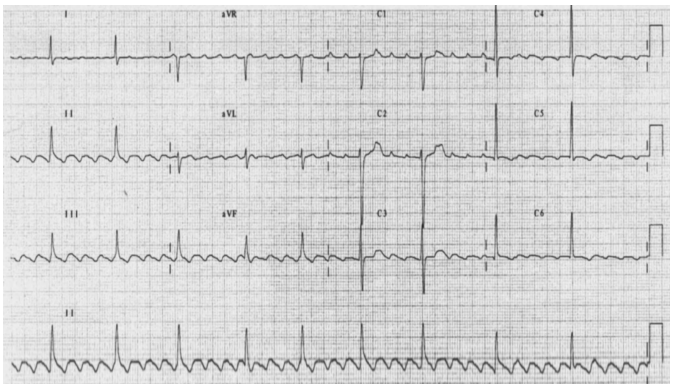

Figure 2 12-Lead ECG of atrial flutter

ATRIAL FIBRILLATION

Definition

AF is characterized by disorganized atrial activity confirmed on the ECG by the substitution of regular P wave activity by rapid fibrillatory waves varying in shape, amplitude, and timing. If AV node conduction is intact, the chaotic atrial activation will result in a rapid and irregular ventricular response. In the elderly, AV conduction may be impaired. A slower ventricular rate is common and sometimes verges on a symptomatic bradycardia (see Figure 3). Occasionally complete AV block may be seen.

Classification

A classification proposed by Gallagher and Camm (1997) is a useful system based on the time course of the arrhythmia and treatment intentions (see Figure 4). When the first episode is detected, it is important to understand that its duration may be uncertain and there may have been previous episodes, which were not symptomatic, remembered, or documented. The AF is then classified into the following categories according to its time course and intervention: paroxysmal atrial fibrillation (PAF), persistent, and permanent. PAF is characterized by recurrent episodes of AF alternating with sinus rhythm. The characteristic feature is that the episodes of AF terminate spontaneously. If the episodes of fibrillation continue for more than 7 days or patients require intervention to restore sinus rhythm, this is termed *persistent AF*. Permanent AF is more a statement of intent rather than a pathological description and is reserved for patients in whom AF is resistant to conversion or accepted, and there are no further attempts to achieve sinus rhythm.

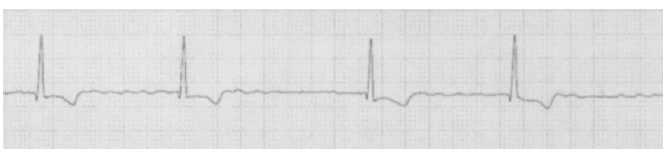

Figure 3 Rhythm strip of patient in AF with a bradycardic ventricular response

Epidemiology

AF is more common with increasing age and is the commonest sustained arrhythmia in the elderly. An analysis of 1.4 million patients registered with 211 general practices in England and Wales showed that prevalence rates increase with age from <1 in 1000 in those under 35 years to >100 in 1000 in those aged 85 years and older (Majeed *et al.*, 2001). A review of population based studies published between 1989 and 1994 calculated that approximately 70% of individuals with AF are between the ages of 65 and 85 years (Feinberg *et al.*, 1995). We are in part a victim of our own success owing to prognostic improvements made in coronary heart disease and heart failure, conditions known to predispose to the development of AF. This, together with an aging population, has led to the description of a near-epidemic of AF (Camm, 2002). In 2000, the projected direct cost of AF to the National Health Service (NHS) was calculated at £459 million, 0.98% of total NHS expenditure (Stewart *et al.*, 2004), a conservative estimate as costs related to stroke rehabilitation and anticoagulant related hemorrhage were not considered.

Etiology

Valvular AF

It is essential to make a distinction between valvular versus nonvalvular AF because of the consequence for stroke risk. In the Framingham Study, patients with rheumatic heart disease and AF had a 17-fold increase in stroke risk compared to age matched controls (Wolf *et al.*, 1978). There have been no randomized controlled trials to assess the efficacy of anticoagulation in this group, but the benefits are clear and no controversy exists.

Nonvalvular AF

AF occurring in the absence of rheumatic mitral stenosis or a prosthetic heart valve is termed *nonvalvular AF* (Fuster *et al.*, 2001), which can then be further subdivided:

1. **With associated cardiovascular disease**

Hypertension (*see* **Chapter 48, Hypertension**), heart failure (*see* **Chapter 50, Heart Failure in the Elderly**), and coronary artery disease (*see* **Chapter 46, Ischemic Heart Disease in Elderly Persons**) are commonly associated with AF, and of these, heart failure carries the highest predictive risk for the development of AF (Kannel *et al.*, 1982). Hypertension is identified as the commonest cardiac

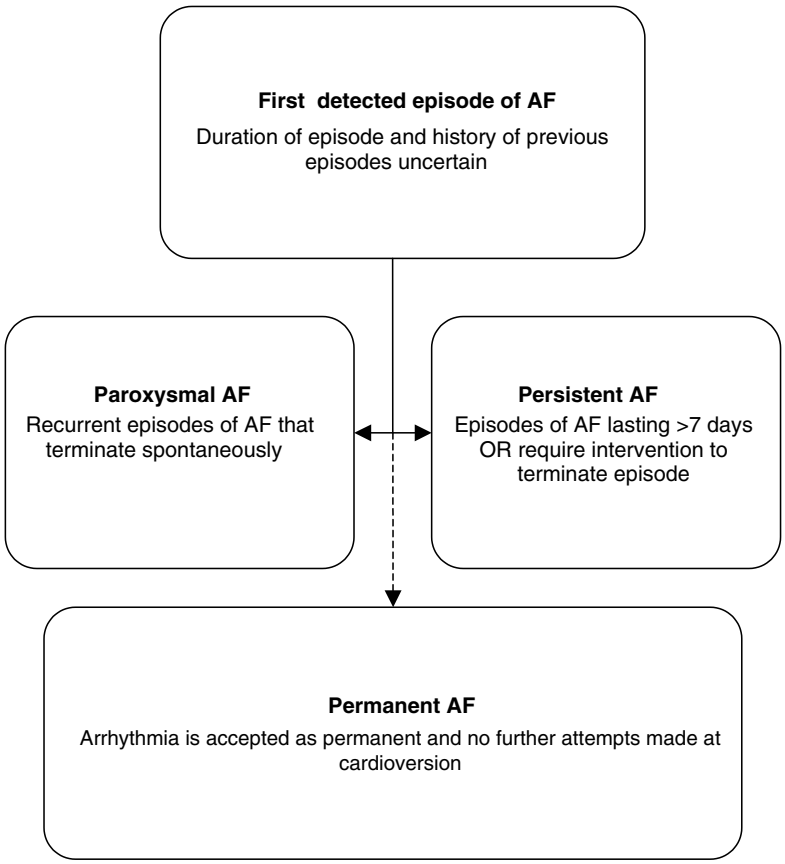

Figure 4 Diagram illustrating the classification of AF

precursor, but because of a high incidence in the general population this does not equate to a strong predictor. However, when associated with left ventricular hypertrophy by electrical criteria on the ECG, this does strengthen its contribution. Coronary artery disease can be both a reversible risk factor (ongoing ischemia or infarction) or irreversible (scar formation from prior infarction).

2. **Reversible causes**

Identifiable precipitants: electrolyte disturbance, sepsis, stress, hyperthyroidism, pulmonary disease, hypoxia, alcohol or caffeine intake, and acute myocardial ischemia or infarction. These factors are all to be considered both in a first detected episode of AF and for the patient with a recent compromise in rate control.

3. **Lone AF**

Patients with a structurally normal heart in whom no identifiable cause can be found for their AF are termed as having lone AF. This is probably rare in the elderly since almost all patients will have a degree of underlying heart disease by this stage. Therefore, such a diagnosis of exclusion should only be made with caution. In a small number of younger patients, sympathetic or vagal overstimulation may trigger AF. If identified in a particular patient, this could influence the choice of antiarrhythmic medication.

Consequences

Mortality

AF is associated with a twofold increase in all-cause mortality as compared to age and sex matched controls (Kannel *et al.*, 1982).

Atrial Remodeling

It is a common finding for patients presenting with new onset AF to spontaneously cardiovert to sinus rhythm within 24 hours of its onset. A study of patients presenting with AF of <72 hours duration showed that in this cohort, spontaneous conversion to sinus rhythm occurred in almost 70% of patients and a clinical duration of AF of <24 hours was the best predictor (Danias *et al.*, 1998). The success of electrical or chemical cardioversion and the subsequent maintenance of sinus rhythm are generally higher with AF of a shorter duration. These observations are consistent with the concept that AF itself is capable of inducing an

electrical remodeling of the atria, which in turn sustains the arrhythmia. Electrophysiological artificial maintenance of AF in an animal model has been shown to induce reversible atrial changes (shortened atrial refractoriness) that lead to the perpetuation of AF (Wijffels *et al.*, 1995) and eventually to histological (cellular dedifferentiation, fibrosis) and gross structural changes (atrial dilatation).

Hemodynamic Function

With the chaotic activation inherent in AF, synchronous atrial mechanical function is not possible. Therefore, the left ventricle can only fill passively, without the late diastolic contribution from atrial contraction. This in turn can lead to a marked decrease in cardiac output in those patients with already impaired ventricular filling (e.g. hypertensives). A further deterioration in hemodynamic function results from the irregularly irregular ventricular rhythm and the inappropriate tachycardia if rate control is poor. Postsuccessful cardioversion, the reduction in heart rate, and restored atrial mechanical function lead to quantifiable improvements in left ventricular function (Upshaw, 1997). The return of atrial contraction may be delayed if the AF has been present for a substantial period of time.

Ventricular Changes

A persistent, rapid ventricular rate can lead to impaired left ventricular function, a tachycardia-induced cardiomyopathy. Heart failure may be the presenting complaint. Animal models of chronic rapid pacing and small human studies documenting improvement in ventricular function with rate or rhythm control support this concept (Shinbane *et al.*, 1997). Mechanisms need further elucidation, but it is crucial that, if suspected, rate and/or rhythm control need to be strenuously pursued.

Thromboembolism

The risk of stroke in nonrheumatic AF patients is 5.6 times greater than age matched controls with an identical blood pressure distribution (Wolf *et al.*, 1978). Thrombus formation, often in the left atrial appendage (LAA), is responsible for embolic stroke and systemic embolism in the context of AF. Stroke risk demonstrates a consistent and significant increase with age from 6.7% in those aged from 50 to 59 years to 36.2% for ages from 80 to 89 years (Wolf *et al.*, 1987). Asymptomatic cerebral infarction based on computerized tomography (CT) findings has been found in 14.7–48% of AF patients (Ezekowitz *et al.*, 1995; Feinberg *et al.*, 1990; Petersen *et al.*, 1987). The large variation in incidence is probably due to the use of different radiological definitions of infarction and study size. The two largest studies (Ezekowitz *et al.*, 1995; Feinberg *et al.*, 1990) showed statistically significant associations of silent infarction with increasing age. Compared to non-AF strokes, those occurring in the context of AF have a greater mortality and survivors are more likely to suffer a recurrence and greater disability (Lin *et al.*, 1996). Asymptomatic AF carries the same thromboembolic risk as symptomatic AF and intermittent AF has been shown to also have similar rates of ischemic stroke and predictors as sustained AF (Hart *et al.*, 2000). Pooled data from five trials of anticoagulation (aspirin/warfarin) in AF have demonstrated the following clinical risk factors for stroke in nonrheumatic AF: increasing age, history of hypertension, previous stroke or transient ischaemic attack (TIA) (*see* **Chapter 69, Epidemiology of Stroke**; **Chapter 71, Acute Stroke**), and diabetes (Atrial Fibrillation Investigators, 1994). A pooled analysis of echocardiographic data from three of these trials demonstrated that left ventricular systolic dysfunction (as defined by global or regional wall motion abnormalities shown on 2D transthoracic echo) is an independent risk factor for stroke in AF (Atrial Fibrillation Investigators, 1998). In addition, increased left atrial diameter (measured by m-mode echocardiography) is an independent predictor of thromboembolism (The Stroke Prevention in Atrial Fibrillation Investigators, 1992). The presence of thrombus in the LAA and its precursor, the appearance of spontaneous echo contrast, are also associated with thromboembolism (Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography, 1998). Therefore, patients with AF can be risk stratified for stroke on the basis of clinical and echocardiographic data. This enables informed, balanced decisions to be made regarding the choice of anticoagulation.

Clinical Manifestations

AF can have a diverse clinical presentation, whether symptomatic or asymptomatic. Patients may report experiencing palpitations, dyspnea, or chest pain. Release of atrial natriuretic peptide (ANP) can be associated with polyuria, although this is relatively uncommon in the elderly. Patients may only present with the consequences of disease: thromboembolic complications; heart failure secondary to the tachycardia-induced cardiomyopathy; or symptoms secondary to reduced cardiac output (light-headedness, fatigue). Cognitive impairment secondary to cerebral hypoperfusion or recurrent thromboembolism is important to distinguish as this would identify a potentially treatable cause of impairment. Syncope is not a common presentation of AF and generally indicates additional pathology such as conduction system disease or aortic stenosis.

History and Examination

There needs to be a focused workup concentrating on the following points:

Confirmation of arrhythmia

The clinician should elucidate any prior history of palpitations and associated symptoms. A review of medication past and present, for warfarin or antiarrhythmics, should be

undertaken and response/tolerance to these agents noted. On examination, there is an irregularly irregular pulse and variation in loudness of the first heart sound. When AF is rapid, the second heart sound may not be heard. Notes should be reviewed for any documented evidence of previous arrhythmia (ECG, rhythm strip).

Etiology of arrhythmia

It is essential to identify any possible reversible triggers that may be responsible for a new episode of AF or deterioration in previously well controlled disease. An assessment of associated cardiovascular disease should also be made both for etiology and stroke risk assessment.

Effect of arrhythmia on the patient

It is important to identify a clear pattern of symptoms attributable to the arrhythmia and any indication of cardiovascular compromise. Evidence of end-organ effects such as heart failure or stroke should also be sought for, as this may influence treatment decisions such as anticoagulation.

Patient assessment for management options

A balanced decision regarding the risks and benefits of anticoagulation should be made; it is imperative that any potential bleeding risks (such as previous hemorrhage or history of falls) are identified. A social history (emphasizing exercise tolerance, living conditions, access to support, and cognitive function) is important. A review of medication will establish potential risks of drug interactions and polypharmacy. Issues of noncompliance should be explored as warfarin therapy, in particular, will require stable and consistent administration.

Optimal investigation

ECG documentation is needed for diagnosis. A 12-lead ECG is essential, as this can provide evidence of prior myocardial infarction, left ventricular hypertrophy, and AV node or bundle branch conduction disease. Table 3 details the blood tests to be performed in each patient.

Imaging

Transthoracic echocardiography (TTE) is an essential investigation in any patient with AF, regardless of age. It provides an assessment of the left atrium, mitral valve, and left ventricular function and dimensions, thus providing information regarding etiology and for stroke risk assessment. TTE has its limitations since it cannot reliably exclude the presence of thrombus in the LAA. Transesophageal echocardiography (TOE) is the imaging of choice to examine the LAA for thrombus, or its precursor spontaneous echo contrast. Its role in cardioversion is discussed below. A chest X ray and lung function tests are only required when lung disease is suspected on history or examination. A CT head scan is indicated if there is any evidence of cerebrovascular disease.

Table 3 Necessary blood tests for investigation of AF

Blood tests	Reasoning
Full blood count	Hb and MCV to exclude a bleeding disorder. Platelet count to minimize the risk of bleeding should heparin be required
INR	Baseline INR is justified in the elderly because of their elevated bleeding risks
Liver function tests	In the event of a deranged baseline INR
Urea + electrolytes	Serum potassium is essential and any disturbance must be corrected before starting antiarrhythmics. Renal function must be assessed given that there is a high use of renally excreted drugs in the management of AF in the elderly (although specific drug levels, e.g. digoxin, are not indicated unless subtherapeutic levels or toxicity is suspected)
Thyroid function tests	To be checked if hyperthyroidism is clinically suspected or amiodarone is to be used. Otherwise routine testing is debatable (Vlietstra, 2002)

Management

There are two aims in the management of AF: to prevent thromboembolism and to control the arrhythmia (the options being rate or rhythm control). The classification of AF into paroxysmal, persistent, and permanent is clinically useful as it gives a clear guide to a management strategy for each patient. In PAF, the aim is to maintain sinus rhythm and control the ventricular rate when AF does occur. For a patient with permanent AF, the decision has been made to accept the arrhythmia and instead symptomatic improvement is attained with ventricular rate control. Persistent AF, however, presents the clinician with a dilemma: standard practice has been to strive for sinus rhythm by electrical or pharmacological means, with symptom control, improved hemodynamics, and reduced risk of thromboembolism being the proposed rationale. However, rhythm control medication has the problem of proarrhythmia and recently published randomized controlled trials (Hohnloser *et al.*, 2000; Wyse *et al.*, 2002; Van Gelder *et al.*, 2002; Carlsson *et al.*, 2003) have not supported our assumptions regarding the benefits of rhythm control; these are summarized in Table 4.

The conclusion to draw from these results is that for elderly patients with persistent AF, rate control is generally no worse an option than rhythm control. In a first detected episode of AF, one should consider an attempt at rhythm control and cardioversion is certainly first line therapy for acute hemodynamic compromise secondary to AF. However, in elderly patients who are tolerating the arrhythmia, accepting rate control should not be viewed as a failure. The next section will detail acceptable methods of rate and rhythm control for the elderly. Anticoagulation to prevent thromboembolism needs to be considered whichever strategy is chosen. How a patient is anticoagulated will depend upon the options available, duration of anticoagulation, and a risk benefit analysis for each patient.

Table 4 Randomized controlled trials assessing rate versus rhythm control for atrial fibrillation

Trial	*n*	Mean age (years)	F/U (years)	Results
AFFIRM AF + risk factor for stroke	4060	69.7	3.5 (mean)	No difference in overall mortality No difference in quality of life Increased hospitalization in rhythm control group
PIAF Symptomatic + persistent AF	252	61	1	No difference in symptoms No difference in quality of life Increased walking distance in rhythm control group Increased hospitalization in rhythm control group
RACE Persistent AF postelectrical cardioversion	522	68	2.3 (mean)	No difference in composite end-point (cardiovascular death, heart failure, thromboembolic complications, bleeding, severe drug adverse effects, implantation of pacemaker)
STAF Persistent AF + mild-moderate LV dysfunction	200	65	1.6	No difference in composite end-point (death, cardiopulmonary resuscitation, cerebrovascular event, and systemic embolization) Increased hospitalization in rhythm control group

AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management (Wyse *et al.*, 2002); PIAF, Pharmacological Intervention in Atrial Fibrillation (Hohnloser *et al.*, 2000); RACE, Rate Control versus Electrical cardioversion for persistent atrial fibrillation (Van Gelder *et al.*, 2002); STAF, Strategies of Treatment of Atrial Fibrillation (Carlsson *et al.*, 2003).

Rate control

As has already been discussed, bradycardia is not a normal finding for the elderly and similarly a slow ventricular rate in an elderly patient with untreated AF implies underlying conduction system disease (Falk, 2002). The aim of rate control is to maintain a patient's heart rate at what is physiologically appropriate for the level of exertion. This must not be at the expense of symptomatic pauses or bradycardia. Therapy must be tailored to the individual, but rates of 60 to 80 bpm at rest and 90 to 115 bpm during moderate exercise have been suggested as a target (Fuster *et al.*, 2001). This can be achieved through medication and/or nonpharmacological methods; although not infrequently no specific rate control therapy is needed in the elderly.

Pharmacological Rate Control

Digoxin

Digoxin, a muscarinic agonist, slows AV nodal conduction. This is sufficient to produce adequate rate control for elderly patients with low levels of exertion. This action can be overwhelmed when faced with high sympathetic stimulation which explains why digoxin is less effective during exercise and why patients with previously well controlled AF present with inadequate rate control in the context of an acute illness (Dayer and Hardman, 2002). Although digoxin can be considered as first line therapy for an inactive elderly patient, it should not be solely relied upon in the presence of high sympathetic tone (i.e. sepsis, pain, β-agonist medication). Digoxin also blocks the sodium/potassium ATPase exchange pump by occupying the potassium binding site (hence digoxin toxicity is potentiated in hypokalemia) and can act as a mild positive ionotrope (though probably not in the context of AF). Digoxin has not been shown to be of prognostic benefit in heart failure (Digitalis Investigation Group, 1997) but it can be safely used in patients with heart failure. In comparison to β-blockers and the non-DHP calcium channel antagonists used for rate control, digoxin has a relatively slow onset of action in the order of hours compared to minutes (Falk, 2002). This is acceptable if there is no urgency for rate control to be achieved. Digoxin compared to placebo produces a small but statistically significant reduction in the frequency of symptomatic episodes of PAF (Murgatroyd *et al.*, 1999) probably via a significant reduction in ventricular rate, recorded during patient activated recordings. However, 24-hour ambulatory ECG monitoring during this period failed to show any reduction in frequency, duration of AF, or ventricular rate. Digoxin was well tolerated by these patients and so is not believed to be detrimental in PAF, although its benefit is questionable. Concerns have been expressed as regarding its use in PAF, as digoxin has been shown to augment the shortening in atrial effective refractory period that can predispose to further episodes of AF (Sticherling *et al.*, 2000). Digoxin has no role to play in cardioversion. Neither oral (Falk *et al.*, 1987) nor intravenous (Digitalis in Acute AF Trial Group, 1997) preparations have been shown to be more effective than placebo. Digoxin is excreted in an unchanged form via the kidneys. Serum level monitoring and dose adjustment will be required in renal dysfunction. To reduce the risk of toxicity, a lower dosage than that required in younger patients should initially be used. The dose may then be up-titrated if the response is inadequate. There is an age-related decline in glomerular filtration rate and impaired renal function can easily develop with acute illness or changes to medication, such as introduction of a diuretic.

β-blockers

β-receptor antagonists block the action of catecholamines and hence are particularly useful in the context of high sympathetic drive. This may on occasion also be to their detriment as a decrease in maximal exercise tolerance has been

reported (Atwood *et al.*, 1987) as have measured reductions in VO2 max and cardiac output during exercise (Atwood *et al.*, 1999). A reduction in exercise tolerance is not universal though, and β-blockers remain the most effective agent for controlling ventricular rate during exertion. They should also be considered first line in the context of hypertension, ischemic heart disease, or stable LV dysfunction, although usually more β-blockade is needed for rate control than for heart failure and so β-blocker monotherapy is not useful for patients with both conditions. These agents have a rapid onset of action, but their use is restricted by bronchospasm. In cases of acute pulmonary edema, they should only be considered where there is no doubt that it is has been precipitated by decompensated AF (not an easy diagnosis to be certain of) and used in small, titrated doses.

Nondihydropyridine Calcium Channel Antagonists

Verapamil and diltiazem act directly on the AV node, slowing conduction. Both have a rapid onset of action similar to β-blockers and are a useful alternative in the context of airways disease. These too should be used with caution in pulmonary edema and do not have the prognostic benefits enjoyed by β-blockers in heart disease.

Amiodarone

In cases where amiodarone fails to chemically cardiovert AF, significant improvements in ventricular rate control can occur (Galve *et al.*, 1996). This is clinically useful where rapid control of AF is required to relieve symptoms and effective rate control can provide a significant benefit, even if cardioversion is unsuccessful. However, for the purposes of simple rate control, the agents discussed above are a more practical long-term option.

Combination of Rate Control Agents

A combination of β-blocker and non-DHP calcium channel antagonists is to be used only with caution. These are both negative ionotropes, which together can cause life-threatening hypotension or bradycardia. In addition, verapamil and diltiazem both inhibit the metabolism of propanolol and metoprolol, and hence if used together can result in synergistic detrimental effects (Karralliedde and Henry, 1998). Verapamil can cause a significant and unpredictable elevation in plasma digoxin levels and should not be used together. There are, however, no significant interactions of digoxin with diltiazem (Elkayam *et al.*, 1985), making it a preferred option over verapamil. Digoxin can also be used in combination with β-blockers, but vigilant follow-up is required for any of these combinations as the risk of conduction disease and hence the potential for bradyarrhythmias is more common in elderly patients. Amiodarone causes significant elevation in the plasma levels of digoxin, necessitating a halving of the digoxin dose if used simultaneously with amiodarone (Karralliedde and Henry, 1998).

Recommendations for Rate Control

- Choice of monotherapy on an individual basis: digoxin for patients with low levels of exertion; β-blockers for those with ischemic heart disease and in the absence of contraindications; or calcium channel antagonists (diltiazem or verapamil).
- Combination therapy of the above may be required to achieve adequate rate control at rest and during exercise. Careful dose titration to avoid bradycardia.
- For acute rate control, intravenous β-blocker (in the absence of contraindications) or calcium channel antagonist (diltiazem or verapamil).
- In those patients where adequate rate control cannot be achieved, or medication not tolerated, consider nonpharmacological methods.

Nonpharmacological Rate Control

Permanent Pacemaker

If adequate rate control is only achieved at the expense of an intolerant bradycardia (secondary to medication and/or conduction system disease) the implantation of a permanent pacemaker may be needed in addition to the rate control medication.

Ablate and Pace Strategy

If the ventricular response is refractory to medical rate control therapy or a patient is intolerant of all the available medications, the option of catheter-based ablation of AV node/Bundle of His should be considered. The main benefits of this approach are a reduction in symptoms and improved quality of life (Marshall and Gammage, 2002). Problems arise from the fact that this involves destruction of normal conduction tissue, an irreversible process that renders the patient permanently pacemaker dependent. The Post-AV nodal ablation Evaluation (PAVE) trial demonstrated a statistically significant improvement in functional and exercise capacity for those receiving a biventricular pacing system rather than traditional right ventricular pacing after AV nodal ablation for AF (Doshi *et al.*, 2004). Therefore, biventricular pacing may be important post-AV nodal ablation in order to avoid aggravation of poor LV function. In addition, this is a palliative approach and the thromboembolic risks of AF persist. One retrospective study of 585 patients (mean age 66 years) did demonstrate a low incidence of thromboembolic events postprocedure (Gasparini *et al.*, 1999). However, this study lacked a control group for comparison and choice of antithrombotic medication was physician-led rather than randomized. The patients receiving warfarin had a significantly higher incidence of embolism, compared to those on aspirin or no medication, but this is not as surprising as it first seems given these patients were at greatest risk of embolic events as judged by their physicians.

Rhythm Control

Synchronized DC Cardioversion

In spite of reservations over the putative benefits of a rhythm control strategy, there are instances when an immediate attempt at cardioversion should be made. Patients with acute, uncontrolled AF who become hemodynamically compromised or experience evolving myocardial ischemia/infarction require urgent synchronized electrical DC cardioversion under conscious sedation. If not already anticoagulated within therapeutic range, then the procedure should be preceded with an intravenous bolus of heparin and followed by a continuous infusion maintaining the activated partial thromboplastin time (APTT) at 1.5 to 2 times control. A prospective study of 357 patients (mean age 68 years) presenting with AF of duration that was clinically estimated at $<$48 hours and without prior anticoagulation demonstrated a low incidence of thromboembolism with cardioversion (Weigner *et al.*, 1997). Cardioversion can cause temporary disruption of left atrial mechanical function, which can lead to the development of spontaneous echo contrast and thrombus formation. Therefore, despite the low incidence of thrombus formation in AF of less than 48 hours duration, a risk becomes evident postcardioversion. The duration of risk is uncertain, especially in cases of cardioversion for acute AF. A retrospective, pooled analysis of studies of electrical cardioversion of AF of various durations demonstrated that 98% of embolic episodes occurred within 10 days of cardioversion (Berger and Schweitzer, 1998). Current recommendations are to commence oral anticoagulation with warfarin and maintain an international normalised ratio (INR) of 2 to 3 for at least three to four weeks (Fuster *et al.*, 2001).

Elective DC Cardioversion

Elective cardioversion under short acting general anaesthesia should be considered for patients with a first detected, stable episode of AF. Four weeks of anticoagulation with warfarin must be completed prior to attempted cardioversion of AF greater than 48 hours duration. This been shown to successfully resolve preformed atrial thrombus and results in an 87% improvement in the incidence of thromboembolism at cardioversion (Collins *et al.*, 1995). Where available, an alternative strategy of transesophageal echo guided cardioversion to exclude the presence of LAA thrombus and obviate the need for prior anticoagulation is safe, reduces the time to cardioversion, is associated with fewer hemorrhagic events (Klein *et al.*, 2001), and is cost-effective (Seto *et al.*, 1997). Timing of recovery of left atrial mechanical function is related to duration of prior AF (Upshaw, 1997). If the patient remains in sinus rhythm at four weeks postcardioversion, consideration can only then be given to stopping the warfarin. As discussed above, however, duration of thromboembolic risk is still uncertain, and in the Rate Control versus Electrical Cardioversion trial (Van Gelder *et al.*, 2002) 17% of all thromboembolic complications occurred in the rhythm control arm when warfarin therapy was ceased. Electrolyte imbalances must be excluded prior to an attempt at cardioversion. Acute successful cardioversion is reported with rates of 65 to 90% (Levy *et al.*, 1998), but relapse rates can be high with age, hypertension, AF duration, and New York Heart Association (NYHA) functional class III or IV predicting long-term failure of electrical cardioversion (Van Gelder *et al.*, 1996). In the event of relapse, one further attempt at cardioversion with concomitant use of antiarrhythmic medication is recommended (Fuster *et al.*, 2001). Amiodarone would be a suitable choice for the elderly patient, but consideration must be paid to the risks of such a strategy (proarrhythmic medication, increased hospitalization) as compared to accepting rate control for each individual patient.

Pharmacological Cardioversion

The risk of thromboembolism is present irrespective of the method of cardioversion employed; hence anticoagulation must also be used with pharmacological attempts at rhythm control. The choice of agents that can be used in elderly patients is more restricted than that for younger patients with AF. This is because of the interaction between increased comorbidity in the elderly population and the side-effect profile of medication used.

Amiodarone

Vaughan-Williams class III antiarrhythmic along with sotalol and dofetilide blocks potassium channels, thereby slowing repolarization and prolonging the QT interval. However, amiodarone is quite distinct from the other class members: it also affects calcium and sodium channels; it has an extensive half-life (in the order of 50 days); and it has a broad side-effect profile but a practical safety profile, enabling its use in LV dysfunction and ischemic heart disease. It is indicated for both cardioversion and maintenance of sinus rhythm. The side-effect profile is listed in Table 5. Amiodarone is metabolized by the cytochrome P450 system and so the dosage may have to be increased when used concomitantly with enzyme inducers rifampicin or carbamazepine. Amiodarone itself is an enzyme inhibitor, resulting in increased drug levels of phenytoin or warfarin if used in combination. It is important to consider that because of its long half-life, side effects or interactions may persist for some time, even after discontinuation of the amiodarone.

Sotalol

Another potassium channel blocker, sotalol has additional β-blocking action (class II) that predominates over the class III action at low doses. This may limit its efficacy in the elderly population where intolerance of substantial β-blocker action may prevent high enough dosing for the class III effect to manifest. β Antagonism has its uses, however, and sotalol would be first line therapy to maintain sinus rhythm in a patient with ischemic heart disease.

Table 5 Commonly experienced side effects of amiodarone therapy

System	Adverse effect	Comments
Respiratory	Bronchiolitis obliterans organizing pneumonia	Reversible if detected early, but heart failure may confuse the clinical picture and delay diagnosis
	Chronic interstitial pneumonitis	
Thyroid	Hypo- and hyperthyroidism	Regular monitoring of biochemical thyroid status is essential
Gastrointestinal	Elevation in liver transaminases	Liver failure is rare
	GI upset	
Cardiac	Sinus bradycardia	Avoidance of hypokalemia or the combined use of other class III agents to minimize QT prolongation
	Torsades de pointes	
Ocular	Corneal microdeposits	Considered benign, but visual symptoms require review
Neurological	Peripheral neuropathy	Generally reversible on discontinuation
	Ataxia	
	Tremor	
Skin	Photosensitivity	Advise to reduce exposure to sunlight and continue for few months postdiscontinuation of drug
	Blue-grey discoloration	

Flecainide

Class 1C antiarrhythmic: a sodium channel blocker that delays depolarization and can lead to prolongation of the QRS width. In the light of the Cardiac Arrhythmia Suppression Trial (CAST) where flecainide in postinfarct patients was associated with an increased mortality (Akiyama *et al.*, 1991), concern has been expressed regarding its safety for use in the elderly, who will generally have a degree of ischemic heart disease.

Dofetilide/Ibutilide

These are newer class III agents that may go on to find their niche in the treatment of AF. However, high incidence of ventricular arrhythmias currently limits their use to closely monitored in-patients.

Recommendations for Rhythm Control

- Electrical cardioversion for AF resulting in hemodynamic compromise.
- Elective electrical or pharmacological cardioversion should be considered for patients with a first detected, stable episode of AF, or for patients with intolerable symptoms of AF.
- Choice of pharmacological agent on an individual basis: amiodarone is suitable for patients with left ventricular dysfunction or ischemic heart disease, whereas d-sotalol would be first line in the context of ischemic heart disease.

Nonpharmacological Rhythm Control

A number of nonpharmacological options have been explored to control and prevent AF with varying degrees of success. Currently these procedures are not widely suitable for an elderly population, but can be considered on an individual basis.

Ablation Procedures (Surgical and Catheter Based)

For its continuation, AF needs a critical mass of atrial tissue to allow the spread of multiple waves of depolarization (Lairikyengbam *et al.*, 2003). The maze operation has been developed and refined whereby multiple atrial incisions are made to interrupt abnormal conduction pathways, but maintain a route for sinus impulses from the SA node to pass to the AV node. The procedure achieves maintenance of sinus rhythm at three months in >90% of selected patients (Cox *et al.*, 1996). The major drawback is the requirement for median sternotomy and the use of cardiopulmonary bypass. This has limited its use to patients who are already requiring cardiac surgery for another indication such as valve replacement. Catheter-based approaches have attempted to duplicate the maze procedure without requiring extensive surgery and procedures targeting the left atrium have had more success than those in the right atrium (Fuster *et al.*, 2001). The potential application of catheter ablation has grown since the detection of ectopic beats originating from pulmonary veins that are capable of instigating AF. Short-term studies have shown success in the mapping and ablation of foci for PAF (Haissaguerre *et al.*, 1998; Chen *et al.*, 1999). Refinements need to be made to the localization of foci and choice of energy source used (radiofrequency, laser, or cryoablation). The procedure is time consuming; there is a substantial risk of pulmonary vein stenosis, thromboembolism, and damage to adjacent structures (Wellens, 2000) but may prove useful in selected patients with PAF.

Atrial Pacing

It has been reported that atrial (including dual chamber) pacing has reduced the incidence of AF versus ventricular pacing alone in patients receiving a permanent pacemaker for sick sinus syndrome. Large trials have had conflicting results with reports of reduced incidence of AF (Andersen *et al.*, 1997; Connolly *et al.*, 2000c; Lamas *et al.*, 2002) and no reported differences (Lamas *et al.*, 1998; UKPACE). No trial has yet shown a statistically significant reduction in mortality. Therefore, in those patients receiving a pacemaker for sinus node dysfunction, atrial pacing could be considered

to reduce the incidence of AF. This does not translate to AF patients who do not require a pacemaker for another clinical indication. The importance of the site of atrial pacing and multisite atrial pacing is being investigated and may find a future role in patients with symptomatic, drug refractory AF (Savelieva and Camm, 2002).

Future Possibilities

A variation of the surgical maze procedure has been successfully performed on an experimental canine model without the need for cardiopulmonary bypass (Lee *et al.*, 1999). This could provide the model for a less invasive procedure for humans. Thorascopic LAA obliteration to prevent stroke in high-risk patients (mean age 67 years) has been shown to be technically feasible without producing neurological disability in the short term (Blackshear *et al.*, 2003). Catheter-based occlusion of the LAA in high-risk patients (mean age 69 years) in an attempt to prevent stroke has proved feasible in human studies (Sievert *et al.*, 2002). Finally, a device known as a *Diverter* is being developed for high stroke risk patients. It involves the placement of a long semiporous sheath (Diverter) from the common to external carotid artery and is intended to divert thrombus and embolus away from the internal carotid system.

ANTICOAGULATION

At present there are the following options for thromboprophylaxis: adjusted dose warfarin (INR 2–3); aspirin (325 mg once daily); and low, fixed dose warfarin +/− aspirin.

Adjusted Dose Warfarin (INR 2–3)

A meta-analysis of six trials with patients of mean age 69 years demonstrated that adjusted dose warfarin reduced the relative risk of stroke by 62% (Hart *et al.*, 1999). The benefit was consistent for primary and secondary prevention.

Aspirin

A meta-analysis of six trials with patients of mean age 70 years demonstrated that aspirin reduced the relative risk of stroke by 22% (Hart *et al.*, 1999). Wide ranges of dosages were employed, but statistical significance was only achieved in the Stroke Prevention in Atrial Fibrillation (SPAF) study (SPAF Investigators, 1991), which utilized a dosage of 325 mg once daily.

Adjusted Dose Warfarin or Aspirin?

A meta-analysis of five clinical trials compared adjusted dose warfarin and aspirin with patients of mean age 71 years. Warfarin reduced relative risk of all stroke (ischemic and hemorrhagic) by 36% compared to aspirin (Hart *et al.*, 1999). Twice as many intracranial hemorrhages occurred in the warfarin group, but all-cause mortality was similar.

Is there a Role for Low Dose Warfarin?

The SPAF III study (SPAF Investigators, 1996) investigated the efficacy of low intensity fixed dose warfarin (INR 1.2–1.5) plus aspirin 325 mg versus adjusted dose warfarin. The low dose regimen was associated with a significantly higher incidence of stroke or thromboembolism. The Primary prevention of Arterial Thromboembolism in patients with nonvalvular Atrial Fibrillation (PATAF) study (Hellemons *et al.*, 1997) showed no difference between aspirin 150 mg, adjusted dose warfarin and low dose warfarin, but excluded patients aged over 78 years from the study and so the results cannot be applied to the elderly.

Current Guidelines for Anticoagulation in AF

All elderly patients will require some form of prophylaxis versus thromboembolism (aspirin or warfarin). The choice of agent is based on a risk versus benefit assessment for each individual patient and this decision should be continually reviewed. See Table 6 for a list of indications for warfarin. The classification of AF or presence of atrial flutter does not influence the decision. Adjusted dose warfarin (INR 2–3) is indicated in elderly patients with AF unless there are contraindications, in which case aspirin 325 mg once daily can be considered instead.

Table 6 Indications for adjusted dose warfarin in stroke prevention for patients with nonvalvular AF

Risk category	Low	Moderate	High
Antithrombotic medication	Aspirin 325 mg od or no therapy	Aspirin 325 mg od	Adjusted dose warfarin
Patient features	Age <60 years with no risk factors	Age <60 years with coronary artery disease Age 60–75 years with no high-risk features	Previous thromboembolic event Age >75 years LV dysfunction Diabetes Hypertension LA thrombus or spontaneous echo contrast Enlarged LA

The Under Use of Warfarin in the Elderly

There is considerable evidence for the under use of warfarin, especially in the elderly. In a survey of prevalence of AF and eligibility for anticoagulation in Newcastle, England, only 17% of patients aged over 75 years with AF and no irreversible contraindications were receiving warfarin (Sudlow *et al.*, 1998). A prospective study of 1138 stroke patients admitted to a neurology unit observed that only 12% of patients with AF who suffered a recurrent stroke were receiving warfarin prior to their recurrence (Jorgensen *et al.*, 1997). An American physicians survey reported that not only was older age a deterrent to providing anticoagulation, but also a lower intensity of anticoagulation was sought (McCrory *et al.*, 1995).

Is Old Age a Relative Contraindication to Anticoagulation?

A risk/benefit assessment for anticoagulation has to be made for each patient and this should be based on sound evidence.

1. Bleeding risk

While taking warfarin, most episodes of thrombosis occur at levels of INR <2 (Hylek *et al.*, 1996) and bleeding risk is higher with an INR >3 (SPAF Investigators, 1996). Bleeding risk has inconsistently been associated with increasing age. A recent prospective study of 461 patients aged 75 years or above showed no significant difference in bleeding rates compared to patients aged <70 years and an INR between 2 and 3 was confirmed as the safest and most effective (Palareti *et al.*, 2000). The hurdle to overcome, however, is trying to maintain a patient's INR within the range of 2 to 3. Practical issues are discussed below, but even in the setting of a major clinical trial (SPAF III) only 61% of INR measurements were in that range.

2. Practicalities of regular monitoring in the elderly

Standard monitoring of INR has taken place in the hematology based anticoagulation clinic. Like most hospital outpatient clinics, these can be extremely busy, have inflexibility in appointment times and dates, and can represent a significant challenge for the elderly patient. Where difficulties are perceived, this may even influence the decision to anticoagulate a patient with warfarin. This need not be the case and availability and ease of use can be improved by disseminating the responsibility for monitoring into the community. Reliable and portable machines for measuring prothrombin times are available (Fitzmaurice and Machin, 2001) and dose adjustments can be made by general practitioners or nonclinicians such as pharmacists (Chenella *et al.*, 1983) at practices or visiting nursing homes.

3. Pharmacokinetics of warfarin in the elderly

Cross-sectional and longitudinal (Wynne *et al.*, 1996) studies have both reported a fall in warfarin dose requirements with increasing age. Conclusive mechanisms are yet to be fully elucidated, but reduced drug clearance will play a role in the elderly. Although this does not influence achievement of a steady state of anticoagulation, it does affect how the anticoagulation is induced. The commonly used Fennerty regimen (Fennerty *et al.*, 1984) was first described in patients with a mean age of 52 years. A low dose induction regimen has been shown to induce fewer INR measurements >4.5 and spend more time within therapeutic range for patients aged over 75 years (Gedge *et al.*, 2000). This was achieved at the expense of an increase in mean time to reach therapeutic INR, which although on average was less than a single day (Gedge *et al.*, 2000), may present an unacceptable delay in discharge from hospital.

4. Pharmacodynamics of warfarin the elderly

Issues of noncompliance or inconsistencies in consumption of tablets in elderly patients with dementia are a particular concern for warfarin, a drug with considerable individual variation and a narrow therapeutic window where a greater or lesser effect both carries significant risk. In a study of long-term care facilities, those patients with AF who were also diagnosed as having dementia were less likely to receive warfarin (Gurwitz *et al.*, 1997). Clearly, dementia can encompass a wide range of degrees of cognitive impairment and no one would argue that in the presence of end-stage dementia the benefits of anticoagulation for AF would outweigh the discomfort and inconvenience of regular monitoring and minor bleeding. However, in the context of multiinfarct dementia the benefits of anticoagulation to halt the stepwise decline become more apparent. Indeed, a supervised residential facility provides an environment where compliance issues can be managed.

5. Risks associated with polypharmacy

Numerous interactions have been reported with warfarin. Table 7 lists common agents involved, but is not intended as a comprehensive list. The anticoagulant effect will be reduced by foods that are high in vitamin K such as parsley, broccoli, and liver. Polypharmacy and the risk of falls have to be considered with sedative medication or postural hypotension secondary to antihypertensives.

Table 7 Medications known to interact with warfarin

System	Potentiates anticoagulation	Decreases anticoagulation
Cardiovascular	Amiodarone	Spironolactone
Endocrine	Thyroxine, corticosteroids	–
GI tract	Cimetidine	Cholestyramine
Central nervous	Chlorpromazine, tricyclic antidepressants	Barbiturates, Carbamazepine
Malignancy	Tamoxifen	–
Immune system	Aminoglycosides, metronidazole	Rifampicin

Future Alternatives

Clearly, warfarin therapy has its disadvantages. There are a number of options under investigation that may provide a simpler alternative in the near future. The relatively new antiplatelet agent clopidogrel reduced the combined risk of ischemic stroke, myocardial infarction, or vascular death versus aspirin alone (CAPRIE Steering Committee, 1996) although only 4% of study patients had AF. The AF Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) will compare clopidogrel and aspirin versus warfarin (INR 2 to 3) and clopidogrel and aspirin versus placebo and aspirin, and reports in 2007. The emergence of the fixed dose oral direct thrombin inhibitor ximelagatran is an attractive alternative for the elderly. Pharmacokinetic profile is predictable, hence removing the need for regular monitoring and dose adjustment. Metabolism is independent of the cytochrome P450 system, resulting in less potential for significant drug interactions. Steady state anticoagulation is achieved with one day of dosing and the drug is renally excreted (Reiffel, 2004). Significant side effect of reversible elevation in liver transaminases and a twice-daily dosing regimen are the only limitations. The clinical trials SPORTIF III (Stroke Prevention using the Oral Thrombin Inhibitor ximelagatran in patients with nonvalvular atrial Fibrillation) and SPORTIF V evaluated ximelagatran against warfarin in AF patients with high risk of thromboembolism. SPORTIF III, an open label trial with patients mean age 70 years, demonstrated that ximelagatran was at least as effective as warfarin in preventing stroke and was associated with less minor and major bleeding (Olsson, 2003). SPORTIF V, a double-blinded trial with patients mean age 72 years, produced similar results (Halperin, 2003).

VENTRICULAR ARRHYTHMIAS

A ventricular ectopic beat or premature ventricular contraction (PVC) is a depolarization that originates in the ventricles, has a wide QRS complex, and is followed by a normal compensatory pause (see Figure 5). Five or more consecutively occurring premature ventricular depolarization (PVD)s with a rate in excess of 120 beats per minute is termed *ventricular tachycardia* (VT). VT is defined as nonsustained if lasting less than 30 seconds in duration (see Figure 6) and sustained if lasting greater than 30 seconds or requiring immediate cardioversion. VT is characterized by an ECG appearance of a broad complex (QRS >0.12 seconds) tachycardia, but this

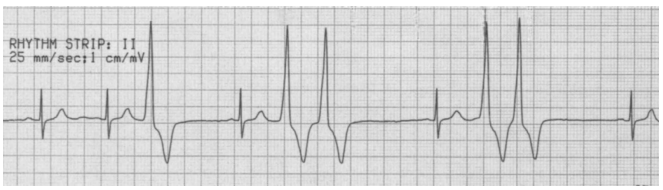

Figure 5 Rhythm strip showing single and paired ventricular ectopic beats followed by normal compensatory pauses

is not specific for VT. An important differential to consider is a supraventricular tachycardia (SVT), which has aberrant conduction (coexistent BBB widening the QRS complex).

How to Differentiate VT from SVT with Bundle Branch Block (BBB)

The primary principle for differentiating the two is that VT originates in the ventricles whereas an SVT is supraventricular in origin. Therefore, the former may have evidence of independent atrial activity (p waves and the possibility of normal capture and fusion beats occurring) and the latter can be influenced by depressing AV node function (adenosine, vagal stimulation.) In addition, ventricular tachycardia is regular. As already discussed, the commonest supraventricular arrhythmia in the elderly is AF, which has an irregularly irregular rhythm. Therefore, an irregularly irregular broad complex tachycardia could be atrial in origin, if not ventricular fibrillation (VF) or torsades (both of which are easier to identify.) Finally, an important point to highlight is that hemodynamic instability is not a reliable discriminating factor. Both arrhythmias can be asymptomatic or symptomatic and it is safer to assume all broad complex tachycardias are ventricular in origin until proven otherwise. Table 8 summarizes these features.

Prognosis

In patients with no clinical evidence of heart disease, single or paired PVDs and nonsustained VT are not associated with an increase in coronary events and do not require treatment with antiarrhythmic medication (Aronow, 1999). However, in patients who are postmyocardial infarction, the frequency of PVDs, runs of PVDs and reduced left ventricular ejection fraction are all independently associated with arrhythmia mortality and total mortality (Bigger *et al.*, 1984). These findings are consistent after the introduction

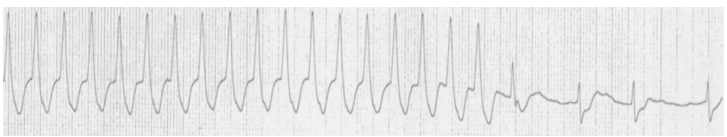

Figure 6 Rhythm strip showing nonsustained ventricular tachycardia

Table 8 Features consistent with differential causes of a broad complex tachycardia

Feature	Ventricular tachycardia (VT) versus Supraventricular tachycardia (SVT) with bundle branch block (BBB)
Men aged >40 years old, with prior myocardial infarction	VT is more likely than SVT with BBB
Hemodynamic stability of patient	Not a reliable discriminator and for safety VT should be the default diagnosis until proven otherwise
Concordance of QRS deflections in chest leads	Positive or negative concordance is more common with VT
Evidence of AV dissociation. Presence of p waves, capture beats (normal QRS beats occurring) or fusion beats (normal QRS fusing with a complex of VT producing a bizarre morphology)	Independent atrial activity is highly suggestive of VT
QRS complex duration	A duration of >140 msec is more common in VT
Lead V1 QRS complex configuration	QRS complexes in lead V1 with two positive peaks (RR′ or RSR′ if there is an intervening S wave) where the R wave height >R′ wave height, is more common in VT
Leads V1 and V6 QRS complex configuration	Lead V1 R wave height <R′ wave height and lead V6 a large R wave flanked by a small Q and S wave (qRs) is suggestive of SVT with BBB
Response to vagal stimulation or adenosine	VT has no response to either as tachycardia originates below the AV node, whereas an SVT with BBB may terminate

of thrombolysis (Maggioni *et al.*, 1993). For a ventricular tachyarrhythmia to develop, a substrate and a triggering factor are required. The substrate can either be structural (infarcted or hypertrophic myocardium resulting in myocytes of differing refractory periods forming a potential reentrant circuit) or electrical (the occurrence of early or delayed afterdepolarizations). The triggering factor is typically a transient influence such as electrolyte imbalance, acute ischemia, or even an antiarrhythmic medication in the case of torsades de pointes.

Investigation

Management of sustained ventricular arrhythmias requires assessment and, when necessary, resuscitation of the patient, together with a brief focused history and examination. The risk factors, features, and end-organ effects of ischemic heart disease and left ventricular dysfunction need to be sought. The presence of reversible precipitants needs to be excluded. If at all possible, a 12-lead ECG should be recorded and blood should be tested for the presence of acute ischemia or electrolyte imbalance (particularly serum potassium and magnesium levels).

Management

The management of VF or sustained VT with hemodynamic compromise is DC cardioversion. However, the aim should be to prevent such an arrhythmia occurring in the first instance. Slower and/or recurrent ventricular tachycardias may be treated with antiarrhythmic agents, such as lidocaine, procainamide, or amiodarone.

Primary Prevention

Postmyocardial infarction patients who experience frequent or complex PVDs are at a greater risk for arrhythmic death and therefore it was hypothesized that medication to suppress these arrhythmias would prevent mortality. Unfortunately, clinical trials testing this hypothesis have had disappointing results. Treatment with flecainide (CAST Investigators, 1989) or d-sotalol (Waldo *et al.*, 1996), despite successfully suppressing PVDs, both lead to an increased mortality in patients' postmyocardial infarction as compared to placebo. Two large primary prevention trials of amiodarone postmyocardial infarction both demonstrated reductions in arrhythmic deaths, but had no effect on total mortality (Cairns *et al.*, 1997; Julian *et al.*, 1997), raising concerns that reductions in fatal arrhythmias are offset by increased mortality from other causes. A meta-analysis of 13 randomized controlled trials of prophylactic amiodarone in patients with recent myocardial infarction or congestive heart failure demonstrated a statistically significant relative risk reduction of 29% in arrhythmic/sudden death (Amiodarone Trials Meta-Analysis (ATMA) Investigators, 1997). A relative risk reduction in total mortality of 13 to 15% (dependent on statistical method employed) was of marginal statistical significance, but importantly there was no increase in nonarrhythmic deaths. Therefore amiodarone, with which there is considerable clinical experience in the treatment of ventricular tachycardia, is useful in preventing arrhythmic deaths and is safe in the context of ischemia and heart failure, but the beneficial effect on total mortality is too small to justify its routine prophylactic use (Connolly, 1999). This was further reinforced by the results of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (Bardy *et al.*, 2004), a three armed, primary prevention study comparing placebo, amiodarone, and implantable cardioverter defibrillator (ICD) in patients with NYHA functional class II or III and left ventricular ejection fraction (EF) <35%. Amiodarone failed to show an improvement in all-cause mortality compared to placebo. Antiarrhythmic medication may not have lived up to expectations in clinical trials but β-blockers and angiotensin converting enzyme (ACE) inhibitors have already been proven to reduce sudden death postmyocardial infarction and in the setting of left ventricular dysfunction. Both should be prescribed at optimal dosage in the absence of contraindications.

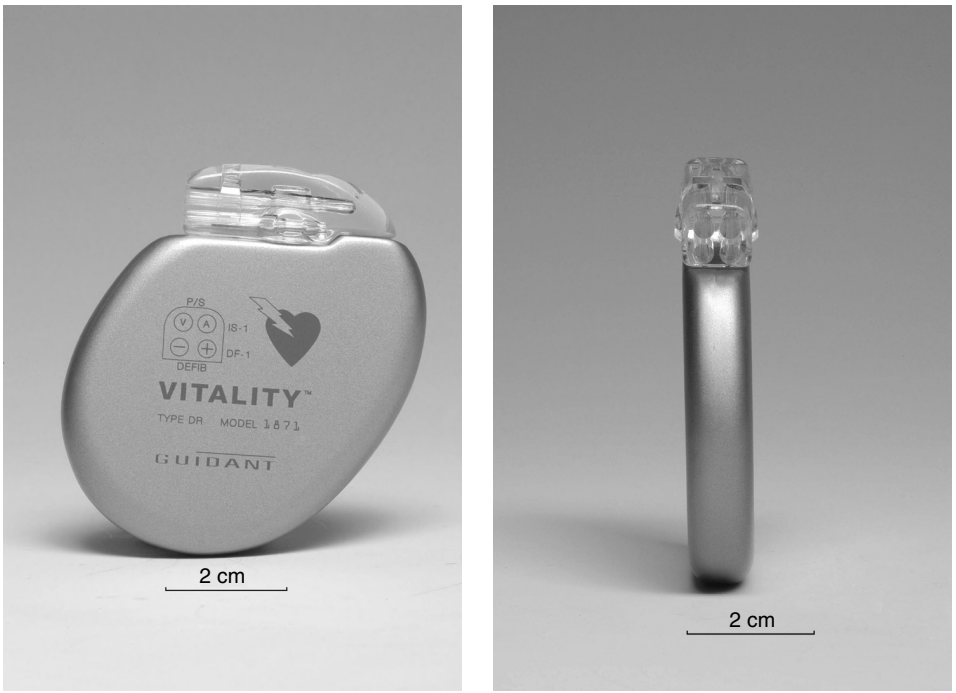

Figure 7 Implantable cardioverter defibrillator

Beyond medication, the ICD has now emerged as the most effective therapy for primary prevention of fatal ventricular tachyarrhythmias. Devices have evolved substantially from the abdominally placed ICD with thoracotomy-requiring epicardial leads to a subclavicular placed device similar to a permanent pacemaker (PPM) (see Figures 7 and 8). The addition of an antitachycardia pacing facility can effectively treat some tachyarrhythmias and reduces the number of shocks delivered. The primary prevention Multicenter Automatic Defibrillator Implantation Trial (MADIT) (Moss *et al.*, 1996) and Multicenter Unsustained Tachycardia Trial (MUSTT) (Buxton *et al.*, 1999) studies have both demonstrated statistically significant reductions in overall mortality as compared to antiarrhythmic medication in patients with previous myocardial infarction (MI), reduced LV ejection fraction, and nonsustained VT who were referred for electrophysiological studies. The subsequent MADIT 2 study (Moss *et al.*, 2002) enrolled patients with prior MI and ejection fraction $<30\%$; there was no requirement for the occurrence of ventricular arrhythmia or the need for electrophysiological study (EPS). There was a statistically significant reduction in overall mortality as compared to conventional medical therapy alone, which persisted for subgroup analysis stratified according to age and sex. However, there was no survival benefit for the prophylactic implantation of an ICD at the time of elective coronary artery bypass surgery in patients with reduced left ventricular ejection fraction and an abnormal signal-averaged ECG (Bigger, 1997). The lack of positive finding in this study may be due to the use of epicardial systems, which are not as effective as more modern devices, and because revascularization, which was employed in both treatment groups, resolved the underlying risk factor, ischemia.

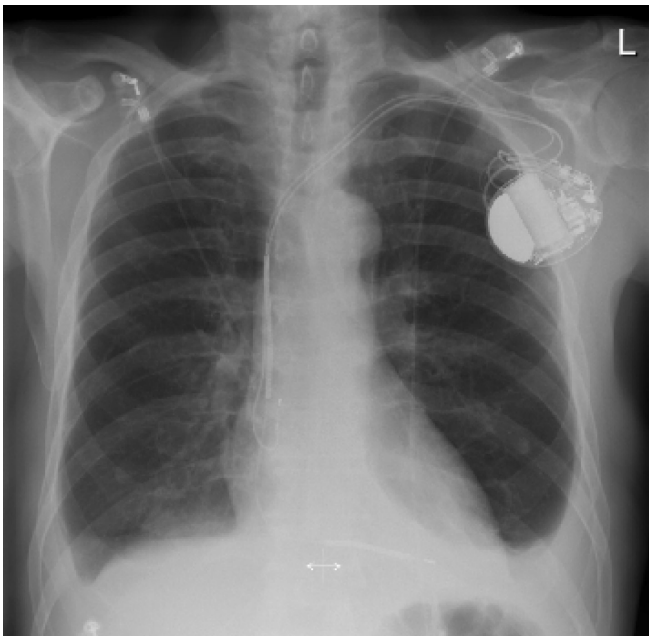

Figure 8 PA chest X ray of a patient with an ICD (atrial and ventricular leads)

Primary Prevention in Dilated Cardiomyopathy

Two significant trials have now begun to define the role of ICD therapy in patients with dilated cardiomyopathy (DCM). The SCD-HeFT consisted of 2521 patients with a mean age of 60 years. It included patients with ischemic DCM and no history of prior sustained VT or VF. All patients had a left

ventricular ejection fraction <35% and were NYHA functional class II or III. ICD therapy was associated with a statistically significant reduction in all-cause mortality compared to best medical therapy alone or in combination with amiodarone (Bardy *et al.*, 2004). There was a good uptake of ACE inhibitor and β-blocker use in all patients. The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) was a smaller study, but consisted only of patients with nonischemic DCM. Again there was a good uptake of prognostic heart failure medication, but amiodarone was not included in the trial. ICD therapy was associated with a statistically significant reduction in arrhythmic death compared to best medical therapy alone, but only a trend toward reduction in all-cause mortality. The trial was not powered to identify specific subgroups who benefited, but based on this data ICD therapy should be considered on an individual basis for patients with severe left ventricular dysfunction and nonischemic DCM (Kadish *et al.*, 2004).

Secondary Prevention

There have been three prospective randomized trials comparing ICD therapy to medication for secondary prevention. The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial (AVID Investigators, 1997) was the largest of these and was the only one to show a statistically significant risk reduction in mortality with ICD therapy as compared to medication. One thousand and sixteen patients with episodes of VF or hemodynamically significant VT were randomized to ICD or antiarrhythmic medication (amiodarone or sotalol). The majority of patients had ischemic heart disease and the mean left ventricular ejection fraction (LVEF) was 32%. The mean age of participants was 65 years, but subgroup analysis showed no difference in outcome for those aged over 70 years. The two smaller trials lacked the statistical power to demonstrate significant benefits, but both showed a trend toward improved survival for all-cause mortality in the ICD group compared to medication. The Canadian Implantable Defibrillator Study (CIDS) trial (Connolly *et al.*, 2000a) included patients presenting with syncope that was most likely secondary to VT and compared ICD therapy to amiodarone solely. The Cardiac Arrest Study Hamburg (CASH) trial (Kuck *et al.*, 2000) also had metoprolol and propafenone treatment limbs. The propafenone limb was stopped early because of excess mortality. Whereas all of the trials included a majority of patients with ischemic heart disease, the CASH trial differed in that the mean LVEF was 46%. A meta-analysis of these trials concluded a 28% relative reduction in death with ICD therapy and patients with a LVEF of >35% derived significantly less benefit (Connolly *et al.*, 2000b).

Implantable Cardioverter Defibrillators and the Elderly

Despite ICD implantation having a greater mortality benefit than conventional treatment, this remains an invasive treatment that may not be suitable for all. As already discussed in the context of the management of AF, the elderly can present additional challenges that have to be taken into account when analyzing the risk versus benefits for any given therapy. Regular follow-up at a tertiary center clinic is essential. Transport and mobility difficulties can be overcome, but patients must be compliant with the strict follow-up to ensure the device continues to function effectively and safely. Appropriate and inappropriate shocks may prove intolerable for some patients and an ICD would be unsuitable for those with significant dementia. Any reduction in medication will be beneficial in the elderly, but antiarrhythmics may still be required in some patients to reduce the burden of arrhythmia and hence shock frequency. Despite these reservations, elderly patients potentially stand the most to gain from ICD therapy. In a multivariate analysis of CIDS (Sheldon *et al.*, 2000), the patients at highest risk of cardiovascular death (age greater than or equal to 70 years, LVEF less than or equal to 35%, and NYHA class III or IV) were found to benefit the most from ICD therapy. In a retrospective study of octogenarians receiving an ICD for primary or secondary prevention, mean survival was 3.8 years (Koplan *et al.*, 2004). By the nature of its design, this study cannot compare survival in octogenarians not receiving an ICD, but survival increased to over 5 years if those with the poorest left ventricular function (EF <30%) and significant renal impairment were excluded. Further studies will have to be undertaken to help further risk stratify elderly patients and identify those most likely to benefit from an ICD, but age alone is not a contraindication for this therapy.

CONCLUSION

The general principles concerning the management of arrhythmias are identical whatever the age of the patient: precipitants and reversible factors must be identified and treated; bradyarrhythmias may require pacing; tachyarrhythmias require immediate electrical cardioversion if causing hemodynamic instability. Elderly patients differ only in the respect that they can present a number of social and medical challenges that have to be factored in to the risk benefit analysis for specific management decisions. These challenges are not insurmountable. For example, by mechanism of action some antiarrhythmics are more suitable for an elderly patient than others, there are a number of means in place for monitoring levels of anticoagulation, and if warfarin is deemed too risky for a patient, there are other options.

KEY POINTS

- Arrhythmias are common in the elderly. The heart is subject to both aging and disease-related changes that predispose to arrhythmia generation and persistence.
- AF is the most common sustained arrhythmia in the elderly and carries a substantial risk of morbidity

and mortality. Careful anticoagulation for stroke prevention is essential and choice of agent needs to be based on an informed assessment of risks versus benefits for each individual patient.
- Rate control is not an inferior option to rhythm control for chronic, hemodynamically stable AF and digoxin may be satisfactory as a sole agent for rate control in the elderly.
- A bradycardia is not a normal finding in the elderly. A sinus bradycardia or a slow ventricular rate in AF without intervention implies an underlying conduction system disturbance. Pacemaker treatment may be needed.
- There are widening indications for implantation of an ICD and selected elderly patients can gain much from the treatment.

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Ischemic Heart Disease in Elderly Persons

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INTRODUCTION

The most common cause of death in elderly persons is ischemic heart disease (IHD). Coronary atherosclerosis is very common in the elderly, with autopsy studies demonstrating a prevalence of at least 70% in persons older than 70 years. The prevalence of IHD is similar in elderly women and men (Aronow *et al.*, 2002a). In one study, clinical IHD was present in 502 of 1160 men (43%), mean age 80 years, and in 1019 of 2464 women (41%), mean age 81 years (Aronow *et al.*, 2002a). At 46-month follow-up, the incidence of new coronary events (myocardial infarction or sudden cardiac death) was 46% in the elderly men and 44% in the elderly women (Aronow *et al.*, 2002a).

IHD is diagnosed in elderly persons if they have either coronary angiographic evidence of significant IHD, a documented myocardial infarction (MI), a typical history of angina pectoris with myocardial ischemia diagnosed by stress testing, or sudden cardiac death. The incidence of sudden cardiac death as the first clinical manifestation of IHD increases with age.

CLINICAL MANIFESTATIONS

Dyspnea on exertion is a more common clinical manifestation of IHD in elderly persons than is the typical chest pain of angina pectoris. The dyspnea is usually exertional and is related to a transient rise in left ventricular (LV) end-diastolic pressure caused by ischemia superimposed on decreased LV compliance. Because elderly persons are more limited in their activities, angina pectoris in elderly persons is less often associated with exertion. Elderly persons with angina pectoris are less likely to have substernal chest pain, and they describe their anginal pain as less severe and of shorter duration than do younger persons. Angina pectoris in elderly persons may occur as a burning postprandial epigastric pain or as pain in the back or shoulders. Acute pulmonary edema unassociated with an acute MI may be a clinical manifestation of unstable angina pectoris due to extensive IHD in elderly persons (Tresch *et al.*, 1992).

Myocardial ischemia, appearing as shoulder or back pain in elderly persons, may be misdiagnosed as degenerative joint disease. Myocardial ischemia, appearing as epigastric pain, may be misdiagnosed as peptic ulcer disease. Nocturnal or postprandial epigastric discomfort that is burning in quality may be misdiagnosed as hiatus hernia or esophageal reflux instead of myocardial ischemia due to IHD. The presence of comorbid conditions in elderly persons may also lead to misdiagnosis of symptoms due to myocardial ischemia.

Elderly persons with IHD may have silent or asymptomatic myocardial ischemia (Aronow and Epstein, 1988; Hedblad *et al.*, 1989; Aronow *et al.*, 2002c). In a prospective study, 133 of 195 men (34%), mean age 80 years, with IHD and 256 of 771 women (33%), mean age 81 years, with IHD had silent myocardial ischemia detected by 24-hour ambulatory electrocardiograms (ECGs) (Aronow *et al.*, 2002c). At 45-month follow-up, the incidence of new coronary events in elderly men with IHD was 90% in men with silent myocardial ischemia versus 44% in men without silent ischemia (Aronow *et al.*, 2002c). At 47-month follow-up, the incidence of new coronary events in elderly women with IHD was 88% in women with silent ischemia versus 43% in women without silent ischemia (Aronow *et al.*, 2002c).

RECOGNIZED AND UNRECOGNIZED MI

Pathy (1967) demonstrated in 387 elderly patients with acute MI that 19% had chest pain, 56% had dyspnea or neurological symptoms or gastrointestinal symptoms, 8% had sudden death, and 17% had other symptoms. Another study showed in 110 elderly patients with acute MI that 21% had no symptoms, 22% had chest pain, 35% had dyspnea,

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Table 1 Presenting symptoms in 110 elderly patients with acute myocardial infarction

Dyspnea was present in 35% of patients
Chest pain was present in 22% of patients
Neurological symptoms were present in 18% of patients
Gastrointestinal symptoms were present in 4% of patients
No symptoms were present in 21% of patients

18% had neurological symptoms, and 4% had gastrointestinal symptom (Table 1) (Aronow, 1987). Other studies have also shown a high prevalence of dyspnea and neurological symptoms in elderly patients with acute MI (Tinker, 1981; Bayer *et al.*, 1986; Wroblewski *et al.*, 1986). In these studies, dyspnea was present in 22% of 87 patients (Tinker, 1981), in 42% of 777 patients (Bayer *et al.*, 1986), and in 57% of 96 patients (Wroblewski *et al.*, 1986). Neurological symptoms were present in 16% of 87 patients (Tinker, 1981), in 30% of 777 patients (Bayer *et al.*, 1986), and in 34% of 96 patients (Wroblewski *et al.*, 1986).

As with myocardial ischemia, some patients with acute MI may be completely asymptomatic or the symptoms may be so vague that they are unrecognized by the patient or physician as an acute MI. Studies have reported that 21 to 68% of MIs in elderly patients are unrecognized or silent (Aronow, 1987; Kannel and Abbott, 1984; Aronow *et al.*, 1985; Muller *et al.*, 1990; Nadelmann *et al.*, 1990; Sigurdsson *et al.*, 1995; Sheifer *et al.*, 2000). These studies also demonstrated that the incidence of new coronary events including recurrent myocardial infarction, ventricular fibrillation, and sudden death in patients with unrecognized MI is similar to that in patients with recognized MI (Kannel and Abbott, 1984; Nadelmann *et al.*, 1990; Sigurdsson *et al.*, 1995; Sheifer *et al.*, 2000; Aronow, 1989a).

DIAGNOSTIC TECHNIQUES

Resting ECG

In addition to diagnosing recent or prior MI, the resting ECG may show ischemic ST-segment depression, arrhythmias, conduction defects, and LV hypertrophy that are related to subsequent coronary events. At 37-month mean follow-up, elderly patients with ischemic ST-segment depression 1 mm or greater on the resting ECG were 3.1 times more likely to develop new coronary events than were elderly patients with no significant ST-segment depression (Aronow, 1989b). Elderly patients with ischemic ST-segment depression 0.5 to 0.9 mm on the resting ECG were 1.9 times more likely to develop new coronary events during 37-month follow-up than were elderly patients with no significant ST-segment depression (Aronow, 1989b). At 45-month mean follow-up, pacemaker rhythm, atrial fibrillation, premature ventricular complexes, left bundle branch block, intraventricular conduction defect, and type II second-degree atrioventricular block were associated with a higher incidence of new coronary events in patients (Aronow, 1991). Numerous studies have also documented that elderly patients with ECG LV hypertrophy have an increased incidence of new coronary events (Kannel *et al.*, 1987; Aronow *et al.*, 1989, 1991).

Numerous studies have shown that complex ventricular arrhythmias in elderly persons with IHD are associated with an increased incidence of new coronary events, including sudden cardiac death (Aronow *et al.*, 1988a,b, 2002d; Aronow and Epstein, 1990). The incidence of new coronary events is especially increased in elderly persons with complex ventricular arrhythmias and abnormal LV ejection fraction (Aronow *et al.*, 1988a) or LV hypertrophy (Aronow *et al.*, 1988b). At 45-month follow-up of 395 men, mean age 80 years, with IHD, complex ventricular arrhythmias detected by 24-hour ambulatory ECGs increased the incidence of new coronary events 2.4 times (Aronow *et al.*, 2002d). At 47-month follow-up of 771 women, mean age 81 years, with IHD, complex ventricular arrhythmias detected by 24-hour ambulatory ECGs increased the incidence of new coronary events 2.5 times (Aronow *et al.*, 2002d).

Exercise Stress Testing

Hlatky *et al.* (1984) found the exercise ECG to have a sensitivity of 84% and a specificity of 70% for the diagnosis of IHD in persons older than 60 years. Newman and Phillips (1988) found a sensitivity of 85%, a specificity of 56%, and a positive predictive value of 86% for the exercise ECG in diagnosing IHD. The increased sensitivity of the exercise ECG with increasing age found in these two treadmill exercise studies was probably due to the increased prevalence and severity of IHD in elderly persons.

Exercise stress testing also has prognostic value in elderly patients with IHD (Glover *et al.*, 1984; Fioretti *et al.*, 1984; Deckers *et al.*, 1984). Deckers *et al.* (1984) showed that the 1-year mortality was 4% for 48 patients 65 years or older who were able to do an exercise stress test after acute MI and 37% for the 63 elderly patients unable to do the exercise stress test after acute MI.

Exercise stress testing using thallium perfusion scintigraphy, radionuclide ventriculography, and echocardiography are also useful in the diagnosis and prognosis of coronary heart disease (CHD) (Iskandrian *et al.*, 1988; Hilton *et al.*, 1992; Crouse *et al.*, 1991). Iskandrian *et al.* (1988) showed that exercise thallium-201 imaging can be used for risk stratification of elderly patients with IHD. The risk for cardiac death or nonfatal MI at 25-month follow-up in 449 patients 60 years or older was less than 1% in patients with normal images, 5% in patients with single-vessel thallium-201 abnormality, and 13% in patients with multivessel thallium-201 abnormality.

Pharmacological Stress Testing

Intravenous dipyridamole-thallium imaging may be used to determine the presence of IHD in elderly patients who

are unable to undergo treadmill or bicycle exercise stress testing (Lam *et al.*, 1988). In patients 70 years or older, the sensitivity of intravenous dipyridamole-thallium imaging for diagnosing significant IHD was 86%, and the specificity was 75% (Lam *et al.*, 1988). In 120 patients older than 70 years, adenosine echocardiography had a 66% sensitivity and a 90% specificity in diagnosing IHD (Anthopoulos *et al.*, 1996). An abnormal adenosine echocardiogram predicted a 3-fold risk of future coronary events, independent of coronary risk factors (Anthopoulos *et al.*, 1996). In 120 patients older than 70 years, dobutamine echocardiography had a 87% sensitivity and a 84% specificity in diagnosing IHD (Anthopoulos *et al.*, 1996). An abnormal dobutamine echocardiogram predicted a 7.3-fold risk of future coronary events (Anthopoulos *et al.*, 1996).

Signal-averaged Electrocardiography

Signal-averaged electrocardiography (SAECG) was performed in 121 elderly postinfarction patients with asymptomatic complex ventricular arrhythmias detected by 24-hour ambulatory ECGs and a LV ejection fraction of 40% or higher (Mercando *et al.*, 1995). At 29-month follow-up, the sensitivity, specificity, positive predictive value, and negative predictive value for predicting sudden cardiac death were 52%, 68%, 32%, and 83% respectively for a positive SAECG; 63%, 70%, 38%, and 87% respectively for nonsustained ventricular tachycardia; and 26%, 89%, 41%, and 81% respectively for a positive SAECG plus nonsustained ventricular tachycardia (Mercando *et al.*, 1995).

CORONARY RISK FACTORS

Cigarette Smoking

The Cardiovascular Health Study demonstrated in 5201 men and women 65 years or older that >50 pack-years of smoking increased 5-year mortality 1.6 times (Fried *et al.*, 1998). The Systolic Hypertension in the Elderly Program pilot project showed that smoking was a predictor of first cardiovascular event and MI/sudden death (Siegel *et al.*, 1987). At 5-year follow-up of 7178 persons ≥65 years in three communities, the relative risk for cardiovascular disease (CVD) mortality was 2.0 for male smokers and 1.6 for female smokers (LaCroix *et al.*, 1991). The incidence of CVD mortality in former smokers was similar to those who had never smoked (LaCroix *et al.*, 1991). At 40-month follow-up of 664 men, mean age 80 years, and at 48-month follow-up of 1488 women, mean age 82 years, current cigarette smoking increased the relative risk of new coronary events 2.2 times in men and 2.0 times in women (Aronow and Ahn, 1996) At 6-year follow-up of older men and women in the Coronary Artery Surgery Study registry, the relative risk of MI or death was 1.5 for persons 65 to 69 years and 2.9 for persons 70 years and older who continued smoking, compared with quitters during the year before study enrollment (Hermanson *et al.*, 1988).

Elderly men and women who smoke cigarettes should be strongly encouraged to stop smoking to reduce the development of IHD. Smoking cessation will decrease mortality from IHD, other CVD, and all-cause mortality in elderly men and women.

Hypertension

Systolic hypertension in elderly persons is diagnosed if the systolic blood pressure is 140 mm Hg or higher from two or more readings on two or more visits (Chobanian *et al.*, 2003). Diastolic hypertension in elderly persons is similarly diagnosed if the diastolic blood pressure is 90 mm Hg or higher (Chobanian *et al.*, 2003). In a study of 1819 persons, mean age 80 years, living in the community, the prevalence of hypertension was 71% in elderly African-Americans, 64% in elderly Asians, 62% in elderly Hispanics, and 52% in elderly whites (Mendelson *et al.*, 1999).

Isolated systolic hypertension in elderly persons is diagnosed if the systolic blood pressure is 140 mm Hg or higher with a diastolic blood pressure of less than 90 mm Hg (Chobanian *et al.*, 2003). Approximately two-thirds of elderly persons with hypertension have isolated systolic hypertension (Mendelson *et al.*, 1999).

Isolated systolic hypertension and diastolic hypertension are both associated with increased IHD morbidity and mortality in elderly persons (Applegate and Rutan, 1992). Increased systolic blood pressure is a greater risk factor for IHD morbidity and mortality than is increased diastolic blood pressure (Applegate and Rutan, 1992). The higher the systolic or diastolic blood pressure, the greater the morbidity and mortality from IHD in elderly women and men. The Cardiovascular Health Study demonstrated in 5202 elderly men and women that a brachial systolic blood pressure >169 mm Hg was associated with a 2.4-fold greater 5-year mortality (Fried *et al.*, 1998).

At 30-year follow-up of persons 65 years and older in the Framingham Heart Study, systolic hypertension was related to a greater incidence of IHD in elderly men and women (Kannel and Vokonas, 1986). Diastolic hypertension correlated with the incidence of IHD in elderly men but not in elderly women (Kannel and Vokonas, 1986). At 40-month follow-up of 664 elderly men and 48-month follow-up of 1488 elderly women, systolic or diastolic hypertension was associated with a relative risk of new coronary events of 2.0 in men and 1.6 in women (Aronow and Ahn, 1996). Recent data from Framingham also suggests the importance of increased pulse pressure, a measure of large artery stiffness. Among 1924 men and women aged 50 to 79 years, at any given level of systolic blood pressure of 120 mm Hg or greater, the risk of IHD over 20 years rose with lower diastolic blood pressure, suggesting that higher pulse pressure was an important component of risk (Franklin *et al.*, 1999). Among 1061 men and women aged 60 to 79 years in

the Framingham Heart Study, the strongest predictor of IHD risk was pulse pressure (hazard ratio = 1.24) (Franklin *et al.*, 2001).

Elderly persons with hypertension should be treated with salt restriction, weight reduction if necessary, discontinuation of drugs that increase blood pressure, avoidance of alcohol and tobacco, increase in physical activity, decrease in dietary saturated fat and cholesterol, and maintenance of adequate dietary potassium, calcium, and magnesium intake. In addition, antihypertensive drugs have been shown to reduce IHD events in elderly men and in elderly women with hypertension (Amery *et al.*, 1985; Dahlof *et al.*, 1991; MRC Working Party, 1992; SHEP Cooperative Research Group, 1991; Staessen *et al.*, 1997; Gueyffier *et al.*, 1999; Aronow, 2002a, 2003a).

Elderly persons with IHD should have their blood pressure reduced to less than 135/85 mm Hg and to less than 130/80 mm Hg if diabetes mellitus or chronic renal disease is present (Chobanian *et al.*, 2003). JNC 7 pointed out that most patients with hypertension will require two or more antihypertensive drugs to achieve this blood pressure goal (Chobanian *et al.*, 2003). The drugs of choice for treating IHD with hypertension are β-blockers and angiotensin-converting enzyme (ACE) inhibitors (Chobanian *et al.*, 2003; Ryan *et al.*, 1999). If a third antihypertensive drug is needed, a thiazide diuretic should be administered (Chobanian *et al.*, 2003).

Left Ventricular Hypertrophy

Elderly men and women with ECG LV hypertrophy (Kannel *et al.*, 1987; Aronow *et al.*, 1989, 1991) and echocardiographic LV hypertrophy (Aronow *et al.*, 1989, 1991, 1988b; Levy *et al.*, 1989) have an increased risk of developing new coronary events. At 4-year follow-up of 406 elderly men and 735 elderly women in the Framingham Study, echocardiographic LV hypertrophy was 15.3 times more sensitive in predicting new coronary events in elderly men and 4.3 times more sensitive in predicting new coronary events in elderly women than was electrocardiographic LV hypertrophy (Levy *et al.*, 1989). At 37-month follow-up of 360 men and women, mean age 82 years, with hypertension or IHD, echocardiographic LV hypertrophy was 4.3 times more sensitive in predicting new coronary events than was electrocardiographic LV hypertrophy (Aronow *et al.*, 1989).

Physicians should try to prevent LV hypertrophy from developing or progressing in elderly men and women with IHD. A metaanalysis of 109 treatment studies found that ACE inhibitors were more effective than other antihypertensive drugs in decreasing LV mass (Dahlof *et al.*, 1992).

Dyslipidemia

Numerous studies have demonstrated that a high serum total cholesterol is a risk factor for new or recurrent coronary events in elderly men and women (Aronow and Ahn, 1996; Castelli *et al.*, 1989; Wong *et al.*, 1991; Barrett-Connor *et al.*, 1984). At 40-month follow-up of 664 elderly men and at 48-month follow-up of 1488 elderly women, an increment of 10 mg/dl of serum total cholesterol was associated with an increase in the relative risk of 1.12 for new coronary events in both men and women (Aronow and Ahn, 1996).

A low serum high-density lipoprotein (HDL) cholesterol is a risk factor for new coronary events in elderly men and women (Aronow and Ahn, 1996; Castelli *et al.*, 1989; Corti *et al.*, 1995; Zimetbaum *et al.*, 1992; Aronow and Ahn, 1994). In the Framingham Study (Castelli *et al.*, 1989), in the Established Populations for Epidemiologic Studies of the Elderly study (Corti *et al.*, 1995), and in a large cohort of convalescent home patients (Aronow and Ahn, 1996), a low serum HDL cholesterol was a more powerful predictor of new coronary events than was serum total cholesterol. At 40-month follow-up of 664 elderly men and at 48-month follow-up of 1488 elderly women, a decrement of 10 mg/dl of serum HDL cholesterol increased the relative risk of new coronary events 1.70 times in men and 1.95 times in women (Aronow and Ahn, 1996).

Hypertriglyceridemia is a risk factor for new coronary events in elderly women but not in elderly men (Aronow and Ahn, 1996; Castelli *et al.*, 1989). At 40-month follow-up of elderly men and at 48-month follow-up of elderly women, the level of serum triglycerides was not a risk factor for new coronary events in men and was a very weak risk factor for new coronary events in women (Aronow and Ahn, 1996).

Numerous studies have demonstrated that statins reduce new coronary events in elderly men and in elderly women with IHD (Miettinen *et al.*, 1997; Lewis *et al.*, 1998; The LIPID Study Group, 2002; Heart Protection Study Collaborative Group, 2002; Aronow and Ahn, 2002a; Aronow *et al.*, 2002b; Aronow and Ahn, 2002b; Aronow, 2001a, 2002b). The absolute reduction in new coronary events in these studies is greater for elderly persons than for younger persons. In an observational prospective study of 488 men and 922 women, mean age 81 years, with prior MI and a serum low-density lipoprotein (LDL) cholesterol of 125 mg/dl or higher, 48% of persons were treated with statins (Aronow and Ahn, 2002a). At 3-year follow-up, statins reduced new coronary events by 50% (Aronow and Ahn, 2002a).

Current guidelines recommend lipid-lowering therapy in elderly men and women with IHD if their serum LDL cholesterol is 100 mg/dl or higher despite dietary therapy (Ryan *et al.*, 1999; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). However, data from the Heart Protection Study suggest that elderly men and women with IHD should be treated with statins regardless of initial levels of serum lipids (Heart Protection Study Collaborative Group, 2002).

Diabetes Mellitus

Diabetes mellitus is a risk factor for new coronary events in elderly men and women (Aronow and Ahn, 1996;

Castelli *et al.*, 1989; Aronow and Ahn, 2000). In the Cardiovascular Health Study, an elevated fasting glucose level (>130 mg/dl) increased 5-year mortality by 1.9 times (Fried *et al.*, 1998). At 40-month follow-up of 664 elderly men and at 48-month follow-up of 1488 elderly women, diabetes mellitus increased the relative risk of new coronary events by 1.9 times in men and 1.8 times in women (Aronow and Ahn, 1996). Elderly diabetics without IHD have a higher incidence of new coronary events than elderly nondiabetics with IHD (Aronow and Ahn, 2003).

Persons with diabetes mellitus are more often obese and have higher serum LDL cholesterol and triglyceride levels and lower serum HDL cholesterol levels than do nondiabetics. Diabetics also have a higher prevalence of hypertension and LV hypertrophy than do nondiabetics. These risk factors contribute to the increased incidence of new IHD events in diabetics as compared to nondiabetics. Increased age can further amplify these risk factor differences and contribute to greater IHD risk.

Elderly persons with diabetes mellitus should be treated with dietary therapy, weight reduction if necessary, and appropriate drugs if necessary to control hyperglycemia. The hemoglobin A1c level should be maintained at less than 7% (Stratton *et al.*, 2000). Other risk factors such as smoking, hypertension, dyslipidemia, obesity, and physical inactivity should be controlled. The serum LDL cholesterol level should be reduced to less than 100 mg/dl (Ryan *et al.*, 1999; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). The blood pressure should be reduced to less than 130/80 mm Hg (Chobanian *et al.*, 2003). Sulfonylureas should be avoided in person with IHD (Garratt *et al.*, 1999; Aronow and Ahn, 2001a).

Obesity

Obesity was an independent risk factor for new IHD events in elderly men and women in the Framingham Heart Study (Vokonas and Kannel, 2004). Disproportionate distribution of fat to the abdomen assessed by the waist-to-hip circumference ratio has also been shown to be a risk factor for CVD, mortality from CHD, and total mortality in elderly men and women (Kannel *et al.*, 1991; Folsom *et al.*, 1993).

Obese men and women with IHD must undergo weight reduction. Weight reduction is also a first approach to controlling mild hypertension, hyperglycemia, and dyslipidemia. Regular aerobic exercise should be used in addition to diet to treat obesity.

Physical Inactivity

Physical inactivity is associated with obesity, hypertension, hyperglycemia, and dyslipidemia. At 12-year follow-up in the Honolulu Heart Program, physically active men 65 years or older had a relative risk of 0.43 for IHD compared with inactive men (Folsom *et al.*, 1993). Lack of moderate or vigorous exercise increased 5-year mortality in elderly men and women in the Cardiovascular Heart Study (Fried *et al.*, 1998).

Moderate exercise programs suitable for elderly persons include walking, climbing stairs, swimming, or bicycling. However, care must be taken in prescribing any exercise program because of the high risk of injury in this age-group. Group or supervised sessions, including aerobic classes, offered by senior health care plans are especially appealing. Exercise training programs are not only beneficial in preventing CHD (Aronow, 2001b) but have also been found to improve endurance and functional capacity in elderly persons after MI (Aronow, 2001b; Williams *et al.*, 1984).

THERAPY OF STABLE ANGINA

Nitroglycerin is used for relief of the acute anginal attack. It is given either as a sublingual tablet or as a sublingual spray (Aronow and Frishman, 2004). Long-acting nitrates prevent recurrent anginal attacks, improve exercise time until the onset of angina, and reduce exercise-induced ischemic ST-segment depression (Danahy *et al.*, 1977; Danahy and Aronow, 1977). To prevent nitrate tolerance, it is recommended that a 12- to 14-hour nitrate-free interval be established when using long-acting nitrate preparations. During the nitrate-free interval, the use of another antianginal drug will be necessary.

β-Blockers prevent recurrent anginal attacks and are the drug of choice to prevent new coronary events (Aronow *et al.*, 1980). They also improve exercise time until the onset of angina and reduce exercise-induced ischemic ST-segment depression (Aronow *et al.*, 1980). They should be administered along with long-acting nitrates to all patients with angina unless there are contraindications to the use of these drugs. Antiplatelet drugs such as aspirin or clopidogrel should also be administered to all patients with angina to reduce new coronary events (Antithrombotic Trialists' Collaboration, 2002; Aronow and Ahn 2002c; CAPRIE Steering Committee, 1996).

There are no class I indications for the use of calcium channel blockers in the treatment of patients with IHD (Ryan *et al.*, 1999). However, if angina pectoris persists despite the use of β-blockers and nitrates, long-acting calcium channel blockers such as diltiazem or verapamil should be used in elderly patients with IHD and normal LV systolic function and amlodipine or felodipine in patients with IHD and abnormal LV systolic function as antianginal agents (Aronow and Frishman, 2004).

If angina persists despite intensive medical management, coronary revascularization with either coronary angioplasty or coronary artery bypass surgery should be considered (The TIME Investigators, 2001; Aronow, 2001c). The use of other approaches to manage angina which persists despite antianginal drugs and coronary revascularization is discussed elsewhere (Aronow and Frishman, 2004).

ACUTE CORONARY SYNDROMES

Unstable angina pectoris is a transitory syndrome that results from disruption of a coronary atherosclerotic plaque that critically decreases coronary blood flow causing new onset angina pectoris or exacerbation of angina pectoris (Aronow, 2003b). Transient episodes of coronary artery occlusion or near occlusion by thrombus at the site of plaque injury may occur and cause angina pectoris at rest. The thrombus may be labile and cause temporary obstruction to flow. Release of vasoconstriction substances by platelets and vasoconstriction due to endothelial vasodilator dysfunction contribute to a further reduction in coronary blood flow, and in some patients, myocardial necrosis with non-ST-elevation myocardial infarction (NSTEMI) occurs. Elevation of serum cardiospecific troponin I or T or creatine kinase-MB levels occur in patients with NSTEMI but not in patients with unstable angina.

Older patients with unstable angina pectoris should be hospitalized, and depending on their risk stratification, may need monitoring in an intensive care unit (Aronow, 2003b). In a prospective study of 177 consecutive unselected patients hospitalized for an acute coronary syndrome (91 women and 86 men) aged 70–94 years, unstable angina was diagnosed in 54%, NSTEMI in 34%, and ST-segment elevation myocardial infarction (STEMI) in 12% (Woodworth *et al.*, 2002a; Nayak *et al.*, 2002; Woodworth *et al.*, 2002b). Obstructive IHD was diagnosed by coronary angiography in 94% of elderly men and in 80% of elderly women (Woodworth *et al.*, 2002a).

Therapy

Treatment of patients with unstable angina pectoris/NSTEMI should be initiated in the emergency department. Reversible factors precipitating unstable angina pectoris should be identified and corrected. Oxygen should be administered to patients who have cyanosis, respiratory distress, congestive heart failure (CHF), or high-risk features. Oxygen therapy should be guided by arterial oxygen saturation and should not be given if the arterial oxygen saturation is more than 94%. Morphine sulfate should be administered intravenously when anginal chest pain is not immediately relieved with nitroglycerin or when acute pulmonary congestion and/or severe agitation is present.

Aspirin should be administered to all patients with unstable angina pectoris/NSTEMI unless contraindicated and continued indefinitely (Braunwald *et al.*, 2002a). The first dose of aspirin should be chewed rather than swallowed to ensure rapid absorption.

The American College of Cardiology (ACC)/American Heart Association (AHA) 2002 guidelines update state that clopidogrel should be administered for up to 9 months in addition to indefinite use of aspirin in hospitalized patients with unstable angina pectoris/NSTEMI in whom an early noninterventional approach is planned or a percutaneous coronary intervention (PCI) is planned. Clopidogrel should be withheld for 5 to 7 days in patients in whom elective coronary artery surgery is planned (Braunwald *et al.*, 2002a). On the basis of data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (2001) (Mehta *et al.*, 2001) and from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial (Steinhubl *et al.*, 2002), aspirin 80 mg daily plus clopidogrel 75 mg daily should be administered to patients with unstable angina/NSTEMI for at least 1 year.

Nitrates should be administered immediately in the emergency department to patients with unstable angina/NSTEMI (Braunwald *et al.*, 2000b). Patients whose symptoms are not fully relieved with three 0.4 mg sublingual nitroglycerin tablets or spray taken 5 minutes apart and the initiation of an intravenous β-blocker should be treated with continuous intravenous nitroglycerin (Braunwald *et al.*, 2000b). Topical or oral nitrates are alternatives for patients without ongoing refractory symptoms (Braunwald *et al.*, 2000b).

β-Blockers should be administered intravenously in the emergency department unless there are contraindications to their use followed by oral administration and continued indefinitely (Braunwald *et al.*, 2000b). Metoprolol may be given intravenously in 5 mg increments over 1 to 2 minutes and repeated every 5 minutes until 15 mg has been given followed by oral metoprolol 100 mg twice daily. The target resting heart rate is 50 to 60 beats per minute.

An oral ACE inhibitor should also be given unless there are contraindications to its use and continued indefinitely (Braunwald *et al.*, 2000b). In patients with continuing or frequently recurring myocardial ischemia despite nitrates and β-blockers, verapamil or diltiazem should be added to their therapeutic regimen in the absence of LV systolic dysfunction (class IIa indication) (Braunwald *et al.*, 2000b). The benefit of calcium channel blockers in the treatment of unstable angina pectoris is limited to symptom control (Braunwald *et al.*, 2000b). Intra-aortic balloon pump counterpulsation should be used for severe myocardial ischemia that is continuing or occurs frequently despite intensive medical therapy or for hemodynamic instability in patients before or after coronary angiography (Braunwald *et al.*, 2000b).

A platelet glycoprotein IIb/IIIa inhibitor should also be administered in addition to aspirin, clopidogrel, and heparin in patients in whom coronary angioplasty is planned (Braunwald *et al.*, 2002a). Abciximab can be used for 12 to 24 hours in patients with unstable angina/NSTEMI in whom coronary angioplasty is planned within the next 24 hours (Braunwald *et al.*, 2002a). Eptifibatide or tirofiban should be administered in addition to aspirin and low-molecular-weight heparin or unfractionated heparin to patients with continuing myocardial ischemia, an elevated cardiospecific troponin I or T, or with other high-risk features in whom an invasive management is not planned (Braunwald *et al.*, 2002a).

Intravenous thrombolytic therapy is not recommended for the treatment of unstable angina/NSTEMI (Braunwald *et al.*, 2002a). Prompt coronary angiography should be performed without noninvasive risk stratification in patients who fail to stabilize with intensive medical treatment (Braunwald *et al.*,

2000b). Coronary revascularization should be performed in patients with high-risk features to reduce coronary events and mortality (Braunwald *et al.*, 2002a, 2000b; Wallentin *et al.*, 2000; Cannon *et al.*, 2001).

On the basis of the available data, the ACC/AHA 2002 guidelines recommend the use of statins in patients with acute coronary syndromes and a serum LDL cholesterol of 100 mg/dl or higher 24 to 96 hours after hospitalization (Braunwald *et al.*, 2002a). Statins should be continued indefinitely after hospital discharge (Aronow, 2001a, 2002b; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; Braunwald *et al.*, 2002a). The ACC/AHA 2002 guidelines also recommend use of a fibrate or nicotinic acid if the serum HDL cholesterol is less than 40 mg/dl, occurring as an isolated finding or in combination with other lipid abnormalities (Braunwald *et al.*, 2002a).

Patients should be discharged on aspirin plus clopidogrel, β-blockers, and on ACE inhibitors in the absence of contraindications. Nitrates should be given for ischemic symptoms. A long-acting nondihydropyridine calcium channel blocker may be given for ischemic symptoms that occur despite treatment with nitrates plus β-blockers. Hormonal therapy should not be administered to postmenopausal women (Hulley *et al.*, 1998; Grady *et al.*, 2002).

THERAPY OF STEMI

Chest pain due to acute MI should be treated with morphine, nitroglycerin, and β-blockers (Aronow, 2001d). If arterial saturation is lower than 94%, oxygen should be administered. Aspirin should be given on day 1 of an acute MI and continued indefinitely to reduce coronary events and mortality (Ryan *et al.*, 1999; Antithrombotic Trialists' Collaboration, 2002; Aronow and Ahn 2002c; ISIS-2 (Second International Study of Infarct Survival) Collaborative Group, 1988; Krumholz *et al.*, 1995). The first dose of aspirin should be chewed rather than swallowed. Early intravenous β-blockade should be used during acute MI and oral β-blockers continued indefinitely to reduce coronary events and mortality (Ryan *et al.*, 1999; Hjalmarson *et al.*, 1981; Gundersen *et al.*, 1982; Pedersen, 1985; Beta-Blocker Heart Attack Trial Research Group, 1982). ACE inhibitors should be given within 24 hours of acute MI and continued indefinitely to reduce coronary events and mortality (Ryan *et al.*, 1999; Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico, 1996; ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group, 1995; Ambrosioni *et al.*, 1995a; Pfeffer *et al.*, 1992; The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators, 1993; Ambrosioni *et al.*, 1995b). Statins should be given to patients with acute MI and a serum LDL cholesterol of 100 mg/dl or higher 24 to 96 hours after hospitalization (Ryan *et al.*, 1999). Statins should be continued indefinitely after hospital discharge to reduce coronary events and mortality (Ryan *et al.*, 1999; Aronow, 2001a, 2002b; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001).

The ACC/AHA guidelines state that there are no Class I indications for the use of calcium channel blockers during or after acute MI (Ryan *et al.*, 1999). However, if older persons have persistent angina after MI despite treatment with β-blockers and nitrates and are not suitable candidates for coronary revascularization, or if they have hypertension inadequately controlled by other drugs, a nondihydropyridine calcium channel blocker such as verapamil or diltiazem should be added to the therapeutic regimen if the left ventricular ejection fraction (LVEF) is normal. If the LVEF is abnormal, amlodipine or felodipine should be added to the therapeutic regimen.

The ACC/AHA guidelines recommend using intravenous heparin in persons with acute MI undergoing primary coronary angioplasty or surgical coronary revascularization and in persons with acute MI at high risk for systemic embolization such as persons with a large or anterior MI, atrial fibrillation, history of pulmonary or systemic embolus, or LV thrombus (Ryan *et al.*, 1999). In persons with acute MI not receiving intravenous heparin, the ACC/AHA guidelines recommend using subcutaneous heparin 7500 U twice daily for 24 to 48 hours to decrease the incidence of deep venous thrombosis (Ryan *et al.*, 1999).

Thrombolytic therapy is beneficial in the treatment of STEMI in patients younger than 75 years (Ryan *et al.*, 1999; ISIS-2 (Second International Study of Infarct Survival) Collaborative Group, 1988; Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI), 1986; Wilcox *et al.*, 1988; AIMS Trial Study Group, 1988). From the available data, one cannot conclude whether thrombolytic therapy is beneficial or harmful in patients older than 75 years with acute MI (Aronow, 2003c). However, the data favor the use of primary coronary angioplasty in eligible patients younger and older than 75 years with acute MI to reduce coronary events and mortality (Aversano *et al.*, 2002; de Boer *et al.*, 2002; Keeley *et al.*, 2003; Saleem *et al.*, 2004).

THERAPY AFTER MI

Elderly persons after MI should have their modifiable coronary risk factors intensively treated as discussed previously in this chapter. Aspirin or clopidogrel should be given indefinitely to reduce new coronary events and mortality (Ryan *et al.*, 1999; Antithrombotic Trialists' Collaboration, 2002; Aronow and Ahn 2002c; Goldstein *et al.*, 1996). The ACC/AHA guidelines recommend as Class I indications for long-term oral anticoagulant therapy after MI: (1) secondary prevention of MI in post-MI patients unable to tolerate daily aspirin or clopidogrel; (2) post-MI patients with persistent atrial fibrillation; and (3) post-MI patients with LV thrombus (Ryan *et al.*, 1999). Long-term warfarin should be given in a dose to achieve an INR between 2.0 and 3.0 (Smith *et al.*, 2001).

β-Blockers (Table 2) (Ryan *et al.*, 1999; Hjalmarson *et al.*, 1981; Gundersen *et al.*, 1982; Pedersen, 1985; Beta-Blocker Heart Attack Trial Research Group, 1982; Smith *et al.*, 2001; The CAPRICORN Investigators, 2001; Park *et al.*, 1995; Aronow and Ahn, 2001b; Aronow *et al.*, 2001) and ACE inhibitors (Table 3) (Ryan *et al.*, 1999; Pfeffer *et al.*, 1992; The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators, 1993; Ambrosioni *et al.*, 1995b; Aronow *et al.*, 2001; Kober *et al.*, 1995; HOPE (Heart Outcomes Prevention Evaluation) Study Investigators, 2000; Fox, 2003) should be given indefinitely unless contraindications exist to the use of these drugs to reduce new coronary events and mortality. Long-acting nitrates are effective antianginal and antiischemic drugs (Danahy *et al.*, 1977; Danahy and Aronow, 1977).

There are no Class I indications for the use of calcium channel blockers after MI (Ryan *et al.*, 1999).

Teo *et al.* (1993) analyzed randomized controlled trials comprising 20 342 persons that investigated the use of calcium channel blockers after MI. Mortality was insignificantly 4% higher in persons treated with calcium channel blockers. In this study, β-blockers significantly reduced mortality by 19% in 53 268 persons. In another study, elderly persons who were treated with β-blockers after MI had a 43% decrease in 2-year mortality and a 22% decrease in 2-year cardiac hospital readmissions than elderly persons who were not treated with β-blockers (Soumerai *et al.*, 1997). Use of a calcium channel blocker instead of a β-blocker after MI doubled the risk of mortality (Soumerai *et al.*, 1997).

Antiarrhythmic Therapy After MI

A metaanalysis of 59 randomized controlled trials comprising 23 229 persons that investigated the use of class I antiarrhythmic drugs after MI showed that mortality was 14% significantly higher in persons receiving class I antiarrhythmic drugs than in persons receiving no antiarrhythmic drugs (Teo *et al.*, 1993). None of the 59 studies showed a reduction in mortality by class I antiarrhythmic drugs (Teo *et al.*, 1993).

In the Cardiac Arrhythmia Suppression Trials I and II, older age also increased the likelihood of adverse effects including death in persons after MI receiving encainide, flecainide, or moricizine (Akiyama *et al.*, 1992). Compared with no antiarrhythmic drug, quinidine or procainamide did not reduce mortality in elderly persons with coronary artery disease (CAD), normal or abnormal LVEF, and

Table 2 Effect of β-blockers on mortality in older patients after myocardial infarction

Study	Follow-up	Results
Goteborg Trial (94)	90 days	Compared with placebo, metoprolol caused a 45% significant decrease in mortality in patients aged 65–74 years
Norwegian Multicenter Study (95)	17 months (up to 33 months)	Compared with placebo, timolol caused a 43% significant reduction in mortality in patients aged 65–74 years
Norwegian Multicenter Study (96)	61 months (up to 72 months)	Compared with placebo, timolol caused a 19% significant decrease in mortality in patients aged 65–74 years
β-Blocker Heart Attack Trial (97)	25 months (up to 36 months)	Compared with placebo, propranolol caused a 33% significant reduction in mortality in patients aged 60–69 years
Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Trial (98)	1.3 years	Compared with placebo, carvedilol caused a 23% significant reduction in mortality, a 24% significant reduction in cardiovascular mortality, a 40% significant reduction in nonfatal myocardial infarction, and a 30% significant reduction in all-cause mortality or nonfatal myocardial infarction in patients, mean age 63 years

Table 3 Effect of angiotensin-converting enzyme inhibitors on mortality in older patients after myocardial infarction

Study	Follow-up	Results
Survival and Ventricular Enlargement Trial (115)	42 months (up to 60 months)	In patients with MI and LVEF $\leq$40%, compared with placebo, captopril reduced mortality 25% in patients aged $\geq$65 years
Acute Infarction Ramipril Efficacy Study (116)	15 months	In patients with MI and clinical evidence of CHF, compared with placebo, ramipril decreased mortality 36% in patients aged $\geq$65 years
Survival of Myocardial Infarction Long-Term Evaluation Trial (117)	1 year	In patients with anterior MI, compared with placebo, zofenopril reduced mortality or severe CHF 39% in patients aged $\geq$65 years
Trandolapril Cardiac Evaluation Study (118)	24 to 50 months	In patients, mean age 68 years, with LVEF $\leq$35%, compared with placebo, trandolapril reduced mortality 33% in patients with anterior MI and 14% in patients without anterior MI
Heart Outcomes Prevention Evaluation Study (22)	4.5 years (up to 6 years)	In patients aged $\geq$55 years with MI (53%), CVD (88%), or diabetes (38%) but no CHF or abnormal LVEF, ramipril reduced MI, stroke, and cardiovascular death 22%
European trial on reduction of cardiac events with perindopril in patients with stable CAD	4.2 years	In patients, mean age 60 years, with CAD and no CHF, compared with placebo, perindopril reduced cardiovascular death, MI, or cardiac arrest 20%

MI, Myocardial Infarction; LVEF, Left Ventricular Ejection Fraction; CHF, Congestive Heart Failure.

presence versus absence of ventricular tachycardia (Aronow *et al.*, 1990).

Compared with placebo, d, l-sotalol did not reduce mortality in post-MI persons followed up for 1 year (Julian *et al.*, 1982). Mortality was also significantly higher at 148-day follow-up in persons treated with d-sotalol (5.0%) than in persons treated with placebo (Waldo *et al.*, 1996). On the basis of the available data, persons after MI should not receive class I antiarrhythmic drugs or sotalol.

In the European Myocardial Infarction Amiodarone Trial, 1486 survivors of MI with a LV ejection fraction of 40% or less were randomized to amiodarone (743 patients) or to placebo (743 patients) (Julian *et al.*, 1997). At 2-year follow-up, 103 patients treated with amiodarone and 102 patients treated with placebo had died (Julian *et al.*, 1997). In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial, 1202 survivors of MI with nonsustained ventricular tachycardia or complex ventricular arrhythmias were randomized to amiodarone or to placebo (Cairns *et al.*, 1997). Amiodarone was very effective in suppressing ventricular tachycardia and complex ventricular arrhythmias. However, the mortality rate at 1.8-year follow-up was not significantly different in the persons treated with amiodarone or placebo (Cairns *et al.*, 1997). In addition, early permanent discontinuation of drug for reasons other than outcome events occurred in 36% of persons taking amiodarone.

In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation Study, the incidence of pulmonary toxicity was 10% at 2 years in persons receiving amiodarone in a mean dose of 158 mg daily (Greene, 1993). The incidence of adverse effects for amiodarone also approached 90% after 5 years of treatment (Herre *et al.*, 1989). On the basis of the available data, amiodarone should not be used in the treatment of persons after MI.

However, β-blockers have been shown to reduce mortality in persons with nonsustained ventricular tachycardia or complex ventricular arrhythmias after MI in patients with normal or abnormal LV ejection fraction (Friedman *et al.*, 1986; Norris *et al.*, 1984; Aronow *et al.*, 1994; Kennedy *et al.*, 1994). On the basis of the available data, β-blockers should be used in the treatment of elderly persons after MI, especially if nonsustained ventricular tachycardia or complex ventricular arrhythmias are present, unless there are specific contraindications to their use.

In the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, 1016 persons, mean age 65 years, with a history of ventricular fibrillation or serious sustained ventricular tachycardia were randomized to an automatic implantable cardioverter defibrillator (AICD) or to drug therapy with amiodarone or d, l-sotalol (The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators, 1997). Persons treated with an AICD had a 39% reduction in mortality at 1 year, a 27% reduction in mortality at 2 years, and a 31% reduction in mortality at 3 years (The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators, 1997). If persons after MI have life-threatening ventricular tachycardia or ventricular fibrillation, an AICD should be inserted.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II randomized 1232 persons, mean age 64 years, with a prior MI and a LVEF of 30% or less to an AICD or to conventional medical therapy (Moss *et al.*, 2002). At 20-month follow-up, compared with conventional medical therapy, the AICD significantly decreased all-cause mortality 31% from 19.8% to 14.2% (Moss *et al.*, 2002). The effect of AICD therapy in improving survival was similar in persons stratified according to age, sex, LV ejection fraction, New York Heart Association class, and QRS interval (Moss *et al.*, 2002). These data favor considering the prophylactic implantation of an AICD in post-MI persons with a LVEF of 30% or lower.

HORMONE REPLACEMENT THERAPY

The Heart Estrogen/Progestin Replacement Study (HERS) investigated in 2763 women with documented IHD the effect of hormonal therapy versus double-blind placebo on coronary events (Hulley *et al.*, 1998). At 4.1-year follow-up, there were no significant differences between hormonal therapy and placebo in the primary outcome (nonfatal MI or IHD death) or in any of the secondary cardiovascular outcomes. However, there was a 52% significantly higher incidence of nonfatal MI or death from IHD in the first year in persons treated with hormonal therapy than in persons treated with placebo (Hulley *et al.*, 1998). Women on hormonal therapy had a 289% significantly higher incidence of venous thromboembolic events and a 38% significantly higher incidence of gallbladder disease requiring surgery than women on placebo.

At 6.8-year follow-up in the HERS trial, hormonal therapy did not reduce the risk of cardiovascular events in women with IHD (Grady *et al.*, 2002). The investigators concluded that hormonal therapy should not be used to decrease the risk of coronary events in women with IHD (Grady *et al.*, 2002). At 6.8-year follow-up in the HERS trial, all-cause mortality was insignificantly increased 10% by hormonal therapy (Hulley *et al.*, 2002). The overall incidence of venous thromboembolism at 6.8-year follow-up was significantly increased 208% by hormonal therapy (Hulley *et al.*, 2002). At 6.8-year follow-up, the overall incidence of biliary tract surgery was significantly increased 48%, the overall incidence for any cancer was insignificantly increased 19%, and the overall incidence for any fracture was insignificantly increased 4% (Hulley *et al.*, 2002).

REVASCULARIZATION

Medical therapy alone is the preferred treatment in elderly persons after MI (Table 4). The two indications for revascularization in elderly persons after MI are prolongation of life and relief of unacceptable symptoms despite optimal medical management. In a prospective study of 305

Table 4 Overall medical approach to older patients after myocardial infarction

1. Stop cigarette smoking.
2. Treat hypertension with beta-blockers and ACE inhibitors; the blood pressure should be reduced to $<$140/85 mm Hg and to $\leq$130/80 mm Hg in persons with diabetes mellitus or renal insufficiency.
3. The serum LDL cholesterol should be reduced to $<$70 mg/dl with statins if necessary and at least 30% to 40%.
4. Diabetes, obesity, and physical inactivity should be treated.
5. Aspirin or clopidogrel, beta-blockers, and ACE inhibitors should be given indefinitely unless contraindications exist to the use of these drugs.
6. Long-acting nitrates are effective antianginal and antiischemic drugs.
7. There are no Class I indications for the use of calcium channel blockers after MI.
8. Postinfarction patients should not receive Class I antiarrhythmic drugs, sotalol, or amiodarone.
9. An automatic implantable cardioverter defibrillator should be implanted in postinfarction patients at very high risk for sudden cardiac death.
10. Hormone replacement therapy should not be administered to postmenopausal women after MI.
11. The two indications for coronary revascularization in elderly persons after MI are prolongation of life and relief of unacceptable symptoms despite optimal medical management.

patients aged 75 years and older with chest pain refractory to at least two antianginal drugs, 150 patients were randomized to optimal medical therapy and 155 patients to invasive therapy (The TIME Investigators, 2001; Aronow, 2001c). In the invasive group, 74% had coronary revascularization (54% coronary angioplasty and 20% coronary artery bypass surgery). During the 6-month follow-up, one-third of the medically treated group needed coronary revascularization for uncontrollable symptoms. At 6-month follow-up, death, nonfatal MI, or hospital admission for an acute coronary syndrome was significantly higher in the medically treated group (49%) than in the invasive group (19%) (The TIME Investigators, 2001). Revascularization by coronary angioplasty (Laham *et al.*, 2004) or by coronary artery bypass surgery (Stemmer and Aronow, 2004) in elderly persons is extensively discussed elsewhere. If coronary revascularization is performed, aggressive medical therapy must be continued.

KEY POINTS

- Coronary risk factors should be intensively treated in elderly persons with IHD.
- Elderly persons with IHD should be treated indefinitely with antiplatelet drugs, β-blockers, and ACE inhibitors unless contraindications to the use of these drugs exist.
- The data favor the use of primary angioplasty in eligible patients younger and older than 75 years with acute MI to reduce coronary events and mortality.
- Hormone replacement therapy should not be administered to elderly women with IHD.
- The two indications for revascularization in elderly persons with IHD are prolongation of life and relief of unacceptable symptoms despite optimal medical management.

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Valvular Disease in the Elderly

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INTRODUCTION

Valvular heart diseases are among the most predictable causes of heart failure and sudden death (Borer, 2003a; Supino *et al.*, 2002). Though rheumatic fever in children remains a frequent cause of valvular disease in some parts of the world (Agarwal, 1981), including South Africa, parts of Asia and parts of South America, for much of the remainder, the most common underlying etiologies are genetically determined predispositions that are not expressed as functionally or clinically important conditions until after the age of procreation (Hochreiter *et al.*, 1986; Roman *et al.*, 1987; Samanek *et al.*, 1989; Brand *et al.*, 1992; Borer *et al.*, 1998; Perloff, 2003; Follman, 1993). As a result, disease of the heart valves is likely to increase directly as the world's population increases.

Valvular diseases are progressive: relatively modest variants in valve architecture or composition tend, over time, to express themselves as functionally important alterations in valve morphology. Consequently, the prevalence of valve dysfunction, as hemodynamically detectable regurgitation or stenosis, increases with aging (Akasaka *et al.*, 1987; Lindroos *et al.*, 1993; Singh *et al.*, 1999). The progressive nature of valve dysfunction accounts for the observed fact that, with the gradual reduction in mortality in the fifth through eighth decades of life from coronary artery disease, malignancies, and infections, valvular diseases increasingly are emerging as clinically important and quantitatively frequent problems within the aging population. Truly, today, valvular diseases are diseases of aging.

Until the past two decades, the incidence and prevalence of valvular diseases were markedly underestimated. The introduction of echocardiography approximately 40 years ago and, more importantly, perfection of two-dimensional and Doppler echocardiography, achieved during the past 25 years, has provided a previously unavailable accurate, noninvasive, and easily applied method for detection and comprehensive hemodynamic evaluation of valve dysfunction. However, even with the rapidly increasing application of echocardiography, valve abnormalities in clinically healthy individuals were underestimated for many years: those lacking relevant physical signs on routine clinical evaluation, or whose evidence of valve dysfunction remained undetected by physicians without specific training in cardiac evaluation, seldom were referred for echocardiography. Emergence of cross-sectional and longitudinal epidemiological studies in relatively broad populations has begun to redress this deficiency of data (e.g. Akasaka *et al.*, 1987; Lindroos *et al.*, 1993; Singh *et al.*, 1999). The echocardiographic surveys currently available support two overarching conclusions; first, that valvular diseases are quite common, affecting many millions of individuals worldwide, and second, that valvular diseases are manifestations of aging, with incidence and prevalence increasing progressively with chronological age.

PATHOPHYSIOLOGY

Consequences of Valve Disease

The consequences of valvular diseases result from the impact of pressure and volume overloading of the left and right ventricular (LV, RV) myocardium and, often to a lesser extent, of the atrial myocardium as well (Borer *et al.*, 2002; Borer *et al.*, 2004a,b; Carabello, 2002; Starling 2002; Berger, 2004). These influences may be magnified in the elderly because of myocardial changes occurring naturally over time (Lakatta *et al.*, 1997).

Myocardial Cellular Changes (Experimental) with Normal Aging: Systole

Experimental studies indicate that aging is associated with progressive alteration in trans-sarcolemmal ion movement (Capasso *et al.*, 1986; Orchard and Lakatta, 1986; Walker

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et al., 1993), prolongation of calcium sequestration in the sarcoplasmic reticulum (Tate *et al.*, 1990), prolongation of the action potential (possibly as a result of the latter changes) (Capasso *et al.*, 1986; Walker *et al.*, 1993), variation in the proportional expression of contractile protein isoforms (Buttrick *et al.*, 1991), and alterations in receptor coupling and postsynaptic myocardial responses to neural stimuli, generally diminishing capacity for augmentation of contraction with β-adrenergic stimulation (Lakatta, 1993). Taken together, these changes tend to reduce velocity of systolic contraction while prolonging its duration, minimizing the capacity to respond to the increased demands of exercise for cardiac work.

Myocardial Cellular Changes (Experimental) with Normal Aging: Diastole

Coupled with these variations in cardiomyocyte contractile function, loss of ventricular compliance (one form of diastolic dysfunction) progresses with age (Templeton *et al.*, 1979). The basis of this change may be structural alteration and consequently reduced compliance of the large central arteries, increasing impedance to outflow from the LV and resulting in secondary (compensatory) ventricular hypertrophy (Nichols *et al.*, 1985). Intrinsic prolongation of diastolic relaxation, observed in humans as well as experimentally, also may contribute to diastolic dysfunction (Schulman *et al.*, 1992). The impedance-related "pressure loading" may also be one of the stimulants to the observed increase in the formation of myocardial extracellular matrix (ECM), grossly perceived as fibrosis, which can directly impair ventricular compliance (as well as contractility) (Weisfeldt *et al.*, 1971; Anversa *et al.*, 1990). Experimental studies also suggest a gradual loss of cardiomyocytes with advancing age (Anversa *et al.*, 1990), placing increasing loads on the remaining myocytes; perhaps in compensation, these hypertrophy, tending to maintain contractility but altering cellular mechanical characteristics.

The Aging Myocardium in Humans

In the absence of any specific myocardial disease, advancing age is associated with relative maintenance of ventricular chamber size and ejection fraction at rest (Fleg *et al.*, 1995). However, with aging, exercise-induced arterial vasodilatation progressively diminishes, increasing LV loading and diminishing the expected exercise-associated increase in chamber performance, measured as ejection fraction (Port *et al.*, 1980); the ejection fraction response may also represent loss of myocardial contractile reserve associated with the other age-related changes in the cardiomyocyte, described in the preceding text.

Heart rate response to stress also diminishes with age. Perhaps in part, due to the increase in ventricular filling time at lower heart rates, cardiac output during stress tends to be maintained by diastolic ventricular dilatation, which supports stroke volume, rather than by systolic volume diminution that is the more common response to stress in younger subjects (Fleg *et al.*, 1995). In addition, and importantly in any evaluation of the effects of aging on exercise capacity, skeletal muscle performance decreases with age, diminishing the efficiency of cardiac output in sustaining external work.

Superimposition of Valve Disease

The increases in ventricular systolic loading that occur with aging in the absence of disease, detailed earlier, can add to the impact of superimposed valvular disease. Thus, the pressure overload of aortic stenosis (AS) leads to LV cardiomyocyte hypertrophy and hyperexpression of ECM collagen (Weber *et al.*, 1993), with progressive diastolic dysfunction that ultimately results in pulmonary congestion and exertional dyspnea (the cardinal symptom of congestive heart failure). When superimposed on existing hypertrophy and fibrosis of aging, the clinical impact of AS is magnified. (Though the effects may differ quantitatively, similar considerations may relate to the RV and left atrial responses in mitral stenosis (MS).) The hypertrophy of aging may also add importantly to the likelihood of angina when AS is superimposed: even in the absence of coronary artery occlusive disease (CAD), coronary flow can become insufficient to meet the demands of particularly hypertrophied myocardium. The effects of volume loading from aortic regurgitation (AR) or mitral regurgitation (MR) also may be magnified by age-related loss of cardiomyocytes or contractile reserve. However, in theory, the effects of diastolic dysfunction from hypertrophy and fibrosis may have a complex effect in regurgitant valvular diseases: by resisting further ventricular dilatation, these characteristics may retard the rate of increase in ventricular wall stress, the direct cause of myocardial alterations and dysfunction; these same diastolic functional changes may hasten the development of pulmonary and systemic vascular congestion and symptoms.

Importantly, the effects of aging may be modifiable by simple interventions like exercise. For example, among healthy adults older than 65 years, prolonged, sustained endurance training has been found to preserve left ventricular compliance, possibly helping to prevent heart failure, when compared with the effects of a sedentary lifestyle that is associated with age-related diminution in left ventricular compliance and diastolic performance (Arbab-Zadeh *et al.*, 2004).

Age-related alterations in the valves, themselves, can potentiate development of valvular disease. For example, AS is believed most often to result from processes similar to atherosclerosis engrafted upon the aortic valve leaflets and involving the annulus; in addition, cholesterol appears to induce formation of mature lamellar bone within the valve by osteoblast-like cells that are also found in the media of the aorta (and may also contribute to vascular calcification) (Rajamannan *et al.*, 2003). As in arteries, these valvular atherosclerotic processes are slowly progressive. Thus, prolonged survival, itself, enables AS development.

Similarly, increasingly prolonged application of mechanical stresses even on normal valves, and certainly on structurally abnormal valves, can be expected to result in increasing valve deformation with progressively more defective leaflet coaptation during systole, tending to favor development of valvular regurgitation. This tendency may be most obvious in the mitral valve characterized by "myxomatous degeneration" (a histopathological finding in many patients with mitral valve prolapse, the most prevalent cause of MR) (Waller *et al.*, 1982). Myxomatous tissues also are more likely to rupture during the mechanical stress of normal cardiac function, perhaps accounting for the relatively high incidence of ruptured chordae tendineae, with consequent flail mitral leaflet (causing severe MR), observed in patients with mitral valve prolapse (Jeresaty *et al.*, 1985), a problem that increases with aging. (Ruptured chordae also are observed in the valves of patients with acquired rheumatic mitral valve disease; here, too, mere survival is an ally of the pathological process, as continuing mechanical stress on the affected tissues is the most likely basis of rupture.) While myxomatous histology is a well-defined mitral valve structural variant, less obvious or extensive variants undoubtedly also exist, each affecting the mechanical properties of the valve and its response to the mechanical stresses of cardiac contraction.

EPIDEMIOLOGY

Valvular Regurgitation

Evidence to support the likelihood of progressive morphological alteration with age in "normal" valves can be inferred from echocardiographic surveys. One of these, involving 100 normal adult volunteers without evidence of heart disease and ranging in age from 23 to 89 years (mean 45 ± 16), each of whom underwent Doppler echocardiography, found valvular regurgitation in 73% (Berger *et al.*, 1989). Most lesions affected the tricuspid and pulmonic valves. However, echocardiography detected left heart valve disease, as well: MR was present in 21 subjects, mean age 55 ± 18 years; in contrast, mean age among the 79 volunteers without MR was 43 ± 18 years ($p < .01$), consistent with age-related valve alteration. Similar results were reported in an even larger assessment of 176 apparently healthy volunteers aged 40–90 years: prevalence of valvular regurgitation was <5% among those aged 40–49 years and increased progressively with each decade of age, exceeding 50% in those aged 70–79 years and 70% in those above 80 years (Akasaka *et al.*, 1987).

These valve abnormalities were relatively modest and, as required by the study entry criteria, were not apparent clinically. However, when larger unselected populations are studied, a similar relation of age to valve disease has been reported, with the emergence of relatively severe disease in a potentially large subset of persons affected when prevalence data are extrapolated to the population at large (Singh *et al.*, 1999). Thus, analysis of the Framingham Heart Study cohort, including almost 3600 individuals (aged 54 ± 10 years) who underwent color Doppler echocardiography, revealed MR, AR, and/or TR, each most often mild, in approximately 35% of those tested (Singh *et al.*, 1999). However, for all three valves, age was the single common determinant of regurgitation likelihood (odds ratios 1.3/9.9 years for MR, 1.5/9.9 years for TR, and 2.3/9.9 years for AR). Indeed, valvular regurgitation of at least mild severity was present in approximately half the subjects aged ≥70 years, a threefold greater prevalence than among subjects aged <40 years. Valvular regurgitation was moderate or severe (thus potentially limiting life quality and/or length) in approximately 10% of those aged ≥70 years and in <1% of those aged <40 years.

Valvular Stenosis

AS is even more closely associated with aging than regurgitant lesions. In 501 randomly selected volunteers in the Helsinki Aging Study, all aged ≥75 years, severe ("critical") AS was present in 2.9%; critical AS was absent in a comparator population aged 55–71 years (Lindroos *et al.*, 1993). When moderately severe AS also is considered, prevalence among patients aged ≥75 years was 5%. Earlier, smaller series (Aronow and Kronzon, 1991; Roberts *et al.*, 1971, an autopsy series) reported similar frequencies. (The impact of aging on MS is not well defined as this lesion primarily results from rheumatic fever, acquired in childhood.)

Impact of Mild to Moderate Valve Disease on Clinical Outcome

Most of the lesions discovered in broad population studies have been mild. Generally, it is believed that mild valve dysfunction has little impact on clinical outcome. However, recent evidence indicates that even mild to moderate valvular regurgitation may affect lifestyle and longevity (Aviernos *et al.*, 2002). Similarly, mild AS, or aortic sclerosis, is also associated with important natural history implications (Otto *et al.*, 1999), particularly in the elderly. The reasons for this association are complex, including the likelihood that other cardiovascular diseases may share common pathophysiological bases with aortic sclerosis; in these situations, mild AS may modulate or unmask evidence of other disease. This possibility is supported by an earlier study of patients aged greater than 62 years with mild AS, in whom congestive heart failure, syncope or angina pectoris, symptoms typically associated with severe AS, were present in 24% (Aronow and Kronzon, 1991). Similarly, data from the Helsinki Aging Study indicate that among patients aged 75–86 years, a clear survival risk is associated not only with severe AS but also with moderate disease (Iivanainen *et al.*, 1996).

Progression of Valve Dysfunction

Moreover, valvular diseases tend to progress in severity with time, albeit generally at a relatively slow rate. This is inferred from population data for regurgitant disease (Follman, 1993; Sarano *et al.*, 1999) and has been directly demonstrated for AS (Nassimiha *et al.*, 2001). Progression of AS, while slow, is 30% more rapid among patients aged $\geq$75 years than among those aged 60–74 years, indicating that the underlying pathophysiological process is modulated by age-related characteristics. Consistent with these findings, as previously noted, severe valve disease is progressively more prevalent with advancing age. The result is that, as other causes of mortality have fallen among relatively younger people, clinically disabling valvular dysfunction is emerging as a quantitatively important public health problem (Supino *et al.*, 2002), most prominently among older individuals.

CLINICAL MANIFESTATIONS

Confounding by Superimposed Processes in the Elderly

Clinical findings among persons with valve disease (Borer, 2003b) are similar, irrespective of age. Symptoms of exertional dyspnea, exertional central chest discomfort (angina pectoris), presyncope, and syncope are found among elderly patients with valve disease as they are in those who are younger. However, as patients become older, other cardiac and noncardiac abnormalities associated with aging tend to develop and coexist with valvular disease, complicating pathophysiology, confounding interpretation of symptoms, signs, and objective test results, and adding uncertainty in defining therapeutic strategy. Thus, CAD, most often clinically apparent only after age 45 years and progressively more frequent with age, can cause angina (indeed, CAD is the most common cause) in the absence of valve dysfunction. However, when abnormal myocardial workloads (and associated enhancement of myocardial oxygen demand) are present, generated by ventricular outflow obstruction or by wall stress enhancement mediated by abnormal volume loads, angina may result from coronary obstructions insufficient to critically limit oxygen supply when exogenous loads are normal; conversely, valve disease might be insufficiently severe to cause symptoms without the additive effect of moderate coronary obstruction. Angina is uncommon in the patient with regurgitant valvular disease though, when present, particularly in the patient with AR, its implications are ominous. However, in patients with AS, the situation is relatively clear: with the onset of typical angina pectoris, average survival in the unoperated patient is approximately 2 years, that is, 50% of affected patients will die within 2 years unless surgical valve replacement is performed (Kelly *et al.*, 1988). (Earlier investigation had suggested a 5-year average survival after symptom onset among patients with AS and angina (Ross and Braunwald, 1968), but these data predated the routine definition of coronary anatomy at catheterization and the availability of echocardiography to assess outflow obstruction in patients who did not undergo catheterization.) This situation can create a therapeutic dilemma in the older patient. Because of its prognostic implications, and the excellent long-term outcome after valve replacement in patients older than 65 years (Lindblom *et al.*, 1990), angina in a patient with hemodynamically severe AS is considered a strong indication for life-prolonging surgery unless unusual countervailing surgical risk exists. However, if the symptom is not truly attributable to the AS, then the associated risk also may differ, altering the benefit: risk relation of surgery. Recent studies support this concern: associated CAD is an important risk factor for poor outcome among patients with mild to moderate AS (Rosenhek *et al.*, 2004), while hemodynamic severity of AS in symptomatic elderly patients with concomitant CAD is significantly less than among younger patients without coronary occlusions. Unfortunately, no method now exists to distinguish the cause of the symptom when objectively severe AS and CAD coexist. As a result, most such patients undergo surgery.

In addition to confounding interpretation of the causality of angina, associated CAD also can potentiate development of congestive symptoms (equally or more ominous in their prognostic implications than angina (Ross and Braunwald, 1968; Kelly *et al.*, 1988) in patients with AS, and in patients with AR, MR, and MS, as well. For patients with AR and MR, congestive symptoms are associated with a 20% average annual mortality risk. Among patients with MS, for whom the RV is the sole shock organ, mild (New York Heart Association Functional Class II) symptoms are compatible with relatively good survival (80% at 10 years); more marked symptoms imply 0–20% 10-year survival if surgery is not performed (Bonow *et al.*, 1998).

Sinus node disease ("sick sinus syndrome") increases in prevalence with age, increasing the likelihood of presyncope or syncope in patients with AS. If it were known that chronotropic incompetence was the basis of the symptom in an elderly patient, pacemaker therapy rather than valve surgery might suffice. Unfortunately, for this symptom as for angina and dyspnea, unambiguous assignment of causation is not yet achievable. Finally, as previously noted, annular and valve calcification progress more rapidly and are often more extensive in the elderly than in relatively young patients (Nassimiha *et al.*, 2001). Aortic annular calcification may extend to the atrioventricular conduction system, leading to varying degrees of heart block that also can lead to syncope, again confounding the assignment of cause.

The precordial, carotid, jugular, and peripheral pulse variations and associated murmurs typical of AS, AR, MS, MR, and TR generally are not affected by age. These findings are well described elsewhere (Borer, 2003b) and will not be detailed here. However, as with symptoms, structural manifestations of associated disease processes can confound

interpretation of physical signs in the elderly. For example, the previously-noted structural alteration of the arteries with age can increase carotid amplitude and upstroke rate; slowing of upstroke rate, the primary diagnostic finding in hemodynamically severe AS in younger patients, is associated with severe AS in only half of patients aged greater than 80 years. Dorsal kyphosis, another common concomitant of aging, can confound palpation of ventricular impulses, important in detecting volume loading of the RV and/or LV and useful in identifying the pressure loaded ventricle of AS, and can minimize the capacity to hear confirmatory murmurs in any valve disease. (In addition, of course, associated limitation of lung volumes can lead to dyspnea, or can minimize ambient activity with associated deconditioning of the skeletal musculature, potentially confounding detection and/or interpretation of symptoms.)

Life Length Versus Lifestyle: Impact on Therapeutic Decisions

Decision making is further complicated in the older patient owing to disagreement about when life prolongation no longer is a reasonable primary goal of therapy. After some age (increasingly more difficult to define with progressive medical amelioration of the risks associated with common problems of aging), surgery that is life prolonging for younger patients may not be expected realistically to prolong life in an older patient, at which point other methods of symptom relief (pharmacologic, catheter-based) might be most appropriate. At present, defining this point of diminishing returns is not possible with great rigor.

OBJECTIVE TESTING

Thus, in elderly patients, there may be a need for greater reliance on objective testing than in younger patients not only to assess the severity of disease, but also to merely establish or confirm a diagnosis. However, objective testing is not a substitute for symptom history in determining the functional limitation imposed by valve disease. In the elderly, for whom therapy may be aimed more appropriately at improving quality rather than length of life, it follows that objective testing alone may be inadequate for defining appropriate management strategy.

Evaluation of Mechanical Function

Fortunately, echocardiography, the primary modality now employed to confirm the diagnosis of valve disease and to estimate the hemodynamic impact of the lesion, is reasonably accurate in the elderly patient, unless skeletal deformities, like kyphosis, have developed. Generally, for patients with mild valvular disease, echocardiography may be prudent at 2- or 3-year intervals, unless physical signs change. For patients with moderate or severe disease, annual echocardiography may be appropriate, and for patients specifically with AS who are asymptomatic, repetition of echocardiography may be valuable every 6 months. However, recent data indicate that interpretation of echocardiographic findings may require knowledge of hemodynamic alterations that may be common in the absence of disease. Thus, it is now understood that pulmonary artery pressure increases with age even in the absence of a clearly apparent structural cardiac abnormality. This finding may relate to the previously noted loss of diastolic function with age (Schulman *et al.*, 1992). Pulmonary pressures are important in explaining symptoms as a basis for selecting therapy and may be accepted as criteria supporting a recommendation of valve surgery in the absence of symptoms among patients with mitral valve disease (Bonow *et al.*, 1998); thus, the concomitance of valve disease with age-related alteration in pulmonary pressure may confound definition of optimal management. Exercise-induced variations in LV and RV ejection fractions, employed in prognostication among patients with AR and MR (Borer *et al.*, 1998; Rosen *et al.*, 1994; Borer and Bonow, 2003), may deteriorate with aging in the absence of disease (Port *et al.*, 1980), precluding unambiguous assignment of pathophysiological causality to symptoms and assignment of prognostic impact of valve disease.

Electrocardiography

In the absence of confounding associated heart diseases, ventricular tachyarrhythmia is not particularly associated with aging. However, atrial fibrillation (AF) is now understood to be a clinical problem that reaches epidemic proportions as populations age. AF is present in $>10\%$ of those aged greater than 75 years, in the absence of any apparent structural heart disease. This arrhythmia predisposes to intracardiac thrombosis and to thromboembolization; among patients with structural heart diseases (including valve diseases), the risk of such events may be as high as $5-10\%$/year, depending on the valve and the severity of disease. Thus, regular electrocardiography is essential, both to assess rhythm (especially if neck veins assessment is unclear) and to seek new conduction abnormalities that also increase in frequency with aging. Among patients with hemodynamically severe valve disease, 24-hour ambulatory electrocardiography also is useful (perhaps annually) to detect evidence of paroxysmal dysrhythmia that may not be present during examination. Importantly, intrinsic conduction system disease in the elderly not infrequently results in AF with a relatively slow (and relatively regular) ventricular response, so that the patient is unaware of a rhythm disturbance (commonly apparent to younger patients because of the rapidity, and irregularity, of heart rate and associated palpitations).

TREATMENTS APPROPRIATE FOR THE ELDERLY PATIENT

Goals of Treatment

In the absence of data to inform treatment selection when confounding conditions are present, current practice generally tends toward applying surgery when nominally accepted prognostic criteria are met (Bonow *et al.*, 1998; Borer and Bonow, 2003; Borer *et al.*, 2004a; Berger, 2004; Carabello, 2002) at least until the age of 80, and in selected patients perhaps until the age of 85 (Table 1). Application of surgery beyond this age may be appropriate for survival improvement, but is better established for amelioration of symptoms; as previously suggested, the latter often also can be relieved with medication, but among patients aged less than 90 years without associated overt potentially life-threatening disease, medication may not provide symptom relief for the remainder of the reasonably expected life-span. For patients beyond age 90 years, surgery probably is best reserved for patients with symptoms that cannot be acceptably relieved with medication.

Pharmacological Therapy

When pharmacological therapy is an appropriate option for symptom relief, the optimal drug regimen depends upon the symptom (Borer and Brodman, 2003). Congestive symptoms often are most efficiently relieved with diuretics (with appropriate electrolyte supplementation, depending upon the agent selected); angina usually is most efficiently relieved or prevented with nitrates (recently found to be relatively safe even with AS (Khot *et al.*, 2003), though caution must be applied when first administering such agents in this setting). Heart rate slowing, with β-blocking drugs, may be helpful among patients with MR in sinus rhythm (without evidence of important sinus node or conduction system disease) or in AF, primarily to lengthen ventricular filling period to minimize residual pulmonary blood volume. Patients with AF also would require anticoagulation (Borer and Brodman, 2003): the concomitance of AF and structural heart disease results in thromboembolic events at a rate of 5–10% per year in the unanticoagulated patient, whereas the risk of thromboemboli or major hemorrhage is approximately 2% per year with anticoagulation (possibly somewhat higher in the elderly). Efforts at LV afterload reduction for symptom relief may be helpful, but the appropriate drug is unclear. In patients with AR and hypertension, long-acting nifedipine, a dihydropyridine calcium channel blocker, has retarded symptom development in populations not preponderantly elderly (Scognamiglio *et al.*, 1994); this agent has the virtue of low likelihood of inducing renal insufficiency or hyperkalemia (as might be feared with angiotensin converting enzyme inhibitors or angiotensin receptor blockers), but can cause constipation (though not so frequently as calcium channel blockers of other types) and peripheral edema, particularly bothersome adverse effects in the elderly. Other afterload-reducing drugs have not been demonstrated to provide clinical benefit to patients with AR (Supino, in press). No afterload reducers are demonstrably beneficial for MR, though empirical testing of such drugs in individual symptomatic patients might be undertaken. For the asymptomatic patient, other than the possible use of long-acting nifedipine among patients with AR and systolic hypertension, drug treatment must be considered experimental and unproven. Though epidemiological and experimental data have favored cholesterol reduction with

Table 1 Suggested indications for mechanical therapy (surgery or percutaneous valvuloplasty) in the asymptomatic patient aged <85 years

Valve dysfunction must be at least moderately severe for mechanical therapy to be considered; if so, and if the patient's general state of health and personal therapeutic goals warrant consideration of prolongation of life length, rather than solely improvement of life quality, then one or more of the following criteria should be met if the patient is asymptomatic:

AS
- Treadmill exercise tolerance test
  - ≥4 mm electrocardiographic ST segment depression
  - <20 mmHg increase in systolic blood pressure during exercise
  - development of angina or presyncope/syncope
  - induction of ventricular tachycardia (nonsustained or sustained) with exercise
- echocardiogram
  - >4 m second^{-1} transvalvular jet velocity
  - increase in jet velocity of ≥0.3 m second^{-1} in jet velocity during a 12-month interval
  - heavy valvular calcification
  - subnormal LV ejection fraction at rest

AR
- subnormal LV ejection fraction at rest
- echocardiographic LV systolic dimension >55 mm or >25 mm m^{-2}
- LV contractility index ≥−17% (see Borer *et al.* (1998) and Borer and Bonow (2003))
- Fall in LV ejection fraction >5% from rest to exercise
- ?Echocardiographic LV diastolic dimension >80 mm (weak predictor)

MS
- Percutaneous balloon valvuloplasty
  - New York Heart Association Functional Class symptoms ≥ II
  - Pulmonary artery systolic pressure >50 mmHg at rest
  - New onset AF
- Open (surgical) mitral commissurotomy or replacement
  - New York Heart Association Functional Class symptoms ≥ III
  - Pulmonary artery systolic pressure >60 mmHg at rest
  - Persistent LA thrombus or recurring embolization despite anticoagulation
  - New onset AF

MR
- Repair
  - LV ejection fraction at rest <10% above the lower limit of normal (usually <60%)
  - RV ejection fraction subnormal at rest
  - RV ejection fraction failure to rise from rest to exercise
  - Pulmonary artery systolic pressure >50 mmHg at rest
  - Persistent or recurrent paroxysmal AF
  - ?Echocardiographic effective regurgitant orifice area >40 mm (aggressive)
- Replacement
  - LV ejection fraction subnormal at rest
  - RV ejection fraction subnormal at rest

statins (which also appear to minimize bone formation in the aortic valve) to retard progression of AS (Rajamannan *et al.*, 2003; Borer, 2005), a recent randomized controlled trial failed to support this strategy (Cowell *et al.*, 2005). However, the relatively small size of the study cohort (155 patients) and relatively short duration of follow-up (average 2 years), in a disease with slow natural progression of valve dysfunction, suggest the need for additional data before total exclusion of statins as options for preventing AS progression.

Electrophysiological Treatment: Maze Procedure

Since AF is now an accepted indication for surgery among younger patients with severe MR (Grigioni *et al.*, 2002), optimal management among the elderly with MR and AF may be difficult to define. The availability of the catheter-based Maze procedure (a modification of the more definitive open surgical procedure (Cox *et al.*, 1996)) enables successful amelioration of the arrhythmia in the majority of patients in whom its appearance is paroxysmal, and in a smaller proportion of those with persistent AF. The catheter-based Maze procedure is a method of isolating the pulmonary veins (from which most foci of AF generation arise) by inducing endocardial injury with a cryoprobe attached to a percutaneously introduced catheter. Consideration of Maze therapy rather than surgery may be appropriate in some patients to minimize the need for dependence on anticoagulation (with its age-related morbidities) as well as to minimize symptom development that might require surgery. As yet, no data are available to define the proper role of the Maze for AF in patients with concomitant MR, or of the appropriate approach to accounting for age-related AF in patients who also have MR.

Mechanical Treatment: Open Surgical Valve Replacement/Repair

When surgery is required, either for symptom relief or for prophylaxis in patients aged less than 85 years, current data suggest such treatment can be performed relatively safely and with reasonable late postoperative survival. For example, in a study of 100 consecutive patients aged greater than 85 years who underwent cardiac surgery under cardiopulmonary bypass between 1994 and 1997, all patients survived the operation, though 7% died within the succeeding 30 days (Rosengart *et al.*, 2002). However, this cohort primarily included patients with CAD who were undergoing coronary artery bypass grafting, 35% of whom had suffered prior myocardial infarction; 5% had undergone prior coronary artery bypass grafting, and 25% had either diabetes mellitus, chronic pulmonary disease or renal insufficiency (previously defined as risk factors for poor survival among patients aged greater than 80 years and undergoing cardiac surgery (Ko *et al.*, 1991)). Valve surgery was performed in 54 of the 100 patients, 13 as an isolated procedure (three of these had two valves implanted) and 41 in conjunction with coronary bypass grafting. The latter subgroup included several patients in whom the valve lesion was secondary to prior myocardial damage, a situation associated with relatively high perioperative risk irrespective of age. Indeed, there were no perioperative deaths among the 13 patients who underwent valve surgery alone; the median survival was 54 months in this subgroup. When valve surgery was combined with bypass grafting, perioperative mortality was 12% and median survival was 37 months. Bypass grafting alone was associated with 4% perioperative mortality, but median postoperative survival was only 27 months, significantly poorer than for patients undergoing valve surgery. The differences in these results suggest important fundamental pathophysiological differences among patients with these different conditions. These findings were extended in a 10-year evaluation of surgical outcome in 42 consecutive nonagenarians (aged 90 to 97 years) who underwent cardiac surgery with cardiopulmonary bypass (Bacchetta *et al.*, 2003). Again, the cohort included patients who underwent coronary artery bypass grafting alone (18 patients), several of whom were operated on an emergent or urgent basis (a known major risk factor for poor survival), as well as 21 patients who underwent valve surgery alone (5 patients) or together with coronary bypass surgery (16 patients); in two cases, only aortic aneurysm repair was performed. For the great majority of those receiving valves, surgery was elective. No perioperative deaths were recorded among the 21 patients whose valves were replaced or repaired (18 of whom required aortic valve surgery, with or without associated mitral or coronary procedures); all three perioperative deaths occurred among the 18 other patients who required bypass grafting alone. These survival records are remarkable given that half the cohort had congestive heart failure prior to surgery, one-third had suffered previous myocardial infarction, two-thirds had hypertension, almost one in five had diabetes, and one-third had a history of smoking. In such a population, the 7% rate of respiratory complications (pneumonia, respiratory failure, or reintubation) or 12% infection rate (sepsis, wound infection) is not surprising. Perhaps more importantly, despite the three perioperative deaths, 81% of the population remained alive an average of 2.5 years after surgery.

Clearly, additional data are needed to provide stable point estimates of surgical risk among the elderly, but the data now available suggest optimism in the application of surgery when age criteria and prognostic concerns mandate definitive therapy, or when symptoms are not adequately ameliorated by pharmacological therapy.

Mechanical Treatment: Percutaneous Valve Replacement/Repair

Catheter-based balloon valvuloplasty has been assessed in several series for relief of both MS and AS. For the former, the catheter-based approach has been relatively successful.

However, the stenotic mitral valve tends to become increasingly fibrotic and calcified with age, factors that mitigate the utility of balloon valvuloplasty (Palacios, 2002). Nonetheless, this technique may be applied successfully in patients carefully selected for absence of specific echocardiographic findings, and may even provide some relief, *albeit* suboptimal, when preprocedure suitability criteria are absent. Unfortunately, for AS, far more common in the elderly today, balloon valvuloplasty is very disappointing, with only very transient relief even when the procedure is technically successful. Recently, however, another catheter-based approach has been reported, involving percutaneous insertion of a stented prosthesis (Boudjemline and Bonhoeffer, 2002). In the aortic position, the prosthesis is inserted immediately after balloon dilatation of the calcified native stenotic valve. Early periprocedural survival has been disappointing and long-term results are lacking, but considerable effort certainly will be lavished on improving the technique and results, possibly of greatest benefit in the first instance for elderly patients with AS.

MR also has become approachable by percutaneous methodology. Though still highly experimental, the method currently involves placement of a clip over the midportions of the anterior and posterior leaflets of the mitral valve, tethering the leaflets to form a "double orifice" valve and preventing prolapse (Block, 2005). The surgical analogue of this "edge-to-edge" repair (Umana *et al.*, 1998) has been used for several years, generally, but not invariably, as a temporizing measure to relieve symptoms in patients with ventricular dysfunction and secondary MR (due to loss of normal structural support from subvalvular structures). The durability of this form of repair, and its applicability for primary MR, are not yet fully defined. Nonetheless, in theory, the result of edge-to-edge repair by direct suture or by catheter-mediated clipping, is complete relief of MR; this may not be achieved in practice in many cases but, in most reports, MR almost always is reduced in magnitude early after operation. Concerns with application of this method include (1) dearth of information about the durability of the repair, (2) possibility of creating hemodynamically important MS with the clip, though reports to date suggest that obstruction to flow across the valve generally is no more than modest, (3) the potential for the clip to slip from its position; though reapplication is possible, distal embolization may occur. (4) Direct apposition of the leaflets for a period of even many weeks results in cicatrization with irreversible adhesion of the leaflets to one another; if the repair then is found hemodynamically deficient, standard surgical repair may be precluded, resulting in a suboptimal surgical solution, or in valve replacement when repair might have been preferable. (5) Recent experience suggests that, when the surgical edge-to-edge procedure is employed, optimal success is achieved only when a mitral annuloplasty is also effected. An experimental catheter-based approach for this procedure also exists, comprising introduction of an armature into the coronary sinus (which runs along the perimeter of the mitral annulus for a considerable distance) and tightening of the device to constrict the subjacent annulus. With this approach, thrombosis and obstruction to coronary sinus flow may occur, with important compromise to the coronary circulation by development of retrograde obstruction. Both the catheter-based edge-to-edge repair and coronary sinus constrictor are now under study; as technical improvements occur, their application is likely to be greatest, at least initially, among elderly patients for whom open-chest procedures are considered relatively hazardous.

Robotic surgery, currently involving a modified sternotomy and, therefore, not literally totally "percutaneous", is also being developed for mitral valve repair. Early results are promising, but as yet the role of this modality is unclear (Chitwood *et al.*, 2000). This procedure also enables Maze surgery for AF without the trauma of open thoracotomy (Reade *et al.*, 2005).

CONCLUSIONS

Valvular heart disease is a disease of aging. The majority of septuagenarians manifest valve dysfunction by echocardiography, with a substantial proportion (>10%) manifesting hemodynamically severe dysfunction that could be expected to limit length or quality of life. Evaluation of the clinical impact of valve disease in the elderly is confounded by multiple comorbid conditions that also increase in prevalence with aging and that can mimic the symptoms and modulate the physical signs and even the results of objective tests elicited in patients with valve disease. Selection of therapy also is difficult because of the relatively great likelihood of limitation of life length from noncardiac causes; however, assessment of the likely survival in the absence of valve disease is a "moving target" as medical advances mitigate effects of one after another noncardiac condition. Nonetheless, at this time it is difficult to justify application of surgery solely for life prolongation in patients with objectively severe valve disease and "high-risk" prognostic descriptors if the patient is more than 85 years of age. For patients aged less than 85 years, current results would seem to support "prophylactic surgery" for life prolongation in the absence of major comorbidities (physical and psychological) that might independently limit life or substantially increase surgical risk and, importantly, when the patient desires maximization of life length. At present, there is general consensus on this "prophylactic" strategy for patients aged less than 80 years (again excepting those with major relevant comorbidities). Applicability of drug therapy for life prolongation generally remains unproven, with the possible exception of patients with AR and associated systolic hypertension (who are likely to benefit from long-acting nifedipine). For patients whose quality of life is limited by valve disease even if length of life is not a major consideration, surgery is a very reasonable option if comorbidities do not predict unacceptable perioperative risk; in this setting, pharmacological therapy generally has greater applicability than it might for younger patients, in whom symptomatic debility carries prognostic implications that generally would mandate surgery.

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KEY POINTS

- Valvular disease is a disease of aging, present in most individuals aged >70 years, often (>10% of patients) hemodynamically severe.
- Symptoms, signs, and objective findings of valve disease are similar irrespective of age, but their interpretation often is confounded by comorbidities common in the elderly.
- Drug therapy generally is not proven to improve survival, but can mitigate symptoms when contraindications to surgery exist or when life prolongation is not a realistic or desired goal (perhaps age >85 years).
- Surgery can be performed with acceptable morbidity and mortality when considered appropriate for symptom relief even in nonagenarians.
- Percutaneous valve replacement/repair, now largely experimental, may alter risk: benefit relations of mechanical therapy for the elderly in the future.

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Hypertension

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DEFINITION AND PREVALENCE

Hypertension is a common condition in the elderly, with potentially devastating consequences if untreated. It is a major risk factor for cerebrovascular and cardiovascular disease, and may affect up to 70% of individuals over the age of 65. The exact prevalence of hypertension varies with the age, race, and the overall health status of the population studied, as well as the blood pressure cutoff points used to define hypertension. The seventh report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), released in May 2003, defines hypertension as a systolic blood pressure (SBP) >140 mmHg or a diastolic blood pressure (DBP) >90 mmHg (Chobanian *et al.*, 2003). New to the JNC 7 is the category of prehypertension, representing a SBP of 120–139 mmHg or DBP of 80–89 mmHg, previously classified as "normal" or "high normal" blood pressure. This category was introduced, in part, on findings of the Framingham Heart Study suggesting that normotensive individuals at age 55 have a 90% lifetime risk of developing hypertension (Vasan *et al.*, 2002). Normal blood pressure is defined as SBP <120 mmHg and DBP <80 mmHg, reflecting a substantial lowering of the JNC 6 criteria of SBP <139 mmHg and DBP <90 mmHg. The new recommendation was based on the results of 30 worldwide clinical trials conducted since the JNC 6 report was published in 1997, and a report estimating the risk of cardiovascular mortality doubles with each 20/10 mmHg rise in blood pressure, starting at levels as low as 115/75 mmHg (Lewington *et al.*, 2002). A shortcoming of the JNC recommendations is the absence of an age adjustment. The compelling evidence supporting the cardiovascular benefit of treating hypertension in the elderly does not necessarily extend to the very old (Goodwin, 2003), a concept whose recognition eludes many clinicians. What little data exists on subjects over the age of 80 is somewhat conflicting and inconclusive. The very old are a diverse and divergent group of individuals varying in pathophysiology, vigor, and expectations, and therefore not amenable to blanket recommendations. Failing to appreciate this basic, if often neglected, tenet of geriatric care is a failure to provide optimal care and to maximize function and quality of life of the very old. More on this later.

In developed countries, SBP increases steadily with age, whereas DBP increases until the seventh decade of life, after which it plateaus or may even decline. Consequently, the prevalence of isolated systolic hypertension (ISH) (SBP >140 mmHg and DBP <90 mmHg) increases with advancing age, as does widening of the pulse pressure (PP), defined as the difference between SBP and DBP. Contrary to previous belief, it is now widely held that the SBP, rather than DBP, is a better predictor of future cardiovascular disease. Recent epidemiologic data suggests that the PP may be as good a predictor, if not better, of future pathology than the SBP alone. In the Framingham study, the risk of cardiac disease increased at any level of SBP as the DBP declined. When subjects were stratified into four groups of SBP (<120 mmHg, 120–139 mmHg, 140–159 mmHg, and ≥160 mmHg), the relative risks (RRs) for individuals with a DBP 80–89 mmHg were 1.4, 1.9, 1.9, and 4, respectively. However, with a DBP of 70–79 mmHg, the RR increased more steeply (1.1, 2.1, 3.4, 6.8, respectively), suggesting than an increased PP increases the risk of ischemic cardiac disease independently of the SBP (Franklin *et al.*, 1997). The authors conclude that the PP is an important component of the total risk.

In the elderly, as in younger adults, essential hypertension, that is, hypertension without an identifiable cause, is by far the most common type of hypertension. Essential hypertension in older people, however, consists not only of systolic–diastolic hypertension (SDH) but also includes ISH. ISH is rare before the age of 60, however, by age 80, approximately 25–30% of the population has ISH. Epidemiological studies have shown that the overall prevalence of hypertension in noninstitutionalized individuals over the age of 65 is 50–70% (Wolz *et al.*, 2000). More than 60%

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of these persons have ISH (Franklin *et al.*, 1997). In non-institutionalized subjects 65–74 years of age, the National Health and Nutrition Examination Survey (NHANES III) reported a blood pressure above 140/90 mmHg in 53% of non-Hispanic whites, 72% of non-Hispanic blacks, and 55% of Mexicans (Burt *et al.*, 1995). The Hypertension Detection and Follow-up Program (HDFP) estimated SDH in all subjects older than 65 years to be 15% in whites and 25% in blacks. Unlike hypertension in the young, where there is a male predominance, little or no gender difference was noted in the elderly. In the Systolic Hypertension in the Elderly Program (SHEP), the incidence of ISH was estimated to be 8% in subjects aged 60–69, 11% in those 70–79, and 22% in those older than 80 years (Systolic Hypertension in the Elderly Program Cooperative Research Group, 1991).

PATHOPHYSIOLOGY

Blood pressure regulation is a complex process, subject to multiple interacting physiological systems, as well as lifestyle and genetic factors. In its simplest conceptualization, the cardiovascular system is governed by Ohm's law, which, when adapted to a hemodynamic system, states that flow (Q) is proportional to the pressure gradient (ΔP) and inversely proportional to the resistance (R) across a conduit.

$$Q = \frac{\Delta P}{R} \text{ or } \Delta P = Q \times R$$

In terms of the cardiovascular system, BP is the product of cardiac output and vascular resistance. Since cardiac output does not increase with age, hypertension in the elderly is, to a large extent, a result of increased vascular resistance. In SDH, the problem arises at the site of the resistance arterioles, the smaller muscular vessels where 80–90% of arterial resistance occurs. Increased constriction at this level affects both systolic and DBPs. In contrast, ISH develops as a result of large arteries that have become less compliant and therefore less able to accommodate volume changes.

In young normotensive individuals, large elastic vessels contribute little resistance to blood flow. During systole, the aorta and other large arteries expand to accommodate the stroke volume, which attenuates the rise in intra-arterial pressure. During early diastole, elastic recoil of large arteries sustains forward flow, augmenting the DBP despite runoff into arterial branches. Age-related loss of elasticity increases vascular impedance, resulting in a more rapid rise in blood pressure during systole, and to a higher level. The higher peak pressure, coupled with diminished elastic recoil, results in rapid runoff to the periphery, resulting in lower DBP (Figure 1). A low DBP is not entirely benign. Since myocardial perfusion occurs during diastole, diastolic hypotension may result in subendocardial ischemia. While other constituents, no doubt, factor into the pathogenesis of hypertension, age-related loss of arterial elasticity successfully predicts widening of the PP, ISH, and the plateau in DBP that develop with aging. Figure 1 depicts these changes over the course of a single cardiac cycle.

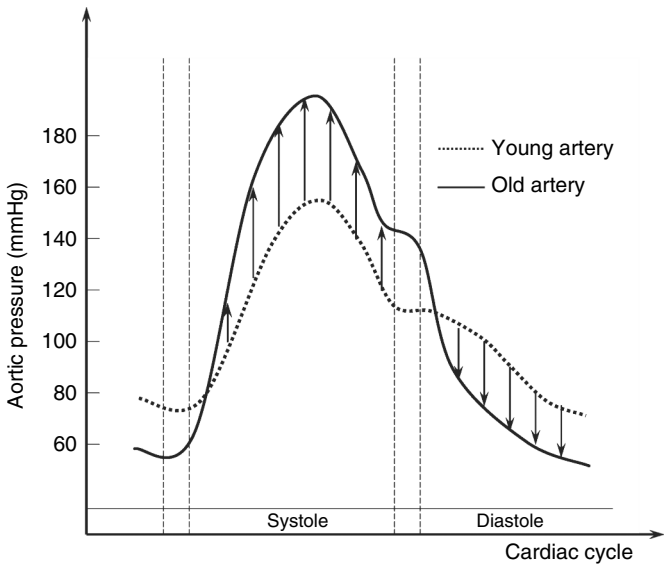

Figure 1 Blood pressure changes in an old versus young artery during a cardiac cycle. The arrows indicate increased pressure during systole and decreased pressure during diastole that older arteries experience due to arteriosclerosis

Aging blood vessels undergo a host of structural and functional changes, resulting in decreased compliance and increased resistance to flow. These changes particularly affect the intima and media of large arteries. With age, elastic fibers progressively decrease in number and elasticity, and the collagen matrix increases. This fibrous transformation results in arteriosclerosis, and is compounded by calcification and an increase in the number and size of vascular smooth muscle cell. The combined effect is a fall in the total cross-sectional area of peripheral vasculature. Furthermore, the dynamic nature of endothelial-derived vasoactive substances that control vascular tone is also affected by age. The delicate balance between vasoconstricting agents (such as endothelin and angiotensin II) and vasodilating agents (such as prostacyclin and nitric oxide) is offset. Nitric oxide (NO), previously termed *endothelial-derived relaxing factor* (EDRF), is a potent vasodilator that has been extensively studied. An age-associated decline in NO-mediated vasodilatation has been demonstrated (Cooper *et al.*, 1994). Decreased secretion of NO as well as a blunted response to NO have also been documented. Endothelial dysfunction, possibly as a direct effect of elevated peak pressure, inhibits secretion of these compounds (Panza *et al.*, 1993). It remains unclear to what extent the imbalance of endothelial-derived vasoactive compounds is a cause or effect of high blood pressure, but impairment of effective vasodilator agents, in the absence of appropriate compensatory mechanisms, will result in increased vascular resistance. The endothelium also

secretes a number of factors that act on smooth muscles in an autocrine manner. These include interlukin-1 and insulin-like growth factor. *In vitro*, these influence the migration and proliferation of smooth muscle cells, which in turn increase vascular rigidity and decrease lumen size.

Despite increased levels of serum norepinephrine that occur in the elderly, the role of the sympathetic nervous system in the pathogenesis of hypertension appears to be more complex than mere overstimulation. The sympathetic nervous system has little clinical impact on older normotensive subjects, even with increased levels of serum norepinephrine. This is due to decreased adrenergic receptor function. Downregulation of β-adrenergic inotropic, chronotropic, and vasodilatory response, as well as α-adrenergic vasoconstrictor response has been documented in the elderly. With receptor downregulation in the face of increased norepinephrine release, α-1-adrenergic vascular tone is comparable in old and young normotensive subjects. It has been proposed by some experts that older hypertensive subjects have a relatively less degree of suppression of α-1 adrenergic relative to β-2 adrenergic activity (Supiano *et al.*, 1999), and age-related hypertension is in part due to diminishing β-mediated vasodilatation while α-mediated vasoconstriction continues relatively unabated. Similar findings have been observed in animal studies.

Decreased carotid baroreceptor sensitivity and responsiveness occurs with age. Consequently, a larger change in blood pressure is needed to trigger the appropriate compensatory response. The impaired reflex is manifested clinically as wide blood pressure fluctuations in the elderly compared to the young, as well as increased susceptibility to clinically significant orthostatic hypotension and postprandial hypotension. The age-related baroreceptor reflex dysfunction is not necessarily limited to hypertensive persons alone, but decreased vascular distensibility at the carotid sinus, as seen in hypertensive subjects, is likely to play a central role in the process, and many antihypertensive medications will further exacerbate the condition.

Aging kidneys undergo multiple changes, which may affect blood pressure regulation. A sodium load is secreted less rapidly and less completely as renal function declines. Similarly, the elderly are more sensitive to free water depletion or repletion than the young. Angiotensin II promotes sodium reabsorption from the distal tubules directly and indirectly through aldosterone release and stimulation of the autonomic nervous system. The renin-aldosterone-angiotensin axis, however, is less responsive with age. There is a decrease in serum renin levels and activity, which may be the result of decreased functional glomeruli, and a decrease in serum angiotensin II and aldosterone levels. The net effect of these changes is toward sodium retention. Free water retention ensues to maintain sodium homeostasis. It has been suggested that chronic extracellular volume expansion due to sodium and water retention leads to increased vascular resistance through the mechanism of autoregulation of organ blood flow. These observations are consistent with the high prevalence of salt sensitivity among older hypertensive individuals. Atrial natriuretic peptide (ANP) is released primarily from the atria in response to stretch due to volume overload. ANP acts both as a peripheral vasodilator and a natriuretic/diuretic hormone. Brain natriuretic peptide (BNP) was initially identified in the brain but is also present in the ventricles. It is homologous to ANP, and its serum concentration is normally approximately one-fifth that of ANP. In heart failure, levels of BNP can increase dramatically. A simple serum assay has been devised for the measurement of BNP and is now commonly used in the management of heart failure. Several variants of ANP and related hormones have been identified. Of note is a hormone with a digitalis-like effect. This putative hormone appears to be ouabain or an isomer of ouabain and binds the digitalis receptor on the sodium-potassium-adenosine triphosphatase pump in an inhibitory manner. This hormone differs from ANP in that it increases vascular resistance. A proposed mechanism is that the Na-K-ATPase inhibitor facilitates renal sodium excretion but also diminishes intracellular sodium release resulting in increased concentrations of sodium in smooth muscle cells. Passive sodium-calcium exchange subsequently results in increased intracellular calcium, and, therefore, vascular tone (Blaustein, 1996; Jackson, 2000). These mechanisms may explain the high incidence of salt sensitivity in subjects with essential hypertension, but more investigation is needed to fully determine the role this mechanism plays in the pathogenesis of hypertension.

Not all the aforementioned mechanisms have conclusively been shown to be age-related changes, independent of disease and lifestyle influences. In some populations, the incidence of hypertension changes little with age, and the overall prevalence is low. To some extent, hypertension is an affliction of modern society. Until very recent history, humans employed the hunter-gatherer lifestyle for survival. Such "primitive" peoples experienced vigorous daily physical activity and a diet rich in potassium and fiber and low in fat and sodium. Patterns of nature lead to periods of diminished food intake, and obesity was virtually unheard of in these communities. Modern-day populations who enjoy relatively low incidences of hypertension tend to practice daily routines that more closely resemble the primitive lifestyle of old, particularly in regards to nutrition and physical activity. The blood pressure profiles of immigrants from such regions, however, may change over the course of few generations to resemble that of the host community. The over abundance of foods rich in sodium, calories, and fat in Westernized societies, coupled with sedentary levels of activity, without doubt contributes to the epidemic of obesity and hypertension. With the abundance of effective medications available for treatment of hypertension, these potentially modifiable risk factors receive far less attention than they deserve. Finally, there is a clear genetic role in the development of hypertension in some families. Such individuals are likely to develop hypertension early in life. The genetic contribution is complex, involves multiple interacting genes, and is not fully understood at this time. Genetic factors are perhaps the strongest nonmodifiable risk factor for hypertension.

SECONDARY HYPERTENSION

Secondary hypertension occurs in 2–7% of older individuals with high blood pressure. Secondary hypertension should be suspected when the blood pressure is difficult to control despite aggressive management with multiple medications, when there is an acute worsening in blood pressure control, or when diastolic hypertension is present. Early detection of secondary hypertension is important since many causes are potentially reversible or treatable, and specific therapy can be started until a more definitive treatment plan is devised. A detailed history, physical examination, and basic hematological tests are invaluable in guiding the investigation, since many causes of secondary hypertension present with a characteristic spectrum of findings alluding to the diagnosis.

Renovascular disease is the most common cause of secondary hypertension in the elderly. Unlike younger subjects, where fibromuscular dysplasia of the renal artery is the most common cause, atheromatous disease accounts for approximately 90% of renovascular hypertension in the elderly. The prevalence increases with age and is associated with diabetes and hyperlipidemia. Compromised renal artery blood flow results in ischemic-mediated excess rennin production and consequent stimulation of the renin-angiotensin-aldosterone system. In unilateral disease, nephrosclerosis can occur in the unaffected kidney if blood pressure is not controlled. With bilateral renal vascular disease, rapid decline in renal function may occur with the use of an angiotensin-converting enzyme inhibitor (ACE inhibitor) or an angiotensin receptor blocker (ARB). Approximately 30% of cases reveal bilateral renal artery involvement. If adequate blood pressure control cannot be achieved with medications, or if renal function declines precipitously, surgical repair or angioplasty should be considered after confirming the diagnosis with bilateral contrast angiography or magnetic resonance angiography. Not all stenotic lesions are amenable to surgical repair.

Primary aldosteronism classically presents with hypertension, hypokalemia, suppressed renin activity, increased aldosterone secretion, and metabolic alkalosis. Not all affected subjects will present with all these findings. Hypokalemia develops because of excessive renal excretion in response to sodium retention, but approximately a third of subjects with hyperaldosteronism will present with normal or low-normal serum potassium levels. Idiopathic hyperaldosteronism due to bilateral zona glomerulosa hyperplasia consists of 60–70% of cases, while unilateral adenomas contribute to approximately 30–40%. The incidence of hyperaldosteronism in the general geriatric population is less than 2%, but in hypertensive individuals, it may exceed 20%. These findings suggest that some degree of hyperaldosteronism may be a common cause of resistant hypertension, and an important factor in the spectrum of essential hypertension.

Pheochromocytoma may present with paroxysms of hypertension, palpitations, diaphoresis, and headaches, interspaced between periods of no or few clinical findings. Approximately 90% occur in the adrenal glands, and 10% are bilateral. Ten percent are autosomal dominant. Screening tests include measurement of catecholeamines (epinephrine, norepinephrin, or dopamine), or their metabolites (metanephrin, normetanephrin, or vanillylmandilic acid). No single test is a perfect diagnostic tool. Owing to the presence of catecholeamines in the circulation as normal physiologic mediators, and their episodic secretion with pheochromocytoma, the diagnosis often requires multiple tests and high clinical suspicion. The 24-hour urine collection method for fractionated metanephrin has largely been replaced by the more practical and highly sensitive measurement of plasma-free metanephrin. A negative test during a paroxysmal episode essentially rules out pheochromocytoma, whereas markedly elevated levels strongly support the diagnosis. Unfortunately, in most cases of suspected pheochromocytoma, results are intermediate. Owing to the low prevalence of this condition, the positive predictive value of most tests is low. False positive tests may be due to dietary and other exogenous factors, such as caffeine, nicotine, acetaminophen, tricyclic antidepressants, drug withdrawal (clonidine, benzodiazepine, alcohol), and many more. Stress, physical activity, and pain may sufficiently increase serum levels of catecholeamines to interfere with interpretation of the results, and blood collection as well as the 24-hour urine collection must be done under as calm and stress-free conditions as possible.

Cushing syndrome is a rare condition that develops in response to prolonged exposure to either excess endogenous cortisol or, more commonly, exogenously administered glucocorticoids. Long-term use of glucocorticoid at pharmacological levels will precipitate many symptoms of Cushing syndrome, including hypertension. Iatrogenic cases may not be entirely avoidable, and chronic steroids should be administered at the lowest effective dose. Endogenous cortisol overproduction is usually adrenocorticotropic hormone (ACTH)-dependent, but approximately 15% of cases result from primary benign adrenal adenoma, independent of ACTH stimulation. Approximately 80% of ACTH-secreting neoplasms arise in the anterior pituitary (Cushing disease). Ectopic production of ACTH makes up the balance of cases, and is often associated with malignancies such as small-cell carcinoma of the lung. The peak incidence of adrenal or pituitary adenomas is between the age of 30–40 years, and only ectopic ACTH production due to neoplasm increases with age. Cushing syndrome is diagnosed by measuring serum cortisol levels; low or normal levels exclude the diagnosis, and levels above threefold normal strongly suggest it. Equivocal cases are confirmed by the dexamethasone suppression test.

Other causes of secondary hypertension are exceedingly rare but should be considered when clinical or biochemical evidence supports their presence. Coarctation of the aorta is generally diagnosed in childhood but subtle cases may escape detection until adulthood. Classical findings are elevated blood pressure in the upper extremities with low or normal blood pressure in the lower extremities. A

delayed and attenuated pulse wave in the lower extremities may be present. Headaches and claudication may also be present. Hyperthyroidism may cause increased cardiac output, increased blood volume, and increased vascular resistance, all of which contribute to hypertension. Sleep apnea is relatively common in the elderly and associated with hypertension. Finally, a careful review of medications may uncover an often-overlooked contributing factor for hypertension: medication-induced hypertension. Although medications are rarely the sole cause of established hypertension, optimal management necessitates familiarity with potential offending agents. Many commonly used drugs such as theophyllin, nonsteroidal anti-inflammatory drugs, corticosteroids, tricyclic antidepressants, albuterol, cold/allergy remedies containing sympathomimetics, and many others, are known to increase blood pressure.

DIAGNOSIS OF HYPERTENSION IN THE ELDERLY

The diagnosis of hypertension should never be based on a single blood pressure measurement. Diminished baroreceptor activity in the elderly results in relatively wide fluctuations in blood pressure. The diagnosis should be based on no less than three determinations taken during separate visits. Extreme measurements should be confirmed manually, using an appropriate size bladder and the bell of the stethoscope. Blood pressure should initially be measured in both arms, with the higher measurement being the more accurate one. Taking the blood pressure at the end of the encounter, when rapport has been established, may alleviate some of the anxiety or stress that occasionally accompanies a clinic visit. White-coat hypertension is more common than most clinicians suspect, and is not always accompanied by overt signs of anxiety or trepidation. The term "white-coat syndrome" was allegedly introduced into the medical vernacular in 1983 when it was observed that, on the average, the SBP rose by 27 mmHg, DBP by 15 mmHg, and the pulse by 16 beats per minute, when a doctor entered the hospitalized patient's room, based on intra-arterial pressure monitoring (Mancia *et al.*, 1983). Ambulatory blood pressure monitoring remains the best means of detecting and quantifying this condition, and appears to correlate better with end-organ injury than office blood pressure measurements (Verdecchia *et al.*, 1994; Gosse *et al.*, 1994; Gosse *et al.*, 1997, Staessen *et al.*, 1999; Fagard *et al.*, 2000). White-coat hypertension, also referred to as intermittent office hypertension (IOH), may affect up to 50% of the population to some degree, and 20% of borderline hypertensives by 20 mmHg or more. It is not entirely benign. In a 10-year follow-up study, approximately 70% of subjects with IOH progressed to established hypertension versus 43% of age-matched normotensives (Gustavsen, 2004). An association between white-coat hypertension and increased left ventricular hypertrophy, left ventricular mass, and diastolic failure has been reported (Grandi *et al.*, 2001; Muscholl *et al.*, 1998; Palatini *et al.*, 1998). The degree of carotid artery atherosclerosis in subjects with white-coat hypertension was found to be similar to that in subjects with persistent hypertension (Muldoon *et al.*, 2000). The clinical sequelae of these findings, however, are not entirely clear. A 10-year follow-up study of 479 subjects found a relatively benign cardiovascular outcome in white-coat hypertension compared with sustained mild hypertension (Khattar *et al.*, 1998). Many of these studies, however, were relatively small, included young subjects, or were not entirely clear on enrollment criteria. With current evidence, white-coat hypertension should at the very least justify advice on lifestyle modification, and should be closely monitored. When ambulatory blood pressure monitoring is not feasible, repeated office measurements taken by the nurse have been shown to be significantly lower than those performed by the physician, and comparable to home self-monitoring (Little *et al.*, 2002).

Pseudohypertension is another condition that may result in overestimation of the blood pressure. This occurs when compression of the brachial artery in patients with stiff arteries requires a cuff pressure greater than that of systolic pressure due to atherosclerosis. Intra-arterial pressure measurements can easily detect this condition, but such invasive techniques are seldom necessary. A positive Osler's sign suggests the presence of arterial stiffening. The Osler's maneuver is performed by inflating the cuff to above the SBP while palpating the distal pulse, usually at the radial or brachial site. A palpable, albeit nonpulsating, artery is a positive Osler's sign. Some investigators have found that a positive sign predicts pseudohypertension, and the measurement discrepancy was as much as 50 mmHg (Messerli *et al.*, 1985). Others have found that the maneuver is not sensitive or reliable (Taapatsatis *et al.*, 1991), has a low positive predictive value (Oliner *et al.*, 1993), and therefore is of limited clinical use. For clinical purposes, indirect blood pressure measurement is appropriately suitable for managing the vast majority of older persons with hypertension, and has been demonstrated to be as accurate in the old as it is in younger subjects (O'Callaghan *et al.*, 1983; Vardan *et al.*, 1983). In both age-groups, external cuff measurement tends to underestimate the SBP and overestimate DBP, even in those considered to be at high risk for pseudohypertension (Bos *et al.*, 1992; O'Callaghan *et al.*, 1983). Pseudohypertension should be suspected in patients whose elevated blood pressure remains resistant to adequate drug regiments, who have signs of peripheral hypoperfusion despite normal or high blood pressure, or who show no evidence of end-organ damage despite chronic hypertension. When doubt arises, noninvasive measures, such as the automatic infrasonic recorder or plethysmography, can be utilized to better determine arterial pressure.

Though not directly related to the diagnosis of hypertension, two common conditions that must be evaluated in all older persons are postural hypotension and postprandial hypotension. Neither condition is a disease in itself, but rather the clinical manifestation of abnormal blood pressure regulation due to a variety of causes. Postural hypotension, also termed *orthostatic* or *positional hypotension*, is defined as a drop in SBP of $\geq$20 mmHg and/or DBP of $\geq$10 mmHg from the baseline supine blood pressure upon

assuming a vertical position. Also, individuals who have a lesser drop in blood pressure but experience subjective symptoms of dizziness upon standing are said to have orthostatic hypotension. Chronic hypertension, particularly in the supine position, is a strong predictor of orthostatic hypotension (Harris *et al.*, 1991). Other conditions associated with postural hypotension are dehydration, diabetes, deconditioning, chronic recumbency, the use of certain medications, among many others. Documenting the pulse rate during postural changes is a useful aid in determining the cause of hypotension. For example, the absence of a compensatory increase in the pulse suggests autonomic dysfunction (e.g. diabetes) or drug effect (e.g. β-blockers and nondihydropyridine calcium-channel blockers), whereas an increased pulse response may suggest hypovolemia. Orthostatic blood pressure measurement should be done routinely with every blood pressure check and in all older individuals. When present, fall precautions should be discussed with patients, such as standing slowly and with adequate support.

Postprandial hypotension is essentially a condition of the elderly. It is commonly defined in the literature as a decrease in SBP of $\geq$20 mmHg within two hours of ingesting a meal. Pooling of blood in the splanchnic circulation during digestion, with an inadequate compensatory sympathetic response, appears to be central for the development of postprandial hypotension. In addition, several meal-related vasoactive mediators have been implicated, but the role of these vasodilating peptides remains uncertain. While several studies reported a significant drop in systemic vascular resistance after a meal, serum levels of peptides such as substance P, cholecystokinin, gastrin, and motilin generally remained unchanged. In many studies, insulin infusion has been shown to induce vasodilation in the forearm, independent of hypoglycemia, but no clinical correlation has been found between serum insulin levels and blood pressure following oral glucose ingestion. Whatever the precise mechanism, nearly all older subjects will develop some degree of meal-induced drop in blood pressure and, in most, it remains clinically insignificant. With increasing frailty, the prevalence and severity of postprandial hypotension increases, such that 5–20% of all persons older than 65 years, and up to 36% of nursing home residents, will develop a drop of 20 mmHg or more in SBP (Aronow and Ahn, 1994). When compounded by postural orthostasis, postprandial hypotension can be profound, and is associated with falls and syncope. Postprandial blood pressure should be checked in older persons with symptoms of dizziness, angina, falls, or visual deficits following a meal, and in all nursing home residents. Antihypertensive medications should not be administered prior to meals, and fall precautions should be reviewed with symptomatic individuals. Dietary modifications may also be necessary. Warm food rich in carbohydrates has been shown to worsen hypotension. Smaller, more frequent, low-carbohydrate meals served at room temperature and with ample fluids are the current recommendations. In difficult cases, caffeine, octreotide, vasopressin, and fludrocortisone have been used with varying degrees of success.

ASSESSMENT AND RISK STRATIFICATION

Once the diagnosis of hypertension has been established, a focused medical history and physical examination must be completed, the goals of which are:

1. Risk stratification, consisting mainly of identifying comorbid conditions and lifestyle factors that compound cardiovascular risk.
2. Evaluating end-organ function and documenting any damage.
3. Identifying possible indicators of secondary hypertension.

Hypertension is essentially a silent disease; symptoms usually occur as a result of extreme elevation in blood pressure or the development of end-organ damage. The ultimate goal of assessment and treatment of hypertension is not to achieve a target blood pressure per se, but the long-term prevention of catastrophic cardiovascular events. Blood pressure is only the immediate measurable "marker" of treatment success. Risk stratification, therefore, becomes central in guiding clinicians in determining how aggressively the blood pressure should be lowered, and with which pharmaceutical agent or agents. For example, the JNC 7 report recommends drug intervention for high-risk subjects with prehypertension, but only lifestyle modification for the low-risk group, and the choice of medication is, in part, based on the spectrum of comorbid conditions. High risk is determined by pre-existing cardiovascular disease, presence of injury to target organs at the time of diagnosis, or the presence of other well-known cardiovascular risk factors. Modifiable risk factors include diabetes, dyslipidemia, smoking, obesity, and inactivity, and should be concurrently addressed and/or treated. Nonmodifiable risk factors such as age, gender, race, and family history also affect the patient's risk stratum assignment and should therefore guide treatment. In older persons with hypertension, it may be difficult to differentiate end-organ damage attributable solely to hypertension from concurrent age-related changes. The degree of organ damage and rate of progression is often a useful tool, as age-related physiologic decline, free of pathological influences, tends to follow a predictable, if inexact, trajectory. The medical history, physical examination, and basic diagnostic tests establish a knowledge base from which an individualized treatment plan can emerge.

The medical history should establish a detailed construct of diabetes, dyslipidemia, and cerebrovascular, cardiac, and renal disease. Family history is a strong independent prognosticator, and should be addressed as such. Lifestyle habits should be investigated, including level of physical activity, current or past tobacco use, and dietary customs such as sodium, alcohol, and caffeine use. In addition, any previous blood pressure determinations should be reviewed, along with the effectiveness and tolerance of previous drug interventions, if any. Reasons for noncompliance or discontinuation of medication may influence future choice of medications and improve adherence to the treatment regiment.

A review of medications, including over-the-counter medications and supplements, is important to determine agents that may elevate blood pressure or interfere with treatment. Symptoms suggesting end-organ damage, such as angina, heart failure, stroke, transient cerebral ischemia, claudication, and loss of vision, should be further investigated by physical examination and diagnostic tests. Establishing a baseline measurement of organ function is helpful in determining the success or failure of future treatment. Generally, complete blood count, basic metabolic panel, fasting serum glucose and lipid profile, and urinalysis are sufficient initial workup, unless secondary hypertension is suspected. Abnormal findings on the basic initial assessment should be further investigated. An echocardiogram may be necessary if evidence of myocardial hypertrophy is present on electrocardiogram or chest radiograph. Concentric left ventricular hypertrophy suggests long-standing hypertension, and is associated with increased risk of cardiovascular events as well as diastolic heart failure. If the initial assessment reveals impairment of the kidney function, determination of the glomerular filtration rate and the degree of proteinuria is necessary. This may require a 24-hour urine collection for accurate determination. Establishing baseline renal function has a direct role in determining which class of medications are recommended or contraindicated. Fundoscopic examination through dilated pupils and by an experienced clinician should be done at baseline, and yearly thereafter, particularly when diabetes is present; this tends to be underperformed.

EFFECT OF TREATING HYPERTENSION IN THE ELDERLY – AN OVERVIEW OF CLINICAL TRIALS

The benefit of treating hypertension in the elderly was evident as early as 1967. The Veterans Administration Cooperative Study, which was published in three parts between 1967 and 1972, documented the benefit of treating severe (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1967) and mild (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1970) diastolic hypertension. In subjects over the age of 60, a 70% reduction in the incidence of stroke and 52% reduction in cardiovascular events were observed in the treatment group (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1972). Similar favorable outcomes were documented in the Australian Therapeutic Trial in Hypertension, where a 33% reduction in stroke and 18% reduction in coronary artery disease were noted in the treated subgroup age 60–69 years, compared to the placebo group (Management Committee of the Australian Therapeutic Trial in Hypertension, 1981). In the Hypertension Detection and Follow-up Program, there was a 17% reduction in all-cause mortality after a five-year follow-up period of patients aged 60–69 years, treated for mild diastolic hypertension (HDFP Cooperative Group, 1979). These and other early studies, however, primarily treated diastolic hypertension and had relatively few participants in the geriatric age-group. The subgroup 60–75 years of age in the Veterans Administration Cooperative Study represented only 20% of total enrolment. Treatment of hypertension in the elderly remained tentative and debatable until the mid-1980s, when multiple randomized trials gave credence to the benefits and safety of aggressive blood pressure management even in advanced age. Salient features of these pivotal trials and a summary of their findings are found in Tables 1 and 2.

The SHEP trial addressed ISH in subjects $\geq$60 years of age (Systolic Hypertension in the Elderly Program Cooperative Research Group, 1991). The treatment group received chlorthalidone, with the addition of atenolol if needed, to achieve target blood pressure. The impact of treatment was greatest in reducing the incident of stroke by 36% and cardiovascular events by 32%. The reduction in coronary events was 27%, but not statistically significant. Comparable results were noted in the Systolic Hypertension in Europe (Syst-Eur) trial, which also studied subjects 60 years or older with primarily ISH (Staessen *et al.*, 1997). Treatment was initiated with nitrendipine, with the addition of enalapril and hydrochlorothiazide if necessary. A reduction in stroke by 42%, cardiovascular events by 31%, and coronary events by 26% was noted in the treatment group compared to placebo, all of which were significant. In both studies, reduction in

Table 1 Characteristics of treatment trials that predominantly involved older hypertensive individuals. Trial acronyms and references are found in the body of the text

Trial	*n*	Mean age (years)	Mean baseline BP (mmHg)	Mean follow-up period	Treatment BP (mmHg)	Control BP (mmHg)	Mean BP difference (mmHg)	Intervention	
								First line	Second line
SHEP	4736	71.6	170/77	4.5 years	144/68	155/71	−11/−3	Chlorthalidone	Atenolol
Syst-Eur	4695	70.2	174/85	2.0 years	151/78	161/83	−10/−5	Nitrendipine	Enalapril
Syst-China	2394	66.5	171/86	3.0 years	151/81	159/84	−9/−3	Nitrendipine	Captopril
EWPHE	840	72.0	182/101	4.6 years	148/85	167/90	−19/−5	Maxzide	Methyldopa
STOP-Hyper	1627	76.0	195/102	25 months	167/87	186/96	−19/−8	Diuretic or β-blocker	Diuretic or β-blocker
MRC	4396	70.0	185/91	5.8 years	152/76	168/85	−16/−9	Diuretic or β-blocker	Diuretic or β-blocker
Coope	884	68.7	196/99	4.4 years	162/78	180/89	−18/−11	Atenolol	Diuretic
STONE	1632	66.0	168/100	30 months	146/87	156/90	−9/−5	Nifedipine	Captopril
HYVET-pilot	1283	83.8	182/100	13 months	152/84 151/84	174/95	−22/−11 −23/−11	Diuretic ACE inhibitor	Calcium-channel blocker

n, patient number; BP, blood pressure.

Table 2 Outcome of treatment trials. Trial acronyms and references are found in the body of the text

Trial		Stroke events (total) (%)	Cardiovascular events (total) (%)	Coronary events (total) (%)	Stroke mortality (%)	Cardiovascular mortality (%)	Total mortality (%)
SHEP		−36[a]	−32[a]	−27	−29	−20	−13
Syst-Eur		−42[a]	−31[a]	−26[a]	−27	−27	−14
Syst-China		−38[a]	−37[a]	−37	−58[a]	−39[a]	−39[a]
EWPHE		−32	−38[a]	−47[a]	−32	−27[a]	−9
STOP-Hyper		−45[a]	−40[a]	−13	−76[a]	–	−43[a]
MRC		−25[a]	−17[a]	−19	−12	−9	−3
Coope		−42[a]	–	+3	−70[a]	−22	−3
STONE		−57[a]	−60[a]	−6	–	−26	−45[a]
	Diuretic	−69[a]	–	–	−48	+17	+31
HYVET-pilot	ACE	−37	–	–	−40	+9	+14
	All	−53[a]	–	–	−44	+13	+23

[a]Statistically significant ($p < 0.05$).

cardiovascular mortality (SHEP 20%, Syst-Eur 27%) and total mortality (SHEP 13%, Syst-Eur 14%) were similar and nonsignificant. The Systolic Hypertension in China (Syst-China) trial (Liu *et al.*, 1998) paralleled the Syst-Eur trial, and had similar enrolment criteria, but used captopril as a second line intervention. Treatment outcome results were in line with the previous two studies, with the exception of a larger and statistically significant drop in total and cardiovascular mortality (39% in both cases), possibly due to the slightly younger age of participants. Similarities in trial design and enrollment criteria of these three studies lend themselves to pooling analysis. When combined, a reduction in strokes (37%), coronary vascular disease (25%), cardiovascular events (32%), cardiovascular mortality (25%), and total mortality (17%) was noted in the treatment group compared to placebo, all of which were statistically significant (Staessen *et al.*, 1999).

Other studies addressed systolic–diastolic hypertension. The Swedish Trial in Older Patients with Hypertension (STOP-Hypertension) compared β-blockers or thiazide diuretics to placebo, in patients 70 to 84 years of age (average 76 years) with a mean blood pressure of 195/102 mmHg (Dahlof *et al.*, 1991). In the treatment group, a significant reduction in the incidence of stroke (45%), cardiovascular events (40%), and total mortality (43%) was documented after an average 25-month follow-up period. Myocardial infarctions were reduced by only 12%, which was not statistically significant. These findings were somewhat at odds with those of the European Working Party on High Blood pressure in the Elderly (EWPHE) trial. The baseline systolic and DBP in the EWPHE trial ranged between 160–239 and 90–119 mmHg, respectively (average 182/101 mmHg), and treatment was with hydrochlorothiazide/triamterene for an average follow-up period of 4.6 years (European Working Party, 1985). Unlike the STOP-Hypertension trial, the 9% drop in total mortality and 32% drop in stroke were not statistically significant, whereas the 47% decline in myocardial infarctions was. A significant 38% drop in cardiovascular events was similar to that found in the STOP-Hypertension trial (40%).

The Medical Research Council (MRC) working party trial studied both systolic and diastolic hypertension, and randomized participants aged 65–74 years to a diuretic or β-blocker treatment group, or to placebo (MRC Working Party, 1992). After an average follow-up period of 5.8 years, the mean blood pressure in the two treatment groups were similar, and significantly lower than the placebo group. The combined treatment group had a statistically significant 25% reduction in stroke and 17% reduction in cardiovascular events. The 19% reduction in coronary events, 9% reduction in cardiovascular mortality, and 3% reduction in total mortality were not significant. However, when treatment groups were analyzed separately, stroke and cardiac events were significantly lower in the diuretic group by 31 and 44%, respectively. The β-blocker treatment group showed no such reduction in these end points. It is not surprising that outcome is not only related to risk stratification but to the choice of antihypertensive agent as well. From the above trials, however, it appears that treatment of hypertension in the elderly generally has a greater impact on stroke reduction than coronary and cardiovascular event reduction, and that this effect is independent of drug choice. This pattern is seen in other trials. Both the Shanghai Trial of nifedipine in the Elderly (STONE) (Gong *et al.*, 1996) and the Coope and Warrender Trial (Coope and Warrender, 1986) showed a statistically significant reduction in stroke (57 and 42%, respectively) and a nonsignificant reduction in coronary heart disease (6 and 3%, respectively). Neither demonstrated a sizable change in cardiovascular mortality, but the STONE trial revealed a significant 45% drop in total mortality, versus a nonsignificant 3% in the Coope and Warrender trial. Variability in treatment outcome among studies is partly due to study design, but the importance of selection criteria in treatment risk/benefit determination, independent of other study parameters, must also be stressed. Subjects with higher initial SBP and wider PP are likely to experience greater treatment benefit, as are those in higher risk stratum. It is estimated that the reduction in all-cause mortality in the highest risk group is nine times that of the lowest risk group (Ogden *et al.*, 2000), emphasizing the importance of establishing an individualized treatment plan based on risk stratification, rather than on generalized guidelines *per se*. The above reasoning also introduces the concept of treatment risk, a principle that until recently has largely been overlooked, and will be discussed shortly.

Other end points have been investigated in more recent studies, notably the relationship between hypertension and cognitive decline or dementia. Data from the dementia project of the Syst-Eur trial show a significantly lower rate of development of dementia in the treatment group (Forette *et al.*, 1998), but the analysis was underpowered, and the conclusion difficult to generalize with authority. The Study on Cognition and Prognosis in the Elderly (SCOPE) showed a nonsignificant 11% reduction in the incidence of cognitive decline in the group treated with candesartan compared to placebo (Lithell *et al.*, 2003). The investigators concluded that at the very least, there is no evidence supporting a *negative* effect of treating hypertension on cognition in the elderly. The first credible evidence supporting the potential benefit of treating hypertension on dementia came from the Protection Against Recurrent Stroke Study (PROGRESS), whose primary outcome was assessing risk for recurrent stroke (PROGRESS Collaborative Group, 2001). During a four year follow-up period, a 12% overall reduction in the risk of dementia was observed with treatment. This finding was not statistically significant. However, when analyzed separately, the subgroup with prior stroke at baseline showed a 34% ($p = 0.3$) reduction in dementia risk, while the subgroup without prior stroke showed only a 1% change. For cognitive impairment, a similar pattern was noted, with slightly more favorable results. Severe cognitive decline was defined as a drop of three or more points on the Mini Mental Status Examination (MMSE). The overall risk reduction with treatment was 19% ($p = 0.01$). In the subgroup with prior stroke at baseline, reduction in the risk of developing severe cognitive decline was 45% ($p < 0.001$), but only 9% (not significant) in the subgroup without prior stroke.

Various meta-analysis reviews have been designed for that purpose of accommodating variability among individual trials or examining smaller subgroups within larger trials. A meta-analysis of nine trials (Insua *et al.*, 1994) confirms treatment benefit in the elderly. Reduction in stroke morbidity (odds ratio, 0.65; 95% confidence interval, 0.55–0.76), cardiac morbidity (0.85; 0.73–0.99), and total mortality (0.88; 0.80–0.97) was noted. Stroke and cardiac mortality individually were also significantly reduced in the treatment group. Another meta-analysis of eight ISH trials included 15 693 subjects (Staessen *et al.*, 2000). There was a 30% reduction in combined fatal and nonfatal stroke events ($p < 0.0001$), 26% reduction in combined cardiovascular events ($p < 0.0001$), and 13% reduction in total mortality ($p = 0.02$). In untreated patients, after correcting for regression dilution bias and DBP, the relative hazard rates associated with a 10 mmHg higher baseline SBP was 1.26 ($p = 0.0001$) for total mortality, 1.22 ($p = 0.02$) for stroke, but only 1.07 ($p = 0.37$) for coronary events. Treatment benefit was greatest in men, patients with previous cardiovascular complications, and in those who had larger PPs. Diastolic blood pressure was inversely correlated with total mortality, independently of SBP. Treatment effect was also largest in subjects over the age of 70, a topic of contention, which will be discussed next.

Despite compelling evidence supporting the benefit of treating hypertension in older persons (Leonetti and Zanchetti, 2002), the evidence for very old subjects is much less clear (Goodwin, 2003; Heikinheimo *et al.*, 1990; Langer *et al.*, 1989; Satish *et al.*, 2001). "Very old" is arbitrarily defined as >80 years of age, since at that age the risk/benefit advantage begins to waver. Subjects over the age of 80 are absent or underrepresented in most clinical trials, even though this segment of the population is the fastest growing in the Westernized world. The very old also tend to be lumped in the 65-and-over group, whereas they clearly have diverse and distinct characteristics, and data obtained in younger adults cannot instinctively be extrapolated to the very old. As early as 1986, trend analysis of EWPHE data suggested that treatment of hypertension is less effective, or even harmful, above the age of 80 (Amery *et al.*, 1986). Other studies have shown mixed results. The SHEP trial found treatment benefit, particularly in stroke prevention, extending beyond the age of 80. In the Syst-Eur analysis, total and cardiovascular mortality was significantly lower for the treatment group under the age of 80, but not for those 80 years or older. The overall RR for cardiovascular events in the treatment group from the STOP-Hypertension trial was 0.60, but the benefit decreased with increasing age subgroups, and crossed the unity point between the age of 80 and 85 years. These trials enrolled relatively few very old subjects. A meta-analysis of randomized controlled studies that enrolled subjects older than 80 years of age included 1670 subjects followed for a mean period of 3.5 years (Gueyffier *et al.*, 1999). A significant reduction in stroke (34%), cardiovascular events (22%), and heart failure (39%) occurred in the treatment group compared to control. No benefit in cardiovascular death, and a nonsignificant 6% *increase* in all-cause deaths were observed in the treatment group. The trend became stronger when the analysis was limited to five double-blind trials – an 11% ($p = 0.41$) increase in cardiovascular mortality in the treatment group and 14% ($p = 0.05$) increase in total mortality was observed.

Several population-based observational studies have demonstrated an inverse relationship between blood pressure and mortality in the very old. One study (Mattila *et al.*, 1988) enrolled 83% of the population of Temper, Finland, aged 85 years or older ($n = 561$), and a similar study (Boshuizen *et al.*, 1998) enrolled 94% of the residents of Leiden, the Netherlands, aged 85 years or older ($n = 833$). In both studies, the chance of being alive after five years was greatest in those with the highest blood pressure at enrollment. In the Temper study, subjects with SBP ≥200 mmHg at entry had a threefold higher survival rate than those whose SBP was 120–140 mmHg. Similar results were reported in the Helsinki Aging Study (Hakala *et al.*, 1997), where it was estimated that the 5-year mortality declined by 10% for every 10 mmHg increase in SBP at enrolment. These and earlier observational studies are limited to correlations, and constrained by confounding variables in selection criteria. In the Leiden study, for example, low blood pressure was associated with poor health. After adjusting for health status, the inverse relationship disappeared. The Hypertension in

the Very Elderly Trial (HYVET) is the first interventional controlled trial designed to assess the risk and benefit of treating hypertension specifically in subjects older than 80 years (Bulpitt *et al.*, 2001).

Results of the HYVET-pilot study, an international three-way randomized trial, were published in 2003, and set the course for the main trial (Bulpitt *et al.*, 2003). In total, 1283 subjects over the age of 80 were randomly allocated to a diuretic group, angiotensin-converting enzyme inhibitor group, or to a no treatment group. Medications used were bendrofluazide and lisinopril, with the addition of diltiazem in both treatment groups if needed to achieve target blood pressure. After a mean follow-up period of 13 months, the main treatment benefit was noted in reduction of stroke events. In the combined treated groups, the RR for stroke events was 0.47 (95% confidence interval 0.24–0.91, $p = 0.02$). When studied separately, the risk for stroke events was significantly reduced for the diuretic group (RR 0.31, $p = 0.01$), but not the ACE-inhibitor group (RR 0.63, $p = 0.21$). Total mortality in the combined treatment group was increased (RR 1.23, 95% CI 0.75–2.01, $p = 0.42$). Cardiovascular mortality in the combined group, as well as in each treatment group, similarly showed a non-statistically significant increase. The HYVET working group concludes that treatment of 1000 patients over the age of 80 for one year may reduce stroke events by nineteen, but may also be associated with roughly an equal number of nonstroke deaths. As can be expected of pilot studies, confidence intervals (CIs) are wide, and treatment effects do not generally achieve statistical significance, supporting the need for ongoing main trial.

Several explanations have been proposed for the changing risk/benefit profile in the very old (Goodwin, 2003; Hajjar, 2003; Langer *et al.*, 1991), though not all experts agree on the waning benefit of treating hypertension with age (Aronow, 2002; Hajjar *et al.*, 2002). A genetic protective factor may exist in some individuals rendering them less susceptible to complications of hypertension. Selective attrition of imperiled individuals at an early age may result in a more robust older group who are more subject to the complications of treatment than the benefit. Low blood pressure in the very old may also be a marker of underlying disease and poor health, and therefore associated with increased mortality. Furthermore, increased blood pressure may be required with advancing age to perfuse vital organs through atherosclerotic vessels. For example, a low DBP decreases myocardial perfusion, and may result in subendocardial ischemia if exceedingly low. In several studies, at any age, increased coronary mortality was noted with decreased diastolic hypertension. Finally, rectangularization of the survival curve during the latter part of the twentieth century as a result of improved health care and public health measures means that more people in the Western world are approaching the human life span of 100 years. Approximately 75% of all adults will reach the age of 70. This is followed by a rapid increase in mortality rate between the age of 75 and 90 years. Intervening to avert cardiovascular disease during this rapid decline phase will only serve to promote mortality and morbidity from other competing causes. For this reason, many trials report a decline in cardiovascular events associated with treatment of hypertension in the elderly, without a significant corresponding improvement in total mortality.

TREATMENT OF HYPERTENSION

Lifestyle modification is an important first step in the treatment of hypertension and should not be overlooked in the elderly. The trial of nonpharmacologic interventions in the elderly (TONE) demonstrated the effectiveness of salt restriction and weight reduction in elderly hypertensive patients (Whelton *et al.*, 1998). Even a modest 40 meq/day reduction in salt intake, and a 4.7 kg weight loss in obese patients, was accompanied by a 30% decrease in hypertension or in the need to reinstate antihypertensive therapy, even at 30 months follow-up. Recommending weight loss and dietary restrictions, however, must be done with caution. The risk of malnutrition or selective micronutrient deficiencies in the elderly population is high, and may outweigh the benefit of lowering blood pressure if allowed to continue unchecked. The best recommendation at this time is a diet low in total fat, cholesterol, and sodium, and rich in fiber, potassium, and unprocessed fruits and vegetables. The dietary approaches to stop hypertension (DASH) trial (Appel *et al.*, 1997) studied such a diet and demonstrated its effectiveness in lowering SBP and reducing the incidence of future cardiovascular events. While up to two units of alcohol consumption per day appears to be cardioprotective, high alcohol intake may lead to hypertension and should be discouraged. In addition to being a powerful cardiovascular risk factor, smoking directly increases blood pressure. With each cigarette smoked, blood pressure may increase noticeably for up to thirty minutes. Finally, the importance of routine exercise must be stressed. Some older individuals may be limited by underlying cardiovascular or musculoskeletal conditions, and careful screening and guidance to avoid injury must be done prior to initiating an exercise program. Most older persons, however, are capable of undertaking 20 minutes of brisk walking 4 times a week, and the safety and efficacy of aerobic exercise in older individuals has been demonstrated. Even a small decrease in blood pressure may provide significant outcome benefit. In population-based observations, it was estimated that a mean reduction in SBP of only 2 mmHg reduced mortality from stroke by 6%, mortality from coronary events by 4%, and total mortality by 3%. When the mean reduction in SBP was 5 mmHg, the corresponding mortality decreased by 14, 9, and 7%, respectively. This magnitude of change in blood pressure is feasible with lifestyle modification in the elderly, as reported in the JNC 7 report (Chobanian *et al.*, 2003). The approximate SBP reduction associated with adapting a DASH eating plan was 8–14 mmHg; with dietary sodium restriction, 2–8 mmHg; with increased physical activity, 4–9 mmHg; and with limiting alcohol consumption to no more than two drinks per day, 2–4 mmHg.

A large armamentarium of medications is available when nonpharmacologic interventions do not suffice. Principles of treating hypertension in young patients generally apply to the elderly, but with a few distinctions. The JNC 7 report recommends thiazide diuretics as a first-line drug based on the results of the trials previously described and on findings of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a study of nearly 45 000 subjects with the aim of comparing the effectiveness of thiazide diuretics to other classes of antihypertensive drugs (ALLHAT Collaborative Research Group, 2000; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002). Diuretics were found to be at least as effective, or more effective, than ACE inhibitor, alpha blocker, or calcium-channel antagonist in preventing fatal and nonfatal coronary events in the ALLHAT trial. The incidence of all-cause mortality and fatal and nonfatal coronary events was similar in the diuretic, calcium blocker (amlodipine), and ACE-inhibitor (lisinopril) group. The alpha-adrenergic blocker (doxazosin) arm of the trial was terminated prematurely due to increased risk of heart failure. A higher risk of heart failure was also noted with amlodipine compared to chlorthalidone (RR 1.33, 95% CI 1.18–1.49). Thiazide diuretics produce a greater reduction in SBP than DBP, and, therefore, are ideally suited for use with ISH of the elderly, but are less effective with declining renal function. The importance of prescribing thiazide diuretics in low doses must be emphasized. It is prudent to initiate therapy at half the recommended starting dose, and there is little added benefit in advancing the dose above 25 mg hydrochlorothiazide, or the equivalent, beyond which the incidence of adverse effects increase rapidly. At lower doses, the relative safety, favorable side effect profile, low cost, and once-a-day dosing make thiazide diuretics an appealing choice and preferred initial drug for the elderly.

Angiotensin-converting enzyme inhibitors work best in the presence of high rennin levels. In the elderly, rennin levels are typically low. This is only a theoretical limitation, as several studies have shown ACE inhibitors to be effective antihypertensive agents in the elderly. They are best suited for patients with left ventricular systolic dysfunction and for hypertensive persons with diabetes. In the latter group, this class of drugs plays the dual role of blood pressure control and diabetic renal protection. When combined with diuretics, significant first-dose hypotension and postural hypotension may occur. Renal dysfunction and hyperkalemia are relatively common complications and must be closely monitored. Less common is acute renal failure associated with bilateral renal artery stenosis. A chronic nonproductive cough may occur in 5–10% of patients on an ACE inhibitor.

β-adrenergic antagonists are less effective in the old and should probably not be used as an initial or sole antihypertensive agent. β-adrenergic antagonists reduce cardiac output by their negative chronotropic and inotropic cardiac effects, but do not significantly decrease peripheral vascular resistance. As such, they are best suited for secondary prevention of myocardial infarctions from coronary artery disease, for left ventricular systolic failure, or for heart rate control in atrial fibrillation, though a nondihydropyridine calcium-channel blocker would be the initial choice for rate control. A relatively high rate of discontinuation has been noted in the elderly due to side effects (Messerli *et al.*, 1998), which may include fatigue, dizziness, claudication, depression, and erectile dysfunction. Calcium-channel antagonists are a diverse group of compounds and the benefits of one drug in this class may not necessarily be extrapolated to others. Calcium-channel antagonists are generally well tolerated by the elderly, and have been shown to significantly reduce stroke and cardiovascular mortality and morbidity in the Syst-Eur and Syst-China trials. Decreased serum clearance of most calcium-channel antagonists occurs in the elderly, and they may be effective at low doses. In fact, with most antihypertensive agents, it is prudent to start treatment at the lowest or half the lowest recommended dose. The old adage "start low and go slow" is of particular relevance to prescribing antihypertensives in the elderly, who are prone to side effects.

CONCLUSION

Management of hypertension in the elderly has had a significant impact on cardiovascular mortality and morbidity over the past three decades. More awareness and diligence in screening and treating hypertension is necessary if the full treatment benefit is to be realized. Limitations in treating hypertension in the very old, however, must also be considered. The existence of a J-curve phenomenon continues to be debated. Observational as well as interventional studies indicate increasing mortality with lower blood pressure, particularly in the very old. Optimal SBP for the older hypertensive patient may well be 140–160 mmHg. Interventional trials that showed treatment benefit only enrolled subjects with SBP >170 mmHg. The benefit of treating older patients whose pretreatment SBP <160 mmHg is purely inferred. Similarly, the post-treatment SBP in the those trials ranged from approximately 140–170 mmHg, and the benefit of lowering blood pressure to <140 mmHg (or to the JNC 7 recommendations) is only assumed. The strongest and most consistent treatment benefit in most trials is reduction in fatal and nonfatal strokes. There is no evidence that newer, more expensive antihypertensive agents are more effective in reducing mortality and morbidity than older, less expensive drugs. Treatment benefit may be more a function of the degree of blood pressure reduction rather than the specific drug or class of drugs used to lower the blood pressure, though certain classes of antihypertensive agents have characteristic benefits. Since reducing the incidence of cardiovascular disease in the elderly may increase the incidence of other conditions, the ultimate measure of treatment success should be the preservation of functional status and the quality of life of the older person.

KEY POINTS

- The prevalence of hypertension and wide pulse pressure increases with age.
- Treatment of high blood pressure can significantly reduce the risk of cardiovascular mortality and morbidity in older persons.
- On the basis of current interventional trials, significant cardiovascular benefit may result from relatively small improvements in blood pressure, and the optimal SBP in the elderly may be 140–160 mmHg.
- In the very old, treating high blood pressure may not reduce mortality, but significantly decreases the incidence of stroke.
- Treatment of hypertension may aggravate hypotensive conditions commonly seen in the elderly, such as postprandial hypotension and postural hypotension, leading to syncope and falls.

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Mechanisms of Heart Failure

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INTRODUCTION

Regardless of the causes or clinical signs of chronic heart failure (CHF), it is a progressive disease which carries a poor long-term prognosis, despite all currently available therapies. CHF can no longer be considered as simply a contractile disorder or disease of the heart alone. The clinical manifestations of this syndrome are the cumulative result of cellular, molecular, neurohumoral, and signaling adaptations within the cardiovascular system as a whole, and also involving other organ systems including skeletal muscle. Treatments aimed simply at the underlying hemodynamic abnormalities, while capable of providing symptomatic relief, have no impact on the overall progression and mortality of heart failure. On the contrary, therapeutic agents aimed at reducing neurohumoral activation (e.g. β-blockers, ACE-inhibitors, and aldosterone antagonists) are known to have beneficial effects on both disease progression and overall mortality.

Heart failure can be seen as a progressive disorder that is initiated either by damage to the heart itself (resulting in a loss of functioning myocardium), or by a disruption in myocardial function (resulting in an inability to generate force for contraction). The initial effect may have an acute onset, or may have a gradual and insidious onset. Initially, patients may be asymptomatic following an initial decline in cardiac function due to the fact that several compensatory mechanisms, which are able to sustain and modulate left ventricular (LV) function for a period of time are activated. These adaptive processes range from activation of the sympathetic nervous system (SNS) to the retention of salt and water, as well as the activation of certain bioactive molecules responsible for promoting vasodilatation.

However, at some point in time the patient will become symptomatic, accompanied by a further activation of these neurohumoral mechanisms and left ventricular remodeling. Experimental and clinical evidence suggests that this transition occurs independently of the hemodynamic status of the patient.

NEURAL ADAPTATIONS

The Sympathetic Nervous System

Activation of the SNS is recognized to be a prominent feature of congestive heart failure. Although in the short term this may be an adaptive response, in the medium to long term it is maladaptive. The introduction of ^{123}I-MIBG, a structural analogue of norepinephrine, has made it possible to study the integrity and function of the cardiac sympathetic innervation (Merlet *et al.*, 1999b). The adverse cardiac effects of SNS activation in heart failure are mediated by abnormalities ranging from alterations in the β-receptor system and intracellular signaling to changes in myocardial calcium handling and energetics. The profound increase in circulating levels of norepinephrine is a result of both impaired reuptake (due to a lower cardiac output) and excessive release from presynaptic terminals, with the latter playing a greater role. The consequences of sympathetic overactivity manifest in many ways, including (1) direct toxicity to the myocardium; (2) inappropriate sinus tachycardia, which reduces diastolic filling time; and (3) peripheral vasoconstriction resulting in an increased afterload. This pronounced activation is inversely correlated with survival, and studies utilizing ^{123}I-MIBG and myocardial scintigraphy confirm that increased cardiac sympathetic innervation is an independent predictor for fatal outcomes (Merlet *et al.*, 1999a).

1. Abnormal Baroreceptor Sensitivity

Arterial baroreceptors and cardiac mechanoreceptors play an important role in governing the adjustments made by the cardiovascular system to surrounding conditions. Altered activity of these receptors in response to changes in arterial pressure and stretch results in the modulation of efferent activity in the vagal and SNSs. Impaired baroreflex control of the heart and peripheral circulation are thought to play an important pathophysiological role in congestive heart failure, and confers a poor prognosis (Mortara *et al.*, 1997). Impaired

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baroreceptor sensitivity (BRS) favors sympathetic activation and reduced vagal efferent activity. These changes increase the risk of malignant arrhythmias (La Rovere *et al.*, 2001), and SNS activation promotes cardiac myocyte apoptosis, activates the renin-angiotensin-aldosterone system (RAAS), and causes peripheral vasoconstriction. Baroreflex impairment appears to arise from several mechanisms (Nightingale *et al.*, 2003).

(a) There appears to be decreased afferent activity of arterial baroreceptors, cardiac receptors, and vagal afferents. Reduced arterial distensibility, altered cardiac stretch responses due to enhanced interaction between the ventricles in diastole, and increased Na+/K+ ATPase activity have each been proposed to contribute to these changes.
(b) In animal models of heart failure, there is increased activity in sympathetic afferents arising from the heart. These afferents relay to the brainstem and promote increased efferent sympathetic activity.
(c) There is altered central gain within the brainstem favoring increased sympathetic and reduced vagal efferent activity. Reduced local nitric oxide and increased angiotensin II levels appear important in this change.
(d) Peripheral changes in the efferent autonomic neurons and ganglia result in reduced acetylcholine release from vagal neurons and enhanced catecholamine release from sympathetic neurons.

2. Alteration in β-Receptor Signaling Pathways

The human heart expresses $\beta1$- and $\beta2$-receptors at a ratio of around 70 : 30 in normal myocardium, with both subtypes mediating positive chronotropic and inotropic effects via coupling to a stimulatory G-protein (Gs). Additionally, the $\beta2$-receptor appears to be capable of mediating a negative inotropic response via coupling to an inhibitory G-protein (Gi). The $\beta3$-receptor subtype appears to mediate a negative inotropic effect, although its role in heart failure remains uncertain. All three subtypes occur in cardiomyocytes, but each possesses distinct intracellular signaling and functional properties (see Figure 1).

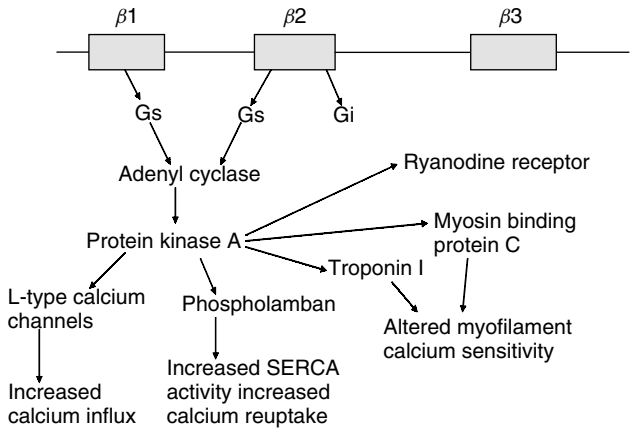

Figure 1 β-Receptor signaling pathways. $\beta1 = \beta$-1 receptor; $\beta2 = \beta$-2 receptor; $\beta3 = \beta$-3 receptor; Gs = stimulatory G-protein; Gi = inhibitory G-protein; SERCA = sarco-endoplasmic reticulum calcium ATPase

The Normal Pathway of β-Receptor Signaling

The three receptor subtypes are known to have differing affinities for their ligands, and each is linked to a specific signaling pathway. In addition, a classic common pathway exists for β-adrenergic signaling. The membrane-bound receptor is coupled to a G-protein, which in turn activates adenyl cyclase. This results in an increased level of cyclic AMP (adenosine monophosphate), whose primary target is protein kinase A (PKA). PKA is capable of phosphorylating several proteins that are essential to the control of cardiac function.

Alterations in β-Adrenergic Signaling in Heart Failure

Cardiac β-receptors, particularly the $\beta1$-subtype, are downregulated in heart failure, and a correlation exists between $\beta1$-receptor number and mRNA levels and disease severity. In addition to the reduction in number of $\beta1$-receptors, the remaining receptors are desensitized due to uncoupling of the receptor from the G-protein. A decrease in Gs levels and adenyl cyclase, combined with an increase in Gi subunits, antagonizes β-adrenergic signaling. These changes may represent an attempt to protect the myocardium from the deleterious effects of chronic β-receptor activation (refer to Table 1) $\beta2$-receptor levels are unchanged in most studies; however, they become more prominent as the number of $\beta1$-receptors diminishes. Although the ratio of $\beta1$:$\beta2$ receptors diminishes, the $\beta2$-receptors do not function normally due to partial uncoupling from the Gs protein, hence stimulation of the receptor does not result in a full inotropic response. This is combined with signaling via the inhibitory Gi protein, resulting in a negative inotropic and antiapoptotic effect. β-Receptor autoantibodies have also been shown to

Table 1 Deleterious effects of chronic sympathetic overactivity

Effect	Mechanism
Reduced synthesis of β-receptors	
Downregulation of β-receptors	Inactivation by phosphorylation
	Internalization of phosphorylated receptors
	Proteolytic digestion of internalized receptors
Impaired diastolic relaxation	Altered calcium handling
Arrhythmias	Increased levels of cAMP
	Calcium stimulation
Energy imbalance	Myocardial oxygen wastage
Myocardial ischemia	Myocardial oxygen wastage
Myocyte apoptosis	
Skeletal muscle apoptosis	
Altered gene expression	

be increased in congestive heart failure, and immunoabsorption of these antibodies results in augmentation of cardiac function (Lohse *et al.*, 2003).

Rationale for the Use of β-Blockers in Heart Failure

β-Blockade acutely exerts negative inotropic effects. The use of β-blockers in CHF was proposed many years ago and salutary effects on symptomatic status and survival have been demonstrated over the past decade. How can the long-term use of an acutely negative inotropic agent lead to an increase in cardiac index, exercise capacity, and survival?

The rationale can be explained on the basis of two mechanisms:

1. Blocking of the detrimental effects of sustained β-receptor stimulation.
2. Resensitization of the cardiac β-receptor system, resulting in restoration of the response to acute increases in SNS activity on exercise.

In a number of clinical trials, β-blockers have shown benefit in all groups of patients regardless of heart rate, blood pressure, and ejection fraction (Bristow, 2000). Carvedilol has also been shown to correct the energy imbalance within cardiomyocytes by inducing a partial shift from the metabolism of fatty acids to glucose. They also result in an increase in β-receptor levels and reversal of failure specific cardiac gene expression.

HUMORAL ADAPTATIONS

1. The Renin-angiotensin-aldosterone System (RAAS)

In patients with congestive heart failure, there is typically persistent activation of the circulating and tissue RAAS, which is inappropriate, given the absence of salt deprivation of intravascular volume contraction, and this activation has pathologic effects. Traditionally, the RAAS has been viewed solely as a circulating system, with the release of renin occurring from the kidney. However, accumulating evidence suggests that the components of the RAAS are capable of being synthesized in a number of tissues, and that tissue levels of angiotensin II can be controlled independently from the circulating RAAS. In fact, renin, angiotensinogen, angiotensin-converting enzyme (ACE), and angiotensin receptors are all present in the heart, suggesting that ang II synthesized locally within the myocardium may be an autocrine/paracrine modulator of cardiac function and structure (Dzau and Re, 2004). The degree of activation provides prognostic information in these patients. The deleterious effects of inappropriate expansion of the intra- and extravascular volumes, as well as organ fibrosis, are mediated in large partly by the actions of aldosterone and angiotensin II (see Figure 2).

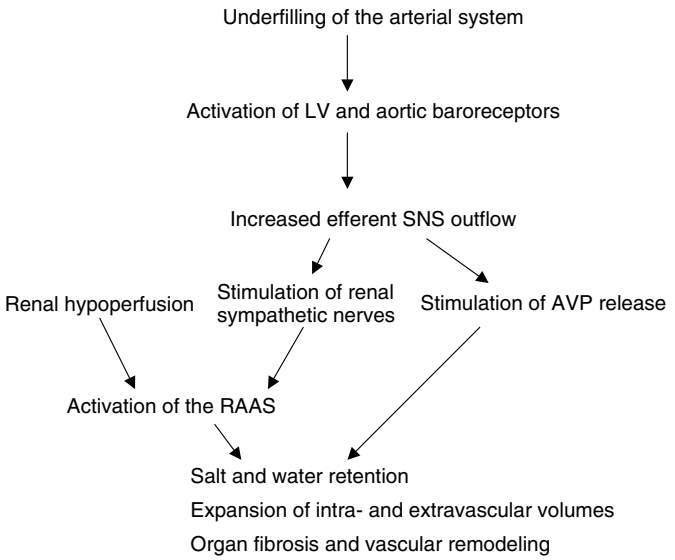

Figure 2 Pathophysiology of salt and fluid retention. LV = left ventricular; RAAS = renin-angiotensin-aldosterone system; AVP = arginine vasopressin; SNS = sympathetic nervous system

Angiotensin II

In addition to increasing aldosterone synthesis and proximal tubular sodium transport, Ang II has other detrimental renal and cardiac effects in patients with heart failure (refer to Table 2). In view of these, ACE-inhibitors are now considered first-line therapy and improve survival in all degrees of severity of heart failure. Ang II exerts its effects via two types of receptors, AT_1 and AT_2. In models of human heart failure, a downregulation of AT_1 receptors has been demonstrated, while the level of AT_2 receptors remains essentially unchanged. However, it remains to be determined whether this results in any altered response to ang II (Asano *et al.*, 1997).

Aldosterone

Aldosterone levels are known to be raised in both the urine and plasma of patients with congestive heart failure, and may reach 20 times the normal level. Its secretion is regulated by angiotensin II, high serum potassium levels, circulating catecholamines, endothelin, and arginine vasopressin (AVP), which are all known to be increased in heart failure. The increase in plasma level is in part due to a decrease in hepatic

Table 2 Effects of angiotensin II

Renal effects
Afferent and efferent arteriolar vasoconstriction
Mesangial contraction
Cardiac effects
Mitogenic effect on cardiac myocytes
Cardiac remodeling including promotion of fibrosis
Other
Stimulation of central thirst center (thereby precipitating hyponatraemia)
Promotes “cardiac cachexia” via effects on skeletal muscle

Table 3 Actions of aldosterone

Increased retention of sodium
Abnormal vasomotor reactivity
Abnormal baroreceptor responsiveness
Endothelial dysfunction
Decreased myocardial norepinephrine reuptake
Coronary and vascular remodeling
Cardiac fibrosis and remodeling (increased fibroblast growth and collagen synthesis via aldosterone-dependant transcriptional regulation of Na/K ATPase, promoting sodium entry into fibroblasts)

clearance, resulting from a reduction in hepatic perfusion. The actions of aldosterone are shown in Table 3.

Not only are plasma levels increased, but the activity of aldosterone is more prolonged and persistent than in normal subjects. Normal subjects experience an escape from the mineralocorticoid-mediated sodium retention which occurs in the collecting ducts, but this is not seen in patients with heart failure, due to a decrease in the delivery of sodium to the distal nephron (as a result of increased angiotensin II-mediated sodium transport in the proximal tubule) (Weber, 2001).

Although ACE-inhibitor therapy in heart failure initially reduces both angiotensin II and aldosterone levels, subsequent "escape" commonly occurs, with reelevation of the levels of each. This is the reason for the beneficial effects of the mineralocorticoid receptor antagonists spironolactone and eplerenone in heart failure (Pitt *et al.*, 1999).

2. **Arginine Vasopressin (AVP)**

AVP is a peptide hormone, which modulates a number of processes implicated in the pathogenesis of heart failure. Through the activation of V1 and V2 receptors it regulates body fluid volume, vascular tone, and cardiovascular contractility. Vasopressin synthesis is significantly and chronically elevated in patients with heart failure, despite the volume overload and reductions in plasma osmolality that are seen in these patients. In patients with heart failure, the mechanisms that control the release of AVP are blunted or lost. Levels of AVP no longer respond to plasma osmolality, but are determined rather by arterial underfilling. Central effects of angiotensin II leading to the release of AVP also contribute. Thus, in response to hyponatremia/hypoosmolality, the normal inhibition of AVP does not occur, accounting for the persistently high levels of AVP seen in this condition. This inappropriate release of vasopressin release stimulates thirst and leads to water retention, which can result in life-threatening hyponatremia. Activation of carotid baroreceptors has also been implicated in the nonosmotic release of AVP during arterial underfilling in patients with heart failure. As mentioned above, two types of receptors exist and mediate opposing effects. Vasopressin-1 receptors result in vasoconstriction, whereas in contrast, the stimulation of vasopressin-2 receptors results in vasodilatation. Activation of vasopressin-1 receptors in vascular smooth muscle cells may contribute to cardiac dysfunction in severe heart failure. In early studies, AVP antagonists have been shown to result in a reduction in systemic vascular resistance and a concomitant increase in cardiac output. Improvements in plasma osmolality, body weight, and serum concentrations have also been demonstrated (Lee *et al.*, 2003).

3. **Natriuretic Peptides**

The three principal members of the natriuretic peptide family are atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C terminal of atrial natriuretic peptide (CNP). Plasma ANP is normally released during atrial distention. In patients with heart failure, plasma ANP levels rise in parallel with the increase in atrial pressures. Plasma levels of BNP, which is released from the ventricle in response to increased wall stress, are also elevated in heart failure (Struthers, 1994). ANP and BNP have effects which tend to oppose those of the RAAS and the SNS. They have natriuretic, diuretic, sympatholytic, and antifibrotic activities.

The natriuretic peptides exert their effects on the kidney at the level of the glomerulus and collecting ducts. Efferent arteriolar constriction and afferent vasodilatation lead to an increase in glomerular filtration rate, and a decrease in sodium reabsorption in the collecting duct. This effectively leads to inhibition of the release of renin and angiotensin, an effect that would clearly be beneficial in heart failure. In addition to their beneficial effects on fluid balance, renal function, and hemodynamics, they may also act as inhibitors of myocyte hypertrophy. However, these beneficial effects are blunted in patients with congestive heart failure. This may be due to decreased sodium delivery to the collecting duct as a result of the overriding effect of the RAAS, or mediated by a downregulation of receptors, and increased degradation by endopeptidases. Natriuretic peptide analogues have been used to treat decompensated heart failure. However, patients with heart failure demonstrate partial resistance to the arterial and renal effects of these peptides (although the effects on capacitance vessels are preserved). It is uncertain at this stage as to what extent this resistance will limit their utility as a therapeutic agent.

4. **Endothelins**

Endothelin is an autocrine and humoral factor that has many important properties that suggest an important role in the pathophysiology of left ventricular remodeling. Three separate genes are known to code for endothelin-1, endothelin-2, and endothelin-3, but only endothelin-1 appears to play a major role in human cardiovascular pathophysiology.

Endothelin-1 is known to be a potent vasoconstrictor and trigger for myocardial hypertrophy, and although it plays only a minor role in normal physiology, it plays a much more vital role in vascular and myocardial function, as well as left ventricular remodeling, in pathophysiological states.

The main site of synthesis is cardiovascular tissue, but synthesis can occur in the brain and kidney. Its synthesis is under the influence of a wide range of stimuli, including

neurohormones, cytokines, thrombin, and mechanical stress (Givertz and Colucci, 1998).

The effects of endothelin-1 are mediated by two receptors, that is, ET_A and ET_B, which are expressed on myocardial cells, vascular smooth muscle cells, vascular endothelial cells, and fibroblasts (refer to Table 4).

Endothelin, thus, has a central role to play in remodeling both through its direct actions as a neurohormone and its indirect actions on other neurohormones. Plasma levels of endothelin-1 are known to be elevated in both acute and chronic heart failure, cardiogenic shock, pulmonary hypertension, and acute coronary syndromes. However, the autocrine actions of endothelin are probably more important than its humoral effects. Endothelin is released abluminally, and plasma concentrations correlate only modestly with local endothelin release. A reasonable correlation exists between plasma levels and the extent of remodeling, as well as between mRNA expression and diastolic wall stress. Not only are endothelin plasma concentrations increased, but the membrane-bound receptors that transduce their extracellular signals (especially ET_B receptors) are significantly increased where ventricular remodeling is also present.

The development of endothelin antagonists has offered a potential therapeutic target, and in initial clinical trials has shown some early promise. However, Endothelin blocker studies have all been negative in heart failure studies to date.

Table 4 Effects of endothelin

Vasoconstriction
Neurohumoral activation – stimulates the release of norepinephrine/ angiotensin II/aldosterone
Potentiation of action of neurohormones
Proinflammatory – increased vascular permeability
– release of cytokines
– increased synthesis of surface adhesion molecules
Proarrhythmic
Pathologic myocardial hypertrophy
Myocardial and vascular fibrosis – due to fibroblast proliferation
Vascular hyperplasia
Early gene expression in myocardium
Mediates apoptosis

5. Cytokines

Since the initial report of increased proinflammatory cytokines in patients with heart failure in 1990, there has been growing interest in their role in the regulation of cardiac structure and function, particularly the role they play in disease progression.

This interest in inflammatory mediators stems from the fact that many aspects of the syndrome of heart failure can be explained on the basis of known biological effects of proinflammatory cytokines. Although initially thought to arise exclusively from the immune system, it is now known that these cytokines are expressed by all nucleated cell types within the myocardium, including the cardiac myocytes. They are thus able to be expressed in the failing human myocardium. They are potent stimuli for the increased expression of inducible nitric oxide synthase (iNOS), which can lead to the local generation of high nitric oxide concentrations. The deleterious effects of cytokines are, at least in part, mediated by nitric oxide (refer to Table 5). The "cytokine hypothesis" proposes that although cytokines do not cause heart failure their overexpression contributes to disease progression by means of their direct toxic effects on the heart, skeletal muscle, and the peripheral circulation. Thus, the elaboration of cytokines, much like the elaboration of neurohormones, may represent a biological mechanism responsible for worsening heart failure.

The expression of proinflammatory cytokines is directly related to worsening NYHA (New York Heart Association) functional status. However, the proinflammatory cytokines are activated earlier in heart failure than the classic neurohormones (NYHA class II versus class III/IV). The circulating levels of both cytokines and neurohormones have prognostic significance in the setting of heart failure. The Vesnarinone Trial (VEST) (Deswal *et al.*, 2001) demonstrated a significant overall difference in survival as a function of increased plasma tumor necrosis factor (TNF) levels. There was also a significant correlation between increased levels on interleukin (IL-6) and soluble TNF-receptor types 1 and 2 and mortality (Mann, 2002; Yousef *et al.*, 2000).

Table 5 Cytokines in congestive heart failure

Cytokine	Acute effect	Chronic effect	Mechanism
TNF	Negative inotropic effects		(1) Immediate pathway (minutes) – activation of neutral sphingomyelinase pathway
	Decrease LV ejection performance		(2) Delayed pathway (hours/days) – NO-mediated blunting of β-adrenergic signaling
	LV Dilatation		Increased MMP activity relative to TIMP activity
		Increased fibrillar collagen content	Increased TIMP activity relative to MMP activity
	Myocyte hypertrophy		
	Altered fetal gene expression		
	Apoptosis		
	Endothelial dysfunction		(1) Induced apoptosis of endothelial cells
			(2) Downregulation of endothelial NO synthase
IL-1 and IL-18	Negative inotropic effect		Delayed pathway (NO-mediated)
IL-6	Negative inotropic effect		Unknown

Apart from the similarities between the cytokine and neurohumoral systems, there are also critical interactions between angiotensin II and cytokine expression. It has become apparent that angiotensin II provokes inflammatory responses, by means of an increase in TNF mRNA and protein synthesis. This increase in the expression of proinflammatory cytokines is mediated by the transcription factor nuclear factor-κB. This has been substantiated by the observation that ACE-inhibitors decrease the short-term expression of cytokines in heart failure. In addition, angiotensin type 1 receptor blockers have been shown to decrease TNF levels to a greater extent than ACE-inhibitors.

Further evidence of an interaction between neurohormones and cytokines comes from the reduction in the expression of proinflammatory mediators in a model of postinfarction LV remodeling in response to β-blockers. It has been proposed that increased endotoxin uptake from the gut into the portal vasculature in heart failure may activate white cells and that this may contribute importantly to increased proinflammatory cytokines.

As a result of a wealth of preclinical data suggesting a vital role for cytokines pathways in the progression of heart failure, they have become a potential therapeutic target. Table 6 summarizes potential therapies and the available trial data.

Despite the hope that TNF antagonism would have a role to play in altering disease progression in the syndrome of heart failure, the negative results of most clinical trials to date has been discouraging, and at present no anticytokine therapies can be advocated as part of routine clinical practice. Small trials with pentoxifylline have been encouraging (Sliwa *et al.*, 1998). This agent decreases TNF synthesis, but has other pleotropic actions, including phosphodiesterase inhibition which might have been responsible for the symptomatic and echocardiographic improvements observed.

Table 6 Potential therapeutic anti-inflammatory agents

Agent	Mechanism of action	Clinical trial outcomes
Pentoxifylline Thalidomide	Block transcriptional activation of TNF	Improvement in LVEF, functional class, and quality of life
Etanercept	Soluble TNF receptor (binds TNF to prevent binding to TNF receptor on target cells)	Stopped prematurely, no benefit demonstrated
Infliximab	Monoclonal antibody that binds and neutralizes TNF	Increased rate of hospitalizations and death
Intravenous immunoglobulin	Modulation of cytokine activity	Increased LVEF
Immune modulation	Restores proinflammatory: anti-inflammatory ratio	Decreased rate of hospitalizations and death

LVEF, left ventricular ejection fraction.

LV REMODELING

LV remodeling is the process by which ventricular size, shape, and function are regulated by mechanical, neurohumoral, and genetic factors. This definition encompasses the changes that occur in chamber size and volume, in the biology of the cardiac myocyte, the volume of myocyte and nonmyocyte components, as well as the geometry and architecture of the left ventricle. Remodeling can be physiological (as seen in athletes, or during normal growth) or pathological. Despite several possible etiological triggers (acute myocardial infarction (MI), pressure- or volume overload, or inflammation), pathological remodeling follows a similar pathway in terms of biological and mechanical changes. The progression of subsequent remodeling is determined by the underlying disease, secondary events (e.g. further ischemia), neurohumoral activation, and treatment.

Natural history studies have shown that progressive LV remodeling is directly related to future deterioration in left ventricular performance and a less favorable clinical outcome in patients with congestive cardiac failure (Vasan *et al.*, 1997).

LV Hypertrophy

Myocardial hypertrophy occurs as a result of chronic hemodynamic overloading of the heart, due to either sustained pressure or volume overload. Adult human cardiac myocytes have a limited capacity to reenter the cell cycle and proliferate; therefore, adaptation to chronic overload occurs by means of changes in cross-sectional area rather than an increase in cell number. Owing to the spatial arrangement of myocytes within the ventricular wall, myocyte cell length contributes to chamber diameter, whereas cell diameter or width contributes to wall thickness.

Triggers for hypertrophy include neurohormones, local growth-promoting peptides, and physical factors which result in myocardial stretch (refer to Table 7). Via an action on specific cell receptors, a cascade of intracellular signaling pathways is activated. This results in a reexpression of the fetal genotype and the serial deposition of new sarcoplasmic elements, resulting in changes in the cardiac myocyte (Cohn *et al.*, 2000).

Initially, the myocardium responds to overload by means of an increase in diameter and cross-sectional area of individual myocytes. The subsequent increase in LV wall thickness,

Table 7 Triggers for myocardial hypertrophy

Neurohormones	Noradrenaline
	Endothelin
	Angiotensin II
	Aldosterone
Local Peptides	Insulin-like growth factor
	Cardiotrophin I
	Fibroblast growth factor
Physical factors	Increased afterload and preload
	Increased wall stress

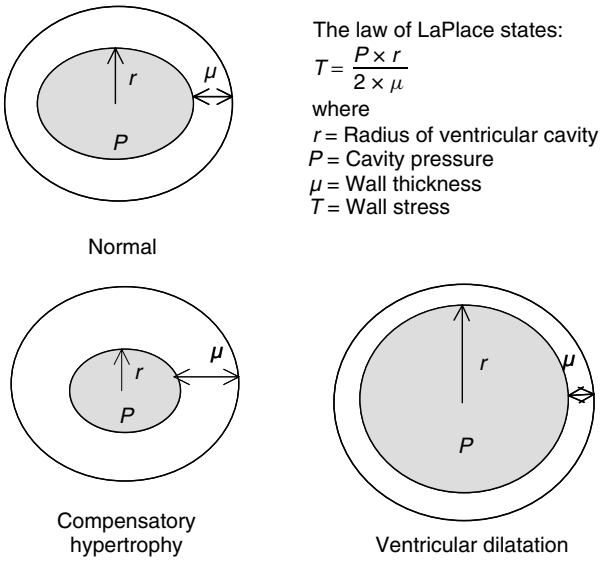

Figure 3 The law of LaPlace. In compensatory left ventricular hypertrophy, the increase in wall thickness results in a lowering of wall stress. However, as the ventricle dilates and thins with ongoing left ventricular remodeling, the increase in chamber radius and decrease in wall thickness leads to an increase in wall stress

without an associated increase in radius of the ventricular chamber, tends to normalize wall stress (see Figure 3). However, this increase in muscle mass disturbs the fine energetic balance of the myocardium, and oxygen diffusion into the center of large myocytes becomes impaired. The combination of wall thickening and increased intramyocardial tension tends to reduce coronary perfusion, thereby aggravating energy starvation. Therefore, hypertrophy stimulates both adaptive changes (normalization of wall stress) and adverse changes (changes in myocardial energetics). In human models of congestive heart failure, a dramatic increase in the myocyte length: width ratio has been documented. In response to chronic volume overload, which is a much less potent stimulus to myocyte hypertrophy than pressure overload, the increase in myocyte length is greater than the increase in diameter. This leads to an increase in chamber dimensions and dilatation, with a subsequent rise in wall stress and afterload, perpetuating the hemodynamic burden on the heart.

Anatomical Changes

Following myocardial injury, a variable process of progressive remodeling occurs. As the heart remodels, a change in chamber size and geometry occurs. It enlarges and becomes less elliptical and more spherical. With these changes in shape, wall thinning occurs. These changes are all maladaptive. An increase in left ventricular end-diastolic volume and wall stress increase the work of the heart, and concomitantly, its oxygen consumption. Increases in wall stress lead to episodic subendocardial ischemia and worsening of left ventricular function (Vatner, 1988). An increase in the sphericity index of the left ventricle results in the papillary muscles being pulled apart, resulting in functional mitral regurgitation (Kono *et al.*, 1992). This leads to a loss of forward blood flow and hemodynamic overloading of the left ventricle. The resultant decrease in cardiac output, increased overloading, and dilatation are sufficient to contribute to disease progression. This renders the heart less responsive to normal homeostatic control mechanisms, fostering a self-perpetuating situation in which worsening neurohumoral activation occurs in response to an inability of the remodeled left ventricle to respond appropriately. At some point, heart failure progresses independently of the neurohumoral status of the patient. Cardiac remodeling results from the combined effects of increased wall stress, progressive myocyte loss, and interstitial fibrosis.

The Cardiac Interstitium

The extracellular matrix (ECM) is a three-dimensional structural network, consisting of interstitial collagen fibers to which other matrix components are attached. Its main physiological functions are to retain tissue integrity and cardiac pump function. The most widely recognized alteration seen in heart failure is the development of perivascular fibrosis around intramyocardial blood vessels. Interstitial fibrosis is also seen. This is accompanied by excessive deposition of fibrillar collagen. This collagen deposition has a dual effect on cardiac function and structure. Increased deposition is a prerequisite to prevent chamber dilatation, but excessive accumulation leads to increased chamber stiffness and a less compliant ventricle, resulting in both systolic and diastolic ventricular dysfunction, ultimately contributing to heart failure. It also increases the risk of ventricular arrhythmias by predisposing to reentrant circuits.

An appropriate balance of synthesis and degradation of the ECM is maintained by a balance between the activity of certain collagenolytic enzymes and their inhibitors (see Figure 4). Ultimately, fibrosis is also under the control of several other regulators, which are capable of activating

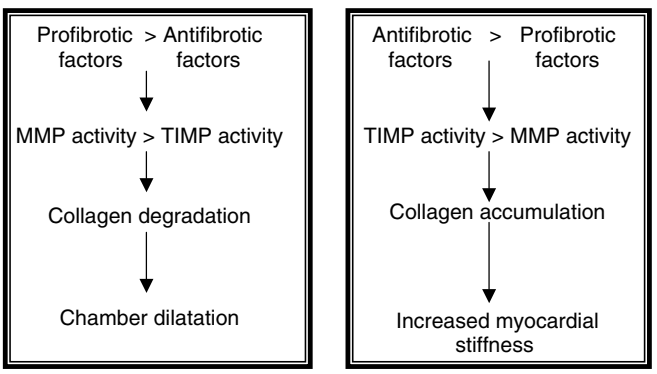

Figure 4 Homeostasis of the extracellular matrix. The balance between collagen degradation and accumulation is controlled by an interplay between the matrix metalloproteinase's (MMPs) and their tissue inhibitors of metalloproteinases (TIMPs)

Table 8 Regulators of extracellular matrix metabolism

Profibrotic	Antifibrotic
Noradrenaline	Atrial natriuretic peptide
Angiotensin II	Brain natriuretic peptide
Endothelin-1	Nitric oxide
Tumor necrosis factor α	
Transforming growth factors β1 and β3	
Interleukins 6 and 1β	
Heat shock protein 47	

the matric metalloproteinases (MMPs) (refer to Table 8). Activation of the circulating and tissue RAAS appears to play a particularly important role in increasing myocardial collagen content (Tsuruda *et al.*, 2004).

Apoptosis

Apoptosis, or programmed cell death, is a physiologic process that plays a complementary, albeit opposite, role to mitosis in the regulation of tissue homeostasis (*see* **Chapter 2, A Biological Perspective on Aging**). It is distinguished from cell necrosis by the fact that cells are eliminated without the induction of a fibrotic reaction. Although apoptosis fulfills a vital role in proliferating tissues such as the bone marrow and gut, in the adult heart it can be catastrophic, as adult cardiac myocytes have a very limited capacity to divide. In the past, it was thought that adult cardiac myocytes were terminally differentiated. Recent evidence suggests that in certain circumstances they can in fact reenter the cell cycle; furthermore, bone marrow–derived mesenchymal stem cells are capable of seeding the heart and differentiating into a number of cardiac cell types, including cardiac myocytes. Nonetheless, it is clear that neither of these two mechanisms of cardiac myocyte regeneration is capable of compensating for a rapid rate of cardiac myocyte loss. The exact importance of apoptosis and its role in heart failure is an area of great interest. Progressive left ventricular dysfunction has been hypothesized to occur due to the ongoing loss of cardiac myocytes as a result of apoptosis. Several of the growth factors that accelerate protein synthesis and hypertrophy also have the capability to induce apoptosis. The most commonly implicated of these bioactive molecules are TGF-β and TNF-α (Krown *et al.*, 1996). It is well accepted that apoptosis does occur in congestive heart failure (Olivetti *et al.*, 1997), and in explanted hearts from end-stage heart failure patients, a 30% reduction in LV and RV (right ventricular) myocytes has been demonstrated. Initially, hypertrophy can compensate by restoring critical muscle mass, but the same bioactive molecules that trigger hypertrophy also stimulate apoptosis, leading finally to a decompensated phase in which the workload for individual myocytes is too great. This is aggravated by the suboptimal chamber dimensions produced by cell loss, which contributes to a chronically increased wall stress and further increases in workload.

MOLECULAR AND CELLULAR ADAPTATIONS

Excitation–Contraction Coupling

Congestive heart failure is closely associated with abnormalities of intracellular calcium handling. The normally integrated physiological signaling pathway that provides graded increases in contraction in response to PKA phosphorylation of the key calcium-handling molecules appears to be defective in failing hearts, representing a maladaptive response.

Normal excitation–contraction coupling requires the three key elements (Figure 5):

1. Calcium entry into the cell via L-type calcium channels (LTCC).
2. "Calcium triggered" calcium release from the sarcoplasmic reticulum via the ryanodine receptor/calcium channel.
3. Calcium reuptake into the sarcoplasmic reticulum via sarco-endoplasmic reticulum ATPase (SERCA2a), the activity of which is negatively modulated by Phospholamban (PLB).

In the failing heart, resting calcium levels have been shown to be increased, the amplitude of the calcium transit is decreased, and its duration prolonged. Specifically in human models, these prolonged calcium transients have been attributed to a decreased reuptake of diastolic calcium into the sarcoplasmic reticulum. These changes are attributable to sympathetic activation and to secondary changes in the function of the key proteins involved in calcium handling.

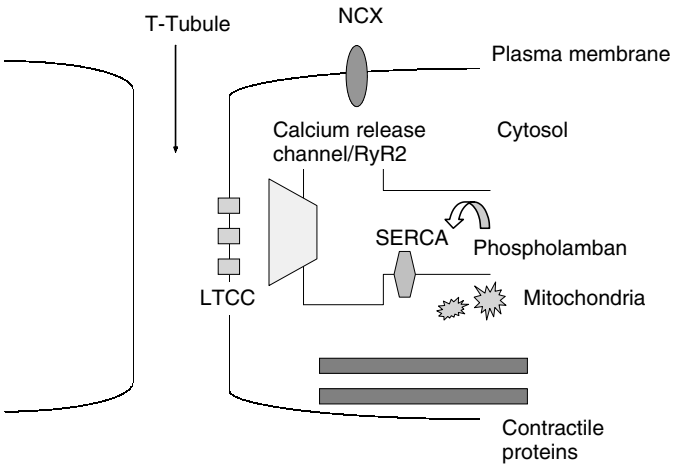

Figure 5 Excitation–Contraction coupling. Calcium enters via the T-tubule and the L-type calcium channels (LTCC) on the plasma membrane. This triggers the release of calcium from the sarcoplasmic reticulum via the calcium release channel/ryanodine receptor (RyR2) complex. In diastole, calcium is taken up into the sarcoplasmic reticulum by SERCA, the sarco-endoplasmic reticulum calcium ATPase pump. SERCA is under the control of phospholamban. Calcium is also extruded from the cell in diastole by the sodium/calcium exchanger (NCX)

1. L-type Calcium Channels (LTCC)

Calcium influx through the LTCC is essential for triggering the release of calcium from the sarcoplasmic reticulum, which ultimately determines the rate and magnitude of contraction. Reduced LTCC density is a general feature of failing hearts, and their state of phosphorylation has been shown to be higher, resulting in a reduction in the magnitude of sarcoplasmic reticulum calcium release and depressed myocardial contractility (Houser and Margulies, 2003).

2. Ryanodine Receptor/Calcium Release Channel (RyR2)

The ryanodine receptor "opens" when cytosolic calcium rises due to the influx of calcium through the LTCC. Phosphorylation of the RyR2 by PKA leads to activation of the channel, and PKA itself is activated by catecholamines. Hyperphosphorylation of RyR2, seen in failing hearts in response to chronic adrenergic signaling, shifts the sensitivity of the RyR2 to calcium-induced calcium release to the left. This results in part from depletion of FKBP12.6, a regulatory protein that functions to stabilize the RyR2/calcium channel in the closed state during diastole. The end result is a leaky channel, causing an aberrant diastolic calcium leak. Chronically leaky RyR2 channels contribute to a depletion of sarcoplasmic reticulum calcium stores and to decreased cardiac myocyte contractility (Marks, 2003).

3. Phospholamban and SERCA2a Activity

PLB and SERCA2a interact closely to control the calcium content of the sarcoplasmic reticulum, and ultimately contractility. SERCA2a mediates reuptake of calcium from the cytosol into the sarcoplasmic reticulum to initiate myocardial relaxation. Hypophosphorylated/unphosphorylated PLB inhibit the activity of SERCA2a. The level of activity of SERCA2a has been demonstrated to be reduced in models of congestive heart failure. This, combined with an increase in the PLB:SERCA2a ratio, contributes to the contractile dysfunction seen in heart failure. SERCA2a overexpression and/or PLB knockout have been shown to rescue cardiac myocyte contractile function in failing myocytes (Koss and Kranias, 1996).

4. Sodium/Calcium Exchanger (NCX)

The NCX is a transsarcolemmal protein that plays a vital role in extruding calcium from the cytosol into the extracellular space and in controlling intracellular calcium concentrations (*see* **Chapter 108, Age-related Changes in Calcium Homeostasis and Bone Loss**). Na/Ca exchange has been shown to be enhanced in the failing heart, due to an upregulation of mRNA and protein levels.

Altered Gene Expression

Numerous changes in myocardial gene expression occur during the adaptation of the heart to chronic overload. Changes in the failing heart tend to recreate the more primitive cardiac myocyte phenotype seen in fetal life. The availability of explanted hearts, obtained at the time of heart transplantation, has added considerably to current knowledge of the molecular alterations which occur in heart failure.

1. Myosin Isoform Switching

Isoform shifts involving most of the contractile proteins have been reported in experimental heart failure. The most extensively studied of these responses take place in myosin. Two types of myosin heavy chain (MyHC) are expressed in mammalian hearts, that is, the alpha- and beta-heavy chains. While hearts expressing more α-MyHC have a more rapid contractile velocity, those expressing more β-MyHC allow for greater economy in force generation. Although both α- and β-MyHC are downregulated in heart failure, the 30-fold decrease in α-MyHC results in an increase in the ratio of β: α-MyHC (Miyata *et al.*, 2000). This alteration leads to a reduction in myosin ATPase enzyme velocity and slows the speed of contraction. Although this adaptive change may initially be viewed as "economical", it ultimately contributes to slowing of both contraction and relaxation.

Changes are also seen in the myosin light chains in heart failure. Although in the rat model cardiac α actin is replaced to some degree by skeletal α actin, leading to increased contractility, this is not a feature of human heart failure.

2. Nonmyosin Isoform Changes

Troponin T is also known to undergo modulation of isoform expression in failing myocardium. In humans, it exists as a dominant adult form, and as a minor isoform that is usually present in fetal life. Studies show up regulation of this minor isoform in both animal and human models of failing myocardium (LeWinter and VanBuren, 2004). However, the functional significance of this change remains uncertain.

3. Metabolic Gene Expression

A switch in energy substrate preference from glucose to free fatty acids is a feature of the transition from fetal to adult cardiac metabolism, and is accompanied by alterations in the expression of genes regulating metabolism. A common feature of cardiac hypertrophy and advanced heart failure in animal models is a reversion to the fetal metabolic gene profile, which occurs by the induction of these fetal genes.

Studies in advanced heart failure suggest a decrease in free fatty acid utilization, accompanied by an increase in glucose metabolism. This is demonstrated by a downregulation of genes encoding enzymes involved in the β-oxidation of fatty acids, as well as downregulation of the Carnitine Palmitoyl Transferase-1 (CPT-1) enzyme (responsible for the cellular uptake of long chain free fatty acids into the mitochondria).

A decrease in the transcript levels of GLUT1 and 4 (glucose transporter enzymes), as evidenced by lower mRNA levels, is seen in the failing heart. The failing human heart also shows a significant decrease of PDK2 (a key regulator of glucose and lactate oxidation), consistent with an increased rate of glucose oxidation. There is controversy as to whether the shift from fatty acids to glucose utilization in advanced

heart failure and in hypertrophy is adaptive or maladaptive. Glucose utilization requires less oxygen to generate an equivalent amount of ATP, and in this sense, the shift may be energetically advantageous. Conversely, inborn errors of fatty acid β-oxidation may result in heart failure (Razeghi *et al.*, 2001).

Altered Myocardial Energetics

Several changes account for the state of energy deprivation in the failing heart.

Although myocardial hypertrophy and ventricular remodeling are an initial attempt at adaptation, the absolute increase in cross-sectional area of individual myocytes leads to a reduction in coronary blood flow. This results in impairment of the diffusion of substrates into myocytes due to an increased intercapillary distance. An imbalance between energy production and consumption occurs, particularly in the subendocardial region of the hypertrophied left ventricle (which is particularly prone to episodic hypoperfusion). A combination of increased wall stress and reduced perfusion in hypertrophied areas can lead to a state of energy starvation so severe as to cause myocyte necrosis. This, combined with ongoing apoptosis, leads to a quantitative defect in absolute myocyte number, compounding ventricular dysfunction. Other adaptations seen in the failing myocardium include a reduction in the ratio of phosphocreatine (PCr) to ATP. Phosphocreatine plays a vital role in the transfer of energy from the mitochondria (where high-energy phosphates are generated) to the cytosol (where they are consumed), thus resulting in the state of energy starvation seen in the failing heart. Evidence also suggests that mitochondrial energy production is impaired in the failing heart, and that mitochondrial DNA is abnormal. This is in part due to the action of free radicals, which damage the DNA, leading to the accumulation of copies of damaged DNA in the heart. Antibody-mediated mitochondrial damage may also occur (Ingwall and Weiss, 2004).

Changes in Skeletal Muscle

It is becoming increasingly clear that noncardiac as well as cardiac factors contribute to exercise limitation in heart failure. Peak aerobic capacity correlates poorly with left ventricular ejection fraction. This has led to a more detailed examination of the role of the skeletal musculature and peripheral circulation in chronic fatigue in these patients.

Numerous alterations have been described in skeletal muscle (Drexler *et al.*, 1992) (refer to Table 9).

There is increasing evidence that proinflammatory mediators play an important role in muscle wasting and fatigue in response to oxidative stress. Sympathetic overactivity leads to the impairment of local vasodilatation, resulting in episodes of hypoperfusion and ischemia, with the subsequent generation of free radicals.

Table 9 Changes in skeletal muscle in heart failure

Muscle atrophy
Fiber switch from type I (oxidative) to type II (glycolytic) type fibers
Decreased myosin heavy-chain type I fibers
Decreased level of mitochondrial enzymes involved in β-oxidation of free fatty acids
Decreased mitochondrial volume density
Decreased cytochrome *c* oxidase levels

TNF has been shown, in animal models, to produce muscle catabolism. This is the net effect of proteosomal degradation and blunting of the trophic effects of insulin on skeletal muscle.

TNF is also known to provoke apoptosis of skeletal muscle myocytes in heart failure, and circulating levels have been shown to correlate with the number of apoptotic nuclei seen on muscle biopsy in heart failure. However, this effect is more prominent in fast-twitch muscle fibers.

As mentioned earlier, the production of free radicals not only increases oxidative stress and stimulates the release on TNF, but also affects contractile function within striated muscle, perpetuating contractile dysfunction (Mann and Reid, 2003).

Recent studies indicate that exercise training has beneficial effects on skeletal muscle inflammation. This occurs by increasing the capacity to buffer free radicals, by increasing the expression of antioxidant genes, and by decreasing skeletal muscle sympathetic nerve activity (Gielen *et al.*, 2003).

Diastolic Ventricular Interaction in Heart Failure

It is self-evident that each ventricle must eject all the blood that it receives from the other ventricle. This phenomenon is known as *series ventricular interaction*, and is a consequence of the Frank-Starling relationship. An overwhelming body of evidence suggests that there is also an important direct interaction between the two ventricles in diastole, due to the fact that the ventricles share a common interventricular septum. Therefore, the filling of one ventricle may effect of the compliance of the other. This phenomenon is known as *direct diastolic ventricular interaction* or DVI (Morris-Thurgood and Frenneaux, 2000). Any changes in volume, pressure, and/or compliance of one ventricle will result in changes in the compliance of the other ventricle. This phenomenon is enhanced by the relatively nondistensible pericardium surrounding the heart. In health this interaction is relatively minor, but it becomes important in situations associated with an elevated RV diastolic pressure or volume.

The true left ventricular distending pressure is equal to the left ventricular end-diastolic pressure (LVEDP) minus the right ventricular end-diastolic pressure (RVEDP). Normally the pericardial pressure and RVEDP are low, but if they are markedly elevated, they contribute to the measured LVEDP. Changes in LVEDP may therefore not accurately reflect changes in the effective LV distending pressure. In models of acute pulmonary embolism, volume loading has been

shown to lead to a reduction in stroke volume despite a measured increase in LVEDP. This can be explained by an increase in the pericardial pressure and RVEDP that occurs in pulmonary embolism, which together lead to a reduction in the true LV distending pressure. The opposite has been shown to occur with volume reduction, leading to an increase in stroke volume.

A similar situation appears to exist in both animal and human congestive heart failure and in animal models of heart failure. In fact, when patients with heart failure are treated with an intravenous nitrate (known to be a potent venodilator), despite a reduction in measured LVEDP, there is an increase in stroke work and contractility. This is explained by a decrease in RVEDP and pericardial pressure, and subsequently a higher true LV distending pressure (Atherton *et al.*, 1997). The presence of DVI in patients with heart failure means that they are unable to utilize the Starling mechanism to increase cardiac output.

KEY POINTS

- Heart failure is a progressive disease, which carries a poor long-term prognosis.
- Treatment aimed at the underlying hemodynamic abnormalities has no impact on heart failure progression or mortality.
- Neurohumoral activation is a prominent feature of heart failure, and contributes to the progression of cardiac dysfunction.
- Left ventricular remodeling encompasses changes in LV geometry, LV hypertrophy, apoptosis, and changes in the cardiac interstitium. It is directly related to future deterioration in cardiac performance.
- Numerous molecular and cellular adaptations occur resulting in abnormal calcium handling and altered gene expression, all of which contribute to myocardial contractile dysfunction.

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Heart Failure in the Elderly

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INTRODUCTION

The combination of age-related changes in the cardiovascular system and the increasing prevalence of cardiovascular disease at older age predispose the older individual to the development of heart failure (HF). As a result, HF is predominantly a disorder of older adults, with persons over age 75 accounting for more than 50% of the nearly 1 million hospitalizations for HF each year in the United States, and over 60% of all HF-related deaths (Hall and Frances, 2003; Popovic, 1999). In addition, both the incidence and prevalence of HF are increasing, primarily due to the aging of the population, and it is anticipated that the number of older adults with clinical HF will double over the next 25 years (Rich, 1997).

Apart from its direct effects on hospitalizations and mortality, HF is an important cause of chronic disability in older adults (Hobbs *et al.*, 2002), and the functional limitations imposed by HF are often a key factor contributing to their entry into a long-term care facility. HF is also one of the most common comorbid conditions in hospitalized older adults who develop delirium (Rockwood, 1989), and HF interacts detrimentally with every major geriatric syndrome. Thus, the societal burden attributable to HF in the aging population is extremely high, and not surprisingly, HF is one of the most costly medical illnesses in the United States today, with an estimated annual expenditure in excess of $40 billion, representing 5.4% of the total health-care budget (O'Connell, 2000).

PATHOPHYSIOLOGY

Cardiovascular Aging

As discussed in **Chapter 44, Cardiac Aging and Systemic Disorders**, normal aging is associated with extensive changes in cardiovascular structure and function. Taken together, these changes result in a marked reduction in cardiovascular reserve, so that older adults are less able to maintain normal cardiac output and intracardiac pressures in response to stress, whether that stress is physiologic (e.g. exercise) or pathologic (e.g. ischemia, anemia, infection). Figure 1 illustrates the striking effect of normal aging on maximum oxygen consumption (VO_2 max) in healthy men and women who have been carefully screened to exclude occult cardiovascular disease (Fleg *et al.*, 2000). Note that the decline in VO_2 max with age is not simply linear, but that it actually accelerates after age 60. Moreover, normal octogenarians often have VO_2 max levels of less than 20 ml O_2/minute/kg, which are similar to those typically observed in middle-aged persons with moderate HF (New York Heart Association class II). Given the normal decline in cardiovascular reserve with increasing age, it is not difficult to understand why an 85-year-old person who suffers an acute myocardial infarction (MI) is substantially more prone to develop HF and cardiogenic shock than a 65-year-old person who suffers an MI of equivalent size. Similarly, older patients are more likely to develop HF in response to numerous other cardiac and noncardiac stressors, such as atrial fibrillation, pneumonia, intravenous fluid administration, or any type of major surgery.

Table 1 summarizes the principal effects of normal aging on cardiovascular structure and function (Rich and Kitzman, 2000; Lakatta and Levy, 2003a,b). Increased vascular stiffness contributes to the progressive rise in systolic blood pressure at older age, and increases impedance to left ventricular (LV) ejection (afterload). Impaired LV relaxation during early diastole (an active, energy-requiring process) and increased myocardial stiffness markedly alter the pattern of LV diastolic filling (preload) and result in a shift in the LV pressure–volume relationship upwards and to the left (Figure 2) (Gaasch *et al.*, 1976). These changes result in an increased reliance on atrial contraction (the "atrial kick") to optimize LV filling, and predispose the older individual to the development of "diastolic" HF (i.e. HF with

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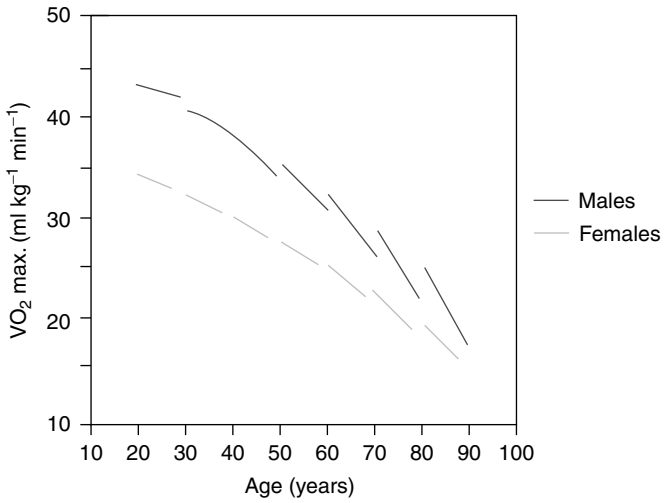

Figure 1 Age and VO_2max in healthy subjects: the Baltimore Longitudinal Study on Aging (Reproduced from Fleg JL *et al.*, 2000 by permisson of Lippincott Williams & Wilkins)

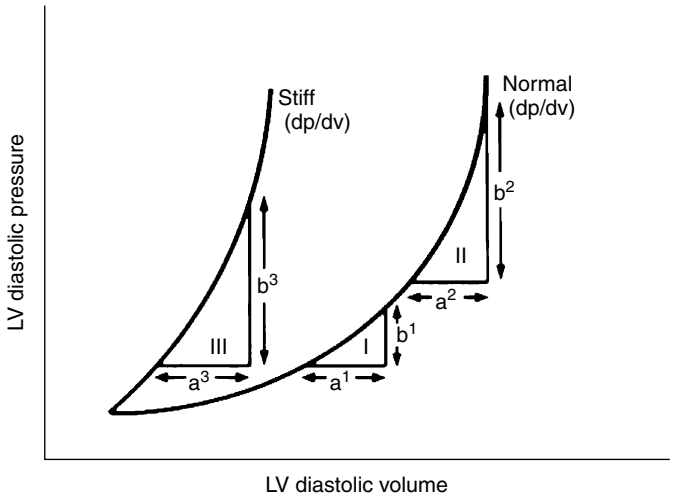

Figure 2 Effect of age on the left ventricular (LV) pressure–volume relationship. Note that there is a shift to the left, such that small increases in left ventricular volume are associated with greater increases in left ventricular pressure compared to younger persons (Adapted from Gaasch WH *et al.*, 1976. Copyright Elsevier)

Table 1 Principal effects of aging on cardiovascular structure and function

Increased vascular "stiffness", impedance to ejection, and pulse-wave velocity
Impaired left ventricular early diastolic relaxation and mid-to-late diastolic compliance
Diminished responsiveness to neurohumoral stimuli, esp. β_1 and β_2 adrenergic stimulation
Altered myocardial energy metabolism and reduced mitochondrial ATP-production capacity
Reduced number of sinus node pacemaker cells and impaired sinoatrial function
Endothelial dysfunction and vasomotor dysregulation

ATP, adenosine triphosphate.

preserved LV systolic function) and atrial fibrillation (Vasan *et al.*, 1999; Kitzman *et al.*, 2001; Khairallah *et al.*, 2004). Diminished responsiveness to β-adrenergic stimulation attenuates the heart rate response to stress and also reduces peak contractility, both of which are dependent on activation of the cardiac β_1-receptors. In addition, peripheral vasodilation is impaired due to reduced responsiveness of arteriolar β_2-receptors, further increasing afterload and limiting skeletal muscle blood flow during exercise. In healthy older adults, mitochondria in the cardiac myocytes are capable of generating sufficient adenosine triphosphate (ATP) to meet the energy needs of the myocardium, but they have reduced capacity to increase ATP production in response to stress, thus further limiting peak cardiac performance. There is also a reduction in the number of functioning sinus node pacemaker cells with increasing age, giving rise to the "sick sinus syndrome" and contributing to chronotropic incompetence; that is, the inability to increase heart rate commensurate with demands. Finally, age-related endothelial dysfunction and vasomotor dysregulation, while not affecting cardiac performance directly, contribute to the development and progression of atherosclerosis and coronary artery disease (CAD). In summary, normal cardiovascular aging exerts deleterious effects on all four of the major determinants of cardiac output – heart rate, contractility, preload, and afterload – thereby greatly reducing peak cardiac performance and cardiovascular reserve. In addition, cardiovascular aging fosters the development of systolic hypertension and CAD, the two leading causes of HF in older adults (Rich, 1997).

Other Organ Systems

Age-associated changes in other organ systems also contribute to the predilection of older adults to develop HF, and may affect the clinical features and response to therapy (Table 2) (Rich and Kitzman, 2000). Renal function declines with age, and older adults are less able to excrete a salt and water load. Pulmonary reserve also declines with age, with decreased vital capacity and increased ventilation-perfusion mismatching, resulting in more severe hypoxemia in the setting of superimposed HF. The central nervous system is less able to maintain cerebral perfusion in response to decreased cardiac output due to impaired autoregulatory capacity, thus increasing the propensity of older HF patients to develop impaired cognition or overt delirium. Thirst is also impaired in older adults, increasing the risk of diuretic-induced dehydration. Sarcopenia, a hallmark of aging, contributes to impaired exercise tolerance and diminished aerobic capacity in older HF patients. Finally, age-related alterations in the alimentary tract, liver, and kidneys result in substantial changes in the absorption, metabolism, and excretion of virtually all medications.

Table 2 Effects of aging on other organ systems

Kidneys
Decline in glomerular filtration rate (GFR), ~8 cc/minute/decade
Impaired water and electrolyte homeostasis
Reduced plasma renin and aldosterone activity
Impaired elimination of renally excreted drugs
Lungs
Loss of elastic recoil
Increased ventilation-perfusion (V/Q) mismatching
Reduced vital capacity and minute ventilation
Nervous system
Diminished reflex responsiveness, esp. baroreceptors
Reduced central nervous system autoregulatory capacity
Impaired thirst mechanism
Musculoskeletal system
Loss of muscle mass and strength (sarcopenia)
Loss of bone mass, esp. in women (osteopenia)
Altered pharmacokinetics and pharmacodynamics of most drugs

CLINICAL FEATURES

Symptoms and Signs

Exertional dyspnea, orthopnea, lower extremity swelling, and impaired exercise tolerance are the cardinal symptoms of HF at both younger and older age. However, with increasing age, which is often accompanied by a progressively more sedentary lifestyle, exertional symptoms become less prominent (Tresch, 2000). Conversely, atypical symptoms, such as confusion, somnolence, irritability, fatigue, anorexia, or diminished activity level, become increasingly more common manifestations of HF, especially after age 80.

Physical signs of HF include elevated jugular venous pressure, hepatojugular reflux, an S_3 gallop, pulmonary rales, and dependent edema. With the exception of rales, each of these features occurs less commonly in older HF patients, in part because of the increasing prevalence of diastolic HF, in which signs of right HF are a late manifestation and a third heart sound is typically absent. On the other hand, behavioral changes and altered cognition, which may range from subtle abnormalities to overt delirium, frequently accompany HF at older age, particularly among institutionalized or hospitalized patients (Rockwood, 1989).

Diagnosis

Accurate diagnosis of the HF syndrome at older age is confounded in part by the increasing prevalence of atypical symptoms and signs (Tresch, 2000). In addition, exertional symptoms may be attributable to noncardiac causes, such as pulmonary disease, anemia, depression, physical deconditioning, or aging itself. Likewise, peripheral edema may be due to venous insufficiency, hepatic or renal disease, or medication side effects (e.g. calcium channel blockers), and pulmonary crepitus may be due to atelectasis or chronic lung disease. Despite these limitations, careful clinical assessment for the presence of multiple symptoms and signs should lead to the correct diagnosis in most cases.

Chest radiography is indicated when HF is suspected, and it remains the most useful diagnostic test for determining the presence of pulmonary congestion. However, chronic lung disease, altered chest geometry (e.g. owing to kyphosis), or poor inspiratory effort may confound interpretation of the chest radiograph in elderly individuals.

Recently, plasma B-type natriuretic peptide (BNP) levels have been shown to be a valuable aid in distinguishing dyspnea due to HF from that related to other causes, such as pulmonary disorders (Maisel *et al.*, 2002). BNP levels tend to be elevated in both systolic and diastolic HF (Krishnaswamy *et al.*, 2001; Lubien *et al.*, 2002), and they also correlate with response to therapy and prognosis (Kazanegra *et al.*, 2001; Anand *et al.*, 2003; de Lemos *et al.*, 2003). However, BNP levels also increase with age in healthy individuals without HF, particularly in women (Figure 3), and, as a result, the specificity and predictive accuracy of BNP levels decline with age (Redfield *et al.*, 2002). Nonetheless, in cases of diagnostic uncertainty, a low or normal BNP level effectively excludes acute HF, whereas a markedly elevated level provides strong evidence in support of the diagnosis.

Proper management of HF is critically dependent on establishing the pathophysiology of LV dysfunction (i.e. systolic vs diastolic), determining the primary and any secondary etiologies (Table 3), and identifying potentially treatable precipitating or contributory factors (Table 4). Differentiating systolic from diastolic dysfunction requires an assessment of LV contractility by echocardiography, radionuclide ventriculography, magnetic resonance imaging, or contrast angiography. Among these, echocardiography is the most widely used and clinically useful noninvasive test for evaluating systolic and diastolic function. In addition, echocardiography provides important information about LV chamber size and wall thickness, atrial size, right ventricular function, the presence and severity of valvular lesions, and pericardial disorders.

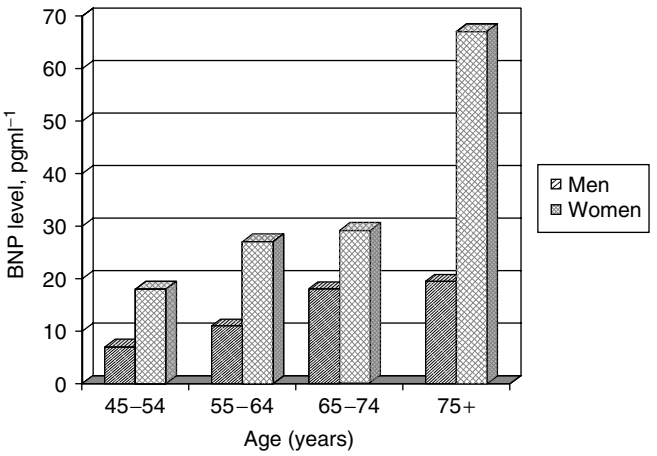

Figure 3 Mean B-type natriuretic peptide (BNP) levels in healthy volunteers according to age and gender (Adapted from Redfield MM *et al.*, 2002. Copyright American College of Cardiology)

Table 3 Common etiologies of heart failure in older adults

Coronary artery disease
Acute myocardial infarction
Chronic ischemic cardiomyopathy
Hypertensive heart disease
Hypertensive hypertrophic cardiomyopathy
Valvular heart disease
Aortic stenosis or insufficiency
Mitral stenosis or insufficiency
Prosthetic valve malfunction
Infective endocarditis
Cardiomyopathy
Dilated (nonischemic)
Alcohol
Chemotherapeutic agents
Inflammatory myocarditis
Idiopathic
Hypertrophic
Obstructive
Nonobstructive
Restrictive (esp. amyloid)
Pericardial disease
Constrictive pericarditis
High-output syndromes
Chronic anemia
Thiamine deficiency
Hyperthyroidism
Arteriovenous shunting
Age-related diastolic dysfunction

Table 4 Common precipitants of heart failure in older adults

Myocardial ischemia or infarction
Uncontrolled hypertension
Dietary sodium excess
Medication noncompliance
Excess fluid intake
Self-induced
Iatrogenic
Arrhythmias
Supraventricular, esp. atrial fibrillation
Ventricular
Bradycardia, esp. sick sinus syndrome
Associated medical conditions
Fever
Infections, esp. pneumonia or sepsis
Hyperthyroidism or hypothyroidism
Anemia
Renal insufficiency
Thiamine deficiency
Pulmonary embolism
Hypoxemia due to chronic lung disease
Drugs and medications
Alcohol
β-adrenergic blockers (incl. ophthalmologicals)
Calcium channel blockers
Antiarrhythmic agents
Nonsteroidal anti-inflammatory drugs
Glucocorticoids
Mineralocorticoids
Estrogen preparations
Antihypertensive agents (e.g. clonidine, minoxodil)

For these reasons, echocardiography is recommended for all patients with newly diagnosed HF or unexplained disease progression (Hunt *et al.*, 2001).

Other diagnostic studies that may be indicated in selected patients include an assessment of thyroid function (esp. in the presence of atrial fibrillation), an exercise or pharmacologic stress test to evaluate for the presence and severity of ischemia, and cardiac catheterization if revascularization or other corrective procedure (e.g. valve repair or replacement) is being contemplated.

Etiology and Precipitating Factors

Systemic hypertension and CAD account for 70–80% of HF cases at older age (Gottdiener *et al.*, 2000; Levy *et al.*, 1996). Hypertension is the most common etiology in older women, particularly those with preserved systolic function (Kitzman *et al.*, 2001; Levy *et al.*, 1996). In older men, HF is more often attributable to CAD (Levy *et al.*, 1996). Other common etiologies include valvular heart disease (esp. aortic stenosis and mitral regurgitation) and nonischemic cardiomyopathy (Table 3). Importantly, HF in the elderly is frequently multifactorial, and it is thus essential to identify all potentially treatable causes.

In addition to determining etiology, it is important to identify factors precipitating or contributing to HF exacerbations (Table 4). Noncompliance with medications and diet is the most common cause of worsening HF (Ghali *et al.*, 1988; Vinson *et al.*, 1990), and patients should be closely questioned about their dietary and medication habits. Other common factors contributing to increased symptoms include ischemia, volume overload due to excess fluid intake (self-inflicted or iatrogenic) (Rich *et al.*, 1996), tachyarrhythmias (esp. atrial fibrillation or flutter), intercurrent infections, anemia, thyroid disease, and various medications or toxins (e.g. alcohol).

Comorbidity

A hallmark of aging is the increasing prevalence of multiple comorbid conditions, many of which impact directly or indirectly on the diagnosis, clinical course, treatment, and prognosis of HF in the elderly (Table 5) (Rich and Kitzman, 2000). As noted previously, renal function declines with age, and octogenarians often have creatinine clearances of <50 cc/minute, despite "normal" serum creatinine levels and the absence of underlying renal disease (Beck, 1998). Older patients are also less able to excrete excess sodium and water (Luckey and Parsa, 2003), and this deficiency may contribute to volume overload. Diuretics tend to be less effective in the elderly, whereas diuretic-induced electrolyte disorders are more common, in part due to reduced capacity of the kidneys to preserve electrolyte homeostasis. Conversely, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) can all contribute to worsening renal function, and older patients are at increased risk for this complication.

Older HF patients are at increased risk for anemia due to comorbid chronic illnesses (renal disease, occult

Table 5 Common comorbidities in older patients

Condition	Implications
Renal dysfunction	Exacerbated by diuretics, ACE inhibitors
Anemia	Worsens symptoms and prognosis
Chronic lung disease	Contributes to uncertainty about diagnosis/volume status
Cognitive dysfunction	Interferes with dietary, medication, activity compliance
Depression, social isolation	Worsens prognosis, interferes with compliance
Postural hypotension, falls	Exacerbated by vasodilators, diuretics, β-blockers
Arthritis	NSAIDs worsen heart failure, antagonize heart-failure medications
Urinary incontinence	Aggravated by diuretics, ACE inhibitors (cough)
Sarcopenia, osteoporosis	Contribute to impaired exercise tolerance
Sensory deprivation	Interferes with compliance
Nutritional disorders	Exacerbated by dietary restrictions
Polypharmacy	Reduced compliance, increased drug interactions
Frailty	Exacerbated by hospitalization; increased fall risk

ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

malignancy), inadequate dietary intake of key nutrients (iron, folate, B12), and use of medications associated with gastrointestinal blood loss (aspirin, warfarin, nonsteroidal anti-inflammatory drugs) (Smith, 2000; Beghe *et al.*, 2004). Anemia contributes to impaired tissue oxygen delivery and impaired exercise tolerance, and may exacerbate myocardial ischemia in patients with underlying CAD. Anemia has also been shown to be an independent predictor of adverse clinical outcomes in patients with HF (Kosiborod *et al.*, 2003; McClellan *et al.*, 2002).

Normal aging is associated with a decline in maximum voluntary ventilation and an increase in ventilation-perfusion mismatching (Zeleznik, 2003). In addition, chronic obstructive and restrictive lung diseases further impair pulmonary function in many older adults. Diminished pulmonary function, in turn, contributes to increased dyspnea and exercise intolerance in older patients with HF, as the lungs are unable to compensate for impaired cardiac performance. In addition, the presence of chronic lung disease often leads to diagnostic uncertainty (is the patient's dyspnea due to HF, pulmonary disease, or a combination of both?), in part by confounding the interpretation of the physical examination and chest radiograph.

Cognitive dysfunction interferes with the patient's ability to participate fully in self-care behaviors, such as weight monitoring, adherence to dietary restrictions, and compliance with prescribed medications. In more severe cases, cognitive impairment substantially limits the patient's ability to provide a reliable medical history, and may prevent recognition of new or worsening symptoms. Patients with cognitive dysfunction are also at increased risk for developing delirium, which may complicate hospital management and result in significant adverse events (e.g. falls, aspiration, infections) (McGann, 2000).

Up to 20% of elderly HF patients have clinically significant depression, which is often unrecognized (Havranek *et al.*, 1999; Freedland *et al.*, 1991). Social isolation, primarily due to the death of one's spouse, also occurs with increasing frequency at elderly age. Both these conditions have been associated with adverse outcomes in elderly HF patients, including increased mortality and hospitalization rates (Jiang *et al.*, 2001; Vaccarino *et al.*, 2001; Krumholz *et al.*, 1998a), in part due to reduced compliance with prescribed medications and recommended behaviors (Carney *et al.*, 1995a,b). In addition, depression has been linked with increased adrenergic tone and ventricular arrhythmias in patients with cardiovascular disease, both of which confer an increased mortality risk in HF patients (Carney *et al.*, 1993, 1995c).

Increased vascular stiffness and impaired baroreflex responsiveness predispose older adults to the development of postural hypotension (Mukai and Lipsitz, 2002), while age-related alterations in sinus node function increase the risk of bradyarrhythmias (sick sinus syndrome). In addition, balance and proprioception decline with age. Taken together, these factors greatly increase the risk of falls in older adults. Standard therapies for HF, including diuretics, vasodilators, and β-blockers, all have the potential to further increase the risk of falls and associated morbidity.

Arthritis is the leading cause of minor disability in older adults, and is widely treated with nonsteroidal anti-inflammatory drugs (NSAIDs) available both by prescription and over the counter. These agents enhance renal sodium and water resorption and have been associated with a significant increase in the risk of hospitalization for HF, even among patients with no prior history of the condition (Page and Henry, 2000). NSAIDs also antagonize the effects of diuretics and ACE inhibitors, and may inhibit the beneficial effects of aspirin in patients with CAD (Kurth *et al.*, 2003). In addition, NSAIDs are a common cause of gastrointestinal bleeding in older adults, thus potentiating the risk of anemia (Lapane *et al.*, 2001).

The prevalence of urinary incontinence increases with age, affecting up to 35% of women and 20% of men over the age of 80 (McGann, 2000). Diuretics and ACE inhibitors (ACE cough) may aggravate incontinence in many patients. However, most patients with mild to moderate incontinence do not report the condition to their physicians unless specifically asked. Instead, they will avoid taking their medication rather than risking embarrassment, especially if they are going to be away from home without ready access to a rest room. The importance of urinary incontinence as a cause for medication noncompliance in the elderly is unknown and it is likely to be under-appreciated, as most clinicians do not routinely inquire about this condition.

Sarcopenia contributes to muscle weakness and impaired exercise tolerance in older persons with or without HF. Osteopenia and osteoporosis compromise the structural integrity of the skeletal system (e.g. as a result of compression fractures), further reducing exercise capacity. In addition, the risk of falls and hip fractures is increased, and,

as noted earlier, these risks may be further potentiated by several of the medications used to treat HF.

Reduced visual and auditory acuity often interfere with patients' ability to comply with therapeutic recommendations, either because they didn't hear the instructions properly, or because they are unable to read printed materials (e.g. medication instructions, pill bottles, nutrition labels). When coupled with social isolation, these deficits can make it particularly difficult for older patients to comply with HF therapy.

Undernutrition is common in older adults and is usually multifactorial, with reduced access to nutritional foods (e.g. owing to loss of independence, social isolation, limited finances), diminished appetite (owing to chronic illness, depression, medications), loss of enjoyment from eating (impaired sense of taste and smell, social isolation), neuromuscular conditions (stroke, Parkinsonism), and mechanical factors (poor dentition, difficulty swallowing) all playing a role. In addition, prevalent medical conditions often lead to the imposition of major dietary restrictions, including protein restriction in patients with hepatic or renal disease, carbohydrate restriction in diabetics, fat and cholesterol restriction in patients with CAD or diabetes, and sodium restriction in patients with hypertension, HF, or renal disease. Moreover, advanced HF itself is often associated with a progressive decline in lean body mass, a condition referred to as *cardiac cachexia* (Anker *et al.*, 1997; *see also* **Chapter 56, Cardiac Cachexia**). Thus, HF *per se*, as well as its treatment (sodium restriction in almost all cases, restriction of other macronutrients in many cases due to prevalent comorbidities), may contribute to the development or progression of undernutrition in older adults, a condition associated with immune deficiency, frailty, and a poor long-term prognosis (McGann, 2000; Persson *et al.*, 2002).

Polypharmacy is common in patients with HF, since drug therapy for HF alone often entails the use of three or more medications, and virtually all elderly HF patients have associated conditions for which they are receiving treatment. Apart from the high cost associated with the use of multiple medications, polypharmacy has an important role in interfering with medication compliance, since the more medications a patient is taking, the less likely it is that they are taking their medications correctly. In addition, there is an exponential relation between the number of medications being taken and the risk of drug interactions, such that patients taking 10 or more medications have over a 90% probability of experiencing one or more clinically significant drug interactions (Nolan and O'Malley, 1988).

The prevalence of frailty increases dramatically with age, especially among persons over the age of 80, and the cardinal features of frailty – weight loss, weakness, slow movement, low physical activity, and exhaustion – overlap significantly with the symptoms of HF (Fried *et al.*, 2001). Frailty confers a poor prognosis, as it tends to be associated with progressive physical and functional decline, and it is also a marker for increased risk for iatrogenic complications, such as falls related to medications. Frailty tends to worsen during hospitalization for acute illness (e.g. a HF exacerbation), and frail patients rarely return to their previous level of function following hospital discharge. Thus, HF and frailty interact in a way that is detrimental to both conditions.

Recent studies indicate that both the number and nature of noncardiac comorbidities have a significant impact on clinical outcomes in older HF patients. In 2003, Braunstein *et al.*, (2003) examined the prevalence of noncardiac comorbidities in Medicare beneficiaries hospitalized with HF. As shown in Figure 4, 86% of patients had two or more noncardiac comorbidities, and more than 25% had six or more noncardiac conditions. In addition, since common geriatric syndromes, such as dementia, depression, incontinence, and frailty, are often clinically unrecognized, it is likely that the true prevalence of noncardiac comorbidities is underestimated by Braunstein's data.

Figure 5 illustrates the relationship between the number of noncardiac comorbidities and the number of hospital admissions among HF patients (Braunstein *et al.*, 2003). Overall, the proportion of patients hospitalized annually increased from about 35% among patients with no comorbidities, to over 90% among patients with nine or more comorbidities. Moreover, approximately half of all hospitalizations were considered potentially avoidable (depicted by the shaded regions in the figure), regardless of the number of comorbidities.

Several studies have also examined the relationship between specific comorbidities and clinical outcomes. Chronic renal insufficiency and anemia have both been shown to be independent predictors of mortality in elderly HF patients (Kosiborod *et al.*, 2003; McClellan *et al.*, 2002; Krumholz *et al.*, 2000; Ezekowitz *et al.*, 2003b), and the presence of cognitive dysfunction has been associated with a striking increase in mortality among older patients hospitalized with HF (Zuccalà *et al.*, 2003). In addition, the use of NSAIDs has been associated with a 60% increase in the risk of hospitalization for HF among elderly patients with no prior history of heart disease, and a 10-fold increase

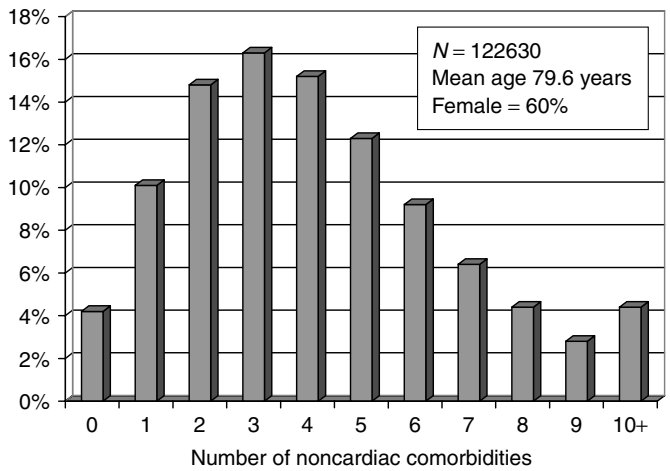

Figure 4 Prevalence of noncardiac comorbidities in Medicare beneficiaries with heart failure (Adapted from Braunstein JB *et al.*, 2003. Copyright American College of Cardiology)

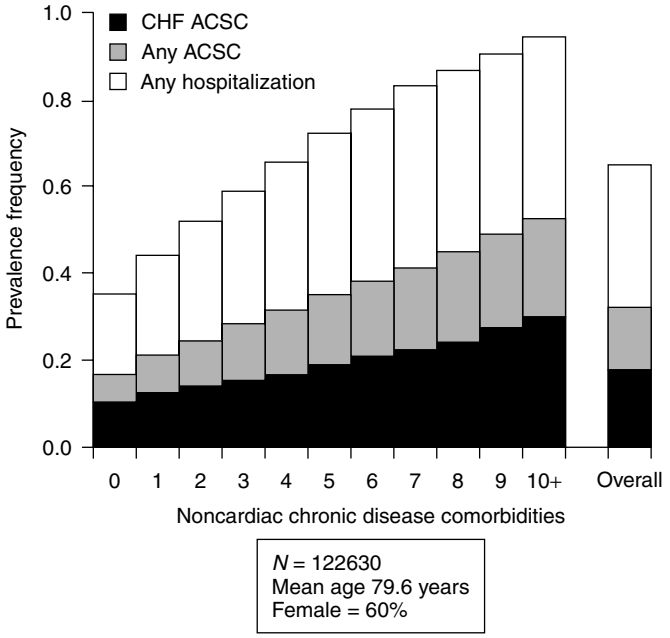

Figure 5 Impact of noncardiac comorbidities on hospital admissions in Medicare beneficiaries with heart failure. ACSC: ambulatory care sensitive conditions; CHF: chronic heart failure (Reproduced from Braunstein JB *et al.*, 2003. Copyright American College of Cardiology)

among patients with preexisting cardiac conditions (Page and Henry, 2000).

In summary, older HF patients almost invariably have one or more age-associated conditions that influence the diagnosis, clinical features, and/or management of HF. Conversely, HF and its therapy often have ramifications for the clinical course and treatment of these comorbid conditions. Consideration of the interactions between HF and prevalent comorbidities is thus a critically important aspect of management in the elderly HF patient.

MANAGEMENT

The principal goals of HF therapy are to relieve symptoms, maintain or enhance functional capacity and quality of life, preserve independence, and reduce mortality. Although it is often stated that quality of life is more important than quantity of life in the very elderly, this in fact is a matter of personal preference. Furthermore, since the elderly HF population is characterized by marked heterogeneity in terms of lifestyle, comorbidity, and personal goals and perspectives, management of HF in the elderly must first and foremost be individualized in accordance with each patient's circumstances and needs.

The basic approach to HF management involves identification and treatment of the underlying etiology and contributing factors, implementation of an effective therapeutic regimen, and coordination of care through the use of a multidisciplinary team.

Etiology and Precipitating Factors

Although HF in the elderly is rarely "curable", proper treatment of the underlying etiology often improves symptoms and delays disease progression. Thus, hypertension should be treated aggressively (Chobanian *et al.*, 2003), and CAD should be managed appropriately with medications and/or percutaneous or surgical revascularization. Similarly, therapy for diabetes and dyslipidemia should be optimized, smoking should be strongly discouraged, and a suitable level of regular physical activity should be prescribed. Alcohol intake should be limited to no more than 2 drinks/day in men and 1 drink/day in women, and alcohol use should be strictly proscribed in patients with suspected alcoholic cardiomyopathy.

Severe aortic stenosis is a common cause of HF in the elderly, which can be effectively treated with aortic valve replacement (Slaughter and Ward, 2000). Perioperative mortality rates are acceptable (less than 10%), and long-term results are excellent even in octogenarians (Geholt *et al.*, 1996). Severe mitral regurgitation may be amenable to surgical therapy (i.e. valve repair or replacement) in selected patients, but the operative results are somewhat less favorable than for aortic valve surgery (Bolling *et al.*, 1996; Marzo *et al.*, 2000). Mitral valve replacement is also effective therapy for severe mitral stenosis; rarely, percutaneous mitral balloon valvuloplasty may be feasible in older patients (Shapiro *et al.*, 1995; Sutaria *et al.*, 2000).

Atrial fibrillation is a common precipitant of HF in elderly patients, especially in the setting of diastolic dysfunction. In patients with recent onset symptomatic atrial fibrillation, many clinicians recommend restoration and maintenance of sinus rhythm if feasible, although the long-term benefits of this approach have not been established (Wyse *et al.*, 2002; Van Gelder *et al.*, 2002). In patients with chronic atrial fibrillation, the ventricular rate should be well controlled both at rest and during activity. Bradycardia is a less common primary cause of HF; when present, implantation of a permanent pacemaker provides definitive therapy (see the section on device therapy). Anemia, thyroid disease, and other systemic illnesses should be identified and treated accordingly.

The importance of compliance with medications and dietary restrictions, including avoidance of excessive fluid intake, cannot be overemphasized. NSAIDs are widely used by older individuals to treat arthritis and relieve chronic pain, but these agents promote sodium and water retention, interfere with the actions of ACE inhibitors and other antihypertensive agents, and may worsen renal function; their use should be avoided whenever possible (Page and Henry, 2000). Similarly, the use of other medications that may aggravate HF should be closely monitored.

Pharmacotherapy

The design of an effective therapeutic regimen is based in part on whether the patient has predominantly systolic or predominantly diastolic LV dysfunction. Although these

two abnormalities frequently coexist (indeed, virtually all individuals over age 70 have some degree of diastolic dysfunction), for purposes of this discussion patients with an ejection fraction <45% (i.e. moderate or severe LV systolic dysfunction) will be considered as having systolic HF, whereas patients with an ejection fraction >45% will be considered as having diastolic HF.

Systolic Heart Failure

In the past 20 years, there has been considerable progress in the treatment of systolic HF. Although most studies have either excluded individuals over 75–80 years of age, or have enrolled too few elderly subjects to permit definitive conclusions, the available data indicate that older patients respond to standard therapies as well or better than younger patients. Therefore, current recommendations for drug treatment of systolic HF are similar in younger and older patients (Hunt *et al.*, 2001).

ACE Inhibitors

ACE inhibitors are the cornerstone of therapy for LV systolic dysfunction, whether or not clinically overt HF is present (Hunt *et al.*, 2001), and the benefits of ACE inhibitors are similar in older and younger patients, both in terms of reducing mortality and improving quality of life (Garg and Yusuf, 1995; Flather *et al.*, 2000). On the other hand, older patients are more likely to have potential contraindications to ACE inhibitors (e.g. renal dysfunction, renal artery stenosis, orthostatic hypotension), and they may also be at increased risk for ACE inhibitor-related side effects, such as worsening renal function, electrolyte disturbances, and hypotension. Nonetheless, a trial of ACE inhibitors is indicated in virtually all older patients with documented LV systolic dysfunction.

In most cases, ACE-inhibitor therapy should be initiated at a low dose (e.g. captopril 6.25–12.5 mg TID or enalapril 2.5 mg BID), and the dosage should be gradually titrated upward to the level shown to be effective in clinical trials (captopril 50 mg TID, enalapril 10 mg BID, lisinopril 20 mg qd, ramipril 10 mg qd) (Garg and Yusuf, 1995; Flather *et al.*, 2000; Pfeffer *et al.*, 1992; The SOLVD Investigators, 1991; The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators, 1993). Once a maintenance dose has been achieved, substituting a once-daily agent (e.g. lisinopril or ramipril) at equivalent dosage may facilitate compliance. Blood pressure, renal function, and serum potassium levels should be monitored closely during dose titration and periodically during maintenance therapy. In patients unable to tolerate standard ACE-inhibitor dosages due to side effects, dosage reduction is appropriate, as there is evidence that even very low doses of these agents (e.g. lisinopril 2.5–5 mg qd) provide some degree of benefit (Packer *et al.*, 1999).

Angiotensin Receptor Blockers

Angiotensin receptor blockers (ARBs) have a more favorable side effect profile than ACE inhibitors, but there is insufficient evidence to conclude that the effects of ARBs on major clinical outcomes (e.g. death, hospitalizations) are equivalent to those of ACE inhibitors (Pitt *et al.*, 1997, 2000; Dickstein and Kjekshus, 2002; Jong *et al.*, 2002). However, recent studies indicate that ARBs reduce mortality and hospitalizations in patients with systolic HF who are intolerant to ACE inhibitors due to cough or other side effects (Maggioni *et al.*, 2002; Granger *et al.*, 2003). In addition, combining an ARB with an ACE inhibitor improves outcomes compared with an ACE inhibitor alone (Cohn and Tognoni, 2001; McMurray *et al.*, 2003). On the basis of available evidence, ACE inhibitors are still considered first-line therapy for HF, but ARBs offer an excellent alternative for patients intolerant to ACE inhibitors, and as adjunctive agents in patients with persistent symptoms despite conventional treatment.

Hydralazine and Isosorbide Dinitrate

The combination of hydralazine 75 mg QID and isosorbide dinitrate 40 mg QID was associated with decreased mortality in a small trial of HF patients less than 75 years of age (Cohn *et al.*, 1986). In a more recent trial that did not exclude elderly patients, these agents were shown to reduce mortality in African–American patients with HF (Taylor *et al.*, 2004). Although ACE inhibitors are superior to hydralazine-nitrates in improving survival (Cohn *et al.*, 1991), the combination provides an additional alternative for ACE inhibitor-intolerant patients and for patients with significant renal insufficiency. Side effects are common with both hydralazine and high-dose nitrates, and the QID dosing schedule is a particular disadvantage for older patients.

β-blockers

β-blockers, once widely viewed as contraindicated in patients with HF, have now been shown to improve LV function and decrease mortality in a broad population of HF patients, including those with New York Heart Association (NYHA) class IV symptoms and patients up to 80 years of age (Packer *et al.*, 1996; CIBIS-II Investigators and Committees, 1999; Lancet, 1999; Packer *et al.*, 2001). As a result, β-blockers are now considered standard therapy for clinically stable patients without major contraindications (Hunt *et al.*, 2001). Use of β-blockers in older patients may be limited by a higher prevalence of bradyarrhythmias and severe chronic lung disease, and older patients may also be more susceptible to the development of fatigue and impaired exercise tolerance during long-term β-blocker administration.

Carvedilol, metoprolol, and bisoprolol have all been shown to improve outcomes in patients with systolic HF, and a recent study found that carvedilol 25 mg twice daily was more effective than metoprolol 50 mg twice daily in reducing mortality (Poole-Wilson *et al.*, 2003). In most cases, β-blocker treatment should be initiated at low dosages in stable patients upon a background of ACE inhibitor and diuretic therapy. Recommended starting dosages are

carvedilol 3.125 mg BID, metoprolol 6.25–12.5 mg BID, and bisoprolol 1.25 mg qd. The dose should be gradually increased at 2- to 4-week intervals to achieve maintenance dosages of carvedilol 25–50 mg BID, metoprolol 50–100 mg BID (or sustained release metoprolol 100–200 mg qd), or bisoprolol 5–10 mg qd. Lower dosages and a slower titration protocol may be appropriate in patients over 75 years of age. Contraindications to β-blockers include marked sinus bradycardia (resting heart rate <45–50 BPM), PR interval $\geq$0.24 seconds, heart block greater than first degree, systolic blood pressure <90–100 mmHg, active bronchospastic lung disease, and severe decompensated HF.

Digoxin

Digoxin improves symptoms and reduces hospitalizations in patients with symptomatic systolic HF treated with ACE inhibitors and diuretics, but it has no effect on total or cardiovascular mortality (The Digitalis Investigation Group, 1997). Although these effects are similar in younger and older patients, including octogenarians (Rich *et al.*, 2001), a recent retrospective analysis has questioned the value of digoxin in women (Rathore *et al.*, 2002). Nonetheless, digoxin remains a useful drug for the treatment of systolic HF in patients of all ages who have limiting symptoms despite standard therapy.

The volume of distribution and renal clearance of digoxin decline with age. In addition, recent data indicate that the optimal therapeutic concentration for digoxin is 0.5–0.8 ng ml^{-1} (Rathore *et al.*, 2003); that is, substantially lower than the traditional therapeutic range of 0.8–2.0 ng ml^{-1}. Moreover, higher concentrations of digoxin are associated with increased toxicity but no greater efficacy (Rathore *et al.*, 2003; Slatton *et al.*, 1997). For most older patients with preserved renal function (est. creatinine clearance >50 cc/minute), digoxin 0.125 mg daily provides a therapeutic effect. Lower dosages should be used in patients with renal insufficiency. Although routine monitoring of serum digoxin levels is no longer recommended, it seems reasonable to measure the serum digoxin concentration 2 to 4 weeks after initiating therapy to ensure that the level does not exceed 0.8 ng ml^{-1}. In addition, a digoxin level should be obtained whenever digoxin toxicity is suspected.

Digoxin side effects include arrhythmias, heart block, gastrointestinal disturbances, and altered neurological function (e.g. visual disturbances). Although, older patients are often thought to be at increased risk for digitalis toxicity, this was not confirmed in a recent analysis from the Digitalis Investigation Group (DIG) trial (Rich *et al.*, 2001). On the other hand, digoxin has significant drug interactions with many medications commonly prescribed for older patients. Among these, cholestyramine and phenytoin reduce digoxin levels, whereas amiodarone, amphotericin, calcium preparations, cyclosporine, erythromycin, itraconazole, propafenone, quinidine, quinine sulfate, reserpine, tetracycline, and verapamil all increase serum digoxin concentrations and the risk of digoxin toxicity.

Diuretics

Diuretics are an essential component of therapy for most patients with HF, and diuretics remain the most effective agents for relieving congestion and maintaining euvolemia. Some patients with mild HF can be effectively controlled with a thiazide diuretic, but the majority will require a loop diuretic such as furosemide or bumetanide. In patients with more severe HF or significant renal dysfunction (serum creatinine >2.0 mg dl^{-1}), the addition of metolazone 2.5–10 mg qd may be necessary to achieve effective diuresis.

In general, diuretic dosages should be titrated to eliminate signs of pulmonary and systemic venous congestion. Common side effects include worsening renal function (often owing to overdiuresis) and electrolyte disorders. To minimize these effects, renal function and serum electrolyte levels (sodium, potassium, magnesium) should be monitored closely during the initiation and titration phase of diuretic use, and periodically thereafter.

Aldosterone Antagonists

Spironolactone is a weak, potassium-sparing diuretic that acts by antagonizing aldosterone. Recently, the addition of spironolactone 12.5–50 mg daily to standard HF therapy has been shown to reduce mortality and hospital admissions in patients with NYHA class III-IV systolic HF, with similar benefits in older and younger patients (Pitt *et al.*, 1999; Pitt and Perez, 2000). Eplerenone, a selective aldosterone antagonist, has also been shown to reduce mortality and sudden cardiac death in patients with LV dysfunction following acute MI (Pitt *et al.*, 2003). Spironolactone is contraindicated in patients with severe renal insufficiency or hyperkalemia, and up to 10% of patients develops painful gynecomastia. In addition, older patients receiving spironolactone in combination with an ACE inhibitor may be at increased risk for hyperkalemia, particularly in the presence of preexisting renal insufficiency or diabetes, and at doses in excess of 25 mg/day (Wrenger *et al.*, 2003; Juurlink *et al.*, 2004).

Approach to Treatment

Figure 6 provides a suggested approach to the pharmacologic treatment of systolic HF. All patients with LV systolic dysfunction, whether asymptomatic or symptomatic, should receive an ACE inhibitor (or an ARB or alternative vasodilator if ACE inhibitors are contraindicated or not tolerated). Patients with stable symptoms and no contraindications should also receive a β-blocker, and diuretics should be administered in sufficient doses to maintain euvolemia. Digoxin and/or an ARB should be considered in patients who remain symptomatic despite the above regimen, and spironolactone should be used in patients with persistent NYHA class III-IV symptoms.

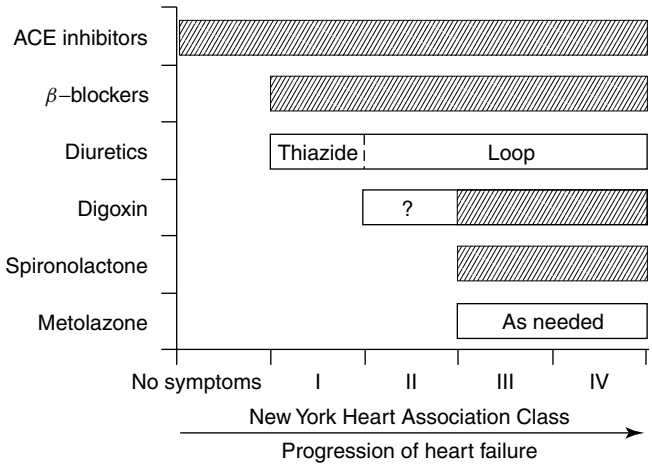

Figure 6 Approach to treatment of systolic heart failure; see text for details. Shaded areas refer to therapies proven to be efficacious in prospective randomized clinical trials. ACE: angiotensin-converting enzyme

Diastolic Heart Failure

Despite the fact that over 50% of elderly HF patients have preserved LV systolic function (Vasan *et al.*, 1999; Kitzman *et al.*, 2001), until recently none of the major HF trials have specifically targeted this disorder. As a result, treatment of diastolic HF remains largely empiric. As with systolic HF, the underlying cardiac disorder and associated contributing conditions should be treated appropriately. In particular, hypertension and CAD should be managed aggressively. Diuretics should be used judiciously to relieve congestion while avoiding overdiuresis and prerenal azotemia. Topical or oral nitrates may be beneficial in reducing pulmonary congestion and orthopnea. On the basis of the results of the Heart Outcomes Prevention Evaluation (HOPE) (Yusuf *et al.*, 2000), an ACE inhibitor such as ramipril 2.5–10 mg daily is appropriate for most older adults with vascular disease, but the value of ACE inhibitors in the treatment of diastolic HF *per se* has not been established. In the recently reported CHARM-preserved trial (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity), the ARB candesartan reduced HF admissions by 16% but had no effect on mortality in patients with HF and a LV ejection fraction >40% (Yusuf *et al.*, 2003). The mean age of patients in CHARM-preserved was 67 years, and 807 patients, comprising 27% of the total population, were ≥75 years of age. However, patients with substantial comorbidity were excluded from CHARM-preserved, so the applicability of the study findings to older HF patients encountered in clinical practice remains unknown.

β-blockers are indicated in patients with CAD (esp. prior MI), but the long-term effects of these agents in diastolic HF are unknown. Calcium channel blockers are effective antihypertensive agents in the elderly, and these drugs may provide symptomatic palliation in selected patients with diastolic HF (Pitt *et al.*, 2000). Digoxin, in addition to its inotropic effect, also facilitates diastolic relaxation, and may improve symptoms and reduce hospitalizations in patients with HF and preserved systolic function (The Digitalis Investigation Group, 1997; Rich *et al.*, 2001). In summary, an array of therapeutic options are available for treating diastolic HF, but none have been shown to reduce mortality; therapy should therefore be individualized and guided by prevalent comorbidities and the observed response to specific therapeutic interventions.

Device Therapy

Although the majority of HF patients can be effectively managed with behavioral interventions and medications, implantable devices are playing an increasingly important role in the management of selected subgroups of the HF population.

Cardiac Pacemakers

Aging is associated with a progressive decline in the number of functioning sinus node pacemaker cells, often leading to the "sick sinus syndrome", which is characterized by inappropriate sinus bradycardia, sinus pauses, and chronotropic incompetence (failure to adequately increase heart rate in response to increased demands) (Adan and Crown, 2003). Since cardiac output is directly proportional to heart rate (Cardiac Output = Heart Rate × Stroke Volume), age-related bradyarrhythmias may contribute to HF symptoms and impaired exercise tolerance. Because there is no effective medical therapy for sick sinus syndrome, implantation of a pacemaker is appropriate in symptomatic patients. The use of β-blockers may also precipitate symptomatic bradyarrhythmias in elderly HF patients. Since β-blockers improve ventricular function and reduce mortality and hospitalizations in patients with systolic HF (Packer *et al.*, 1996; CIBIS-II Investigators and Committees, 1999; Lancet, 1999; Packer *et al.*, 2001), placement of a pacemaker is often preferable to discontinuation of β-blocker therapy.

Cardiac Resynchronization Therapy (CRT)

Recently, a new role has evolved for pacemakers in treating selected patients with advanced HF. Approximately 30% of HF patients have left bundle branch block or other intraventricular conduction abnormality resulting in significant prolongation of the QRS interval (≥120 m seconds). In these patients, LV contraction is often disynchronous and out of phase with right ventricular contraction. Biventricular pacing, with one lead pacing the right ventricle and a second lead pacing the left ventricle through retrograde insertion into the coronary sinus, can "resynchronize" ventricular contraction, thus improving ejection fraction and cardiac output (Kerwin *et al.*, 2000; Bakker *et al.*, 2000). The addition of atrial pacing may provide further benefit by optimizing the timing of atrial and ventricular contraction. The benefits

of CRT in improving ejection fraction, reducing LV cavity size, and enhancing exercise tolerance and quality of life have now been well documented in several randomized trials involving patients with advanced HF symptoms (NYHA class III-IV), reduced ejection fractions, and prolonged QRS durations (Abraham *et al.*, 2002; Linde *et al.*, 2002; Bradley *et al.*, 2003; Young *et al.*, 2003). In addition, a recent meta-analysis suggests that CRT is associated with improved survival (McAlister *et al.*, 2004a). On the basis of these findings, CRT is a reasonable option for carefully selected older patients with advanced HF symptoms despite treatment with conventional therapies.

Implantable Cardioverter Defibrillators (ICDs)

Approximately 40–50% of all deaths in patients with HF occur suddenly, and the majority of these are attributable to ventricular tachycardia (VT) and ventricular fibrillation (VF). Implantable Cardioverter Defibrillators (ICDs) have the capacity to recognize VT and VF, and to restore normal rhythm either by pacing techniques (in the case of VT) or by delivering an intracardiac electrical shock (refractory VT or VF). Moreover, these devices have been shown to significantly improve survival in certain high-risk subgroups of the HF population, including those with resuscitated cardiac arrest, symptomatic sustained VT, and ischemic cardiomyopathy with ejection fraction less than 30% in the setting of prior myocardial infarction (Moss *et al.*, 2002, 1996; Ezekowitz *et al.*, 2003a). Importantly, the survival benefit of ICDs is greatest in patients over 70 years of age with ejection fractions less than 35% and NYHA class III or IV HF symptoms (Sheldon *et al.*, 2000).

In the United States, over half of ICDs are implanted in patients 65 years of age or older. However, despite the established benefits of ICDs in appropriately selected patients, the clinical role of ICDs in elderly HF patients remains a subject of debate (Camm and Nisam, 2000; Exner *et al.*, 2001; Weiss *et al.*, 2002). These devices are expensive, with a total cost of approximately $40 000–$50 000 per device, although a $10 000 "generic" version has recently gained approval. In addition, the societal cost burden is likely to increase substantially as the indications for these devices continue to expand. There are also ethical questions, such as how and when to turn off the device in the terminal stages of HF, or in cases where another life-threatening illness develops (e.g. stroke or cancer). In part because of these reasons, many older patients may elect to forego ICD implantation, even though survival may be enhanced. Although additional study is needed, it is clear that the use of ICDs must be individualized, but older age should not constitute the sole grounds for withholding ICD therapy.

Multidisciplinary Care

The presence of multiple comorbid conditions, polypharmacy, dietary concerns, and a host of psychosocial and financial issues frequently complicate the management of HF in older patients. Moreover, these factors often contribute to poor outcomes in older adults, including frequent hospitalizations (Vinson *et al.*, 1990; Krumholz *et al.*, 1998a). To address these issues, and to provide comprehensive yet individualized care for older HF patients, a coordinated multidisciplinary approach is recommended. Several recent studies have documented the efficacy of multidisciplinary HF disease management programs in reducing hospitalizations and improving the quality of life in older patients, and these interventions have also been reported to lower the overall medical costs (McAlister *et al.*, 2004b; Phillips *et al.*, 2004; Ofman *et al.*, 2004; Rich and Nease, 1999).

Elements of an effective HF disease management program include patient and caregiver education, enhancement of self-management skills, optimization of pharmacotherapy (including consideration of polypharmacy issues), and close follow-up. The structure of a HF disease management team is similar to that of a multidisciplinary geriatric assessment team, and typically includes a nurse coordinator or case manager, dietitian, social worker, clinical pharmacist, home health representative, primary care physician, and cardiology consultant. Specific goals of disease management are to improve patient compliance with medications, diet, and exercise recommendations by enhancing education and self-management skills; provide close follow-up and improved health-care access through telephone contacts, home health visits, and nurse or physician office visits; and optimize the medication regimen by promoting physician adherence to recommended HF treatment guidelines (Hunt *et al.*, 2001), simplifying and consolidating the regimen when feasible, eliminating unnecessary medications, and minimizing the risks for drug–drug and drug–disease interactions.

Exercise

Both HF and normal aging are associated with reduced exercise capacity, in part due to sarcopenia (loss of muscle mass) and alterations in skeletal muscle blood flow and metabolism. Regular physical activity improves exercise performance in healthy older adults, as well as in those with HF, and regular exercise is now recommended for most older HF patients (Hunt *et al.*, 2001; Pina *et al.*, 2003; McKelvie *et al.*, 2002; Hambrecht *et al.*, 2000; Belardinelli *et al.*, 1999; Keteyian *et al.*, 1996). Although supervised exercise programs have been associated with the greatest improvements in exercise performance, such programs are not feasible for most older patients due to lack of availability, travel concerns, and cost constraints. Therefore, most older HF patients should be encouraged to engage in a self-monitored home exercise program that includes stretching exercises, resistance exercises, and aerobic activities. Stretching increases or maintains muscle flexibility and reduces the risk of injury. A daily stretching routine lasting 15–30 minutes and involving all major muscle groups is recommended. Resistance training increases muscle mass and strength and reduces the risk of falls and

frailty (Hare *et al.*, 1999). Older adults initiating a strength training program should use light weights and perform 2–3 sets of 8–12 repetitions for each of 8–12 exercises approximately 2–3 times per week; as with stretching, all major muscle groups should be included in the strength training program.

Aerobic exercise leads to improved physical performance and quality of life, and may increase the likelihood that older adults will remain independent in activities of daily living (McKelvie *et al.*, 2002; Hambrecht *et al.*, 2000; Belardinelli *et al.*, 1999; Keteyian *et al.*, 1996). For most older adults, walking is the most suitable form of aerobic exercise, but stationary cycling and swimming are appropriate alternatives. Older adults embarking on an exercise program should be advised to begin at a comfortable pace and exercise for a comfortable period of time. For HF patients, this may be as little as a few minutes of walking at a slow pace, but patients should not be discouraged by the fact that they are starting at a low level; indeed, data show that the greatest improvements occur in patients with the lowest baseline activity levels. Patients should exercise at least 4 to 5 days per week, gradually increasing the duration of exercise (but not the intensity) until it is possible to exercise comfortably and continuously for 20 to 30 minutes. Once this level of exercise capacity has been achieved, patients may consider further increasing the duration of exercise (e.g. up to 45 minutes) or gradually increasing the intensity. In either case, older HF patients should not exercise strenuously or to exhaustion. Additionally, patients should be instructed to stop exercising and contact their physician if they develop chest pain, undue shortness of breath, dizziness or syncope, or any other symptom that may indicate clinical instability. Finally, contraindications to exercise in elderly HF patients include decompensated HF, unstable coronary disease or arrhythmias, neurological or muscular disorders that preclude participation in an exercise program, or any other condition that would render exercise unsafe.

End of Life

The overall 5-year survival rate for older patients with established HF is less than 50%; that is, the prognosis is worse than for most forms of cancer (Croft *et al.*, 1999; MacIntyre *et al.*, 2000; Stewart *et al.*, 2001). Clinical features portending a less favorable outcome include older age, more severe symptoms and functional impairment, lower LV ejection fraction, underlying CAD, and impaired renal function (Krumholz *et al.*, 2000). Older patients with advanced HF, as evidenced by NYHA class III-IV symptoms, have a 1-year mortality rate of 25–50%; for these patients, HF can properly be considered a terminal illness. In addition, all HF patients are at risk for sudden arrhythmic death, which may occur during periods of apparent clinical stability. For these reasons, it is appropriate to address end-of-life issues early in the course of HF management, and to reconsider these issues periodically as the disease progresses or when changes in clinical status occur.

Although discussing end-of-life issues is often challenging for health-care providers as well as patients and families, specific measures should be undertaken to plan for and facilitate end-of-life care (Freisinger and Butler, 2000). These include the development of an advance directive and the appointment of a durable power of attorney. The advance directive should be as explicit as possible in defining circumstances under which the patient does not want to be hospitalized, placed on a respirator, subjected to other life-sustaining interventions (e.g. a feeding tube), or resuscitated. Since patients may alter their views about these issues as clinical circumstances evolve (Krumholz *et al.*, 1998b), it is important to maintain open communication throughout the disease process.

End-stage HF is frequently accompanied by considerable discomfort and anxiety, and data from the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) indicate that most patients and families have concerns about the quality of end-of-life care (Levenson *et al.*, 2000; Baker *et al.*, 2000). A cardinal principle of end-of-life care is to provide adequate relief of pain and suffering through the judicious use of conventional therapies in conjunction with narcotics (e.g. morphine), sedatives (e.g. benzodiazepines), and other comfort measures. Equally important is the provision of emotional support for the patient and family, assisted by nurses, members of the clergy, social service representatives, and other qualified health-care professionals. In some patients with terminal HF, institutional or home-based hospice care may be appropriate (Pantilat and Steimle, 2004).

PREVENTION

In light of the high prevalence and poor prognosis associated with HF in the elderly, it is evident that more effective means for the prevention of this disorder are needed. At present, the most effective preventive strategies involve aggressive treatment of established risk factors for the development of HF, especially hypertension and CAD. Several studies have shown that even modest declines in blood pressure are associated with substantial reductions in incident HF among elderly hypertensive patients (Table 6) (Amery *et al.*, 1985; Coope and Warrender, 1986; Dahlof *et al.*, 1991; The Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group, 1991; Staessen *et al.*, 1997; Gong *et al.*, 1996). Likewise, treatment of elevated cholesterol levels with an HMG-CoA reductase inhibitor ("statin") has been shown to decrease incident HF following an acute coronary event (Kjekshus *et al.*, 1997). Similarly, it is likely that smoking cessation, weight control in obese patients, and aggressive control of diabetes will all lead to a reduction in HF.

Thrombolytic therapy and coronary angioplasty will reduce infarct size and the subsequent risk for HF in patients with

Table 6 Effect of antihypertensive therapy on incident heart failure in older adults

Trial	*N*	Age range (years)	Reduction in heart failure
EWPHE (Amery *et al.*, 1985)	840	>60	22%
Coope (Coope and Warrender, 1986)	884	60–79	32%
STOP-HTN (Dahlof *et al.*, 1991)	1627	70–84	51%
SHEP (The Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group, 1991)	4736	≥60	55%
Syst-Eur (Staessen *et al.*, 1997)	4695	≥60	36%
STONE (Gong *et al.*, 1996)	1632	60–79	68%

EWPHE, European Working Party on Hypertension in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; STONE, Shanghai Trial of Nifedipine in the Elderly; STOP-HTN, Swedish Trial in Old Patients with Hypertension; Syst-Eur, Systolic Hypertension in Europe Trial.

acute MI, and a more widespread application of reperfusion therapies in elderly patients with acute MI should be strongly encouraged. In addition, asymptomatic LV systolic dysfunction is associated with a high rate of progression to clinical HF, and ACE inhibitors reduce the incidence of HF in these patients (Pfeffer *et al.*, 1992; The SOLVD Investigators, 1992). Therefore, documented systolic dysfunction mandates ACE-inhibitor therapy even in the absence of symptoms. Although routine screening for LV dysfunction is not justified at the present time, screening echocardiography may be worthwhile in high-risk older patients, such as those with known CAD or multiple coronary risk factors (McMurray *et al.*, 1998).

FUTURE DIRECTIONS

Current treatment of HF in the elderly is characterized by marked underutilization of proven therapies (Krumholz *et al.*, 1997), insufficient evidence to guide treatment in major patient subgroups (e.g. octogenarians and beyond, nursing home residents, patients with advanced comorbidities, and individuals with diastolic HF), and inattention to critically important psychobehavioral issues (e.g. compliance, personal preferences, and end-of-life care). Thus, there is a need for additional research aimed at developing more effective strategies for the prevention and treatment of acute and chronic HF in older adults.

As shown in Table 7, several new treatments for HF, both pharmacological and technological, are currently under investigation. While rigorous testing is essential for evaluating the impact of each of these new therapeutic modalities, there is hope that many of these interventions will make significant contributions toward reducing the burden of HF in our progressively aging population.

Table 7 New approaches to the treatment of chronic heart failure

Pharmacologic Agents
Neutral endopeptidase inhibitors
Endothelin receptor antagonists
Cytokine inhibitors
Calcium sensitizers
Therapeutic angiogenesis and antiangiogenesis
Inhibition of apoptosis
Gene therapy and pharmacogenomics
Hereditary disorders (e.g. cardiomyopathies, dyslipidemias)
Modulation of signaling pathways
Targeted therapy based on specific genetic profile
Implantable assist devices
Cell transplantation and growth-factor therapy
Xenotransplantation
Prevention of Cardiovascular Aging

KEY POINTS

- The incidence and prevalence of heart failure (HF) increase progressively with age, and chronic HF is predominantly a disorder of the elderly population.
- Age-related changes in the cardiovascular system, coupled with changes in other organ systems, predispose older patients to the development of HF, and also increase symptom severity, worsen prognosis, and complicate management.
- Compared to younger HF patients, older patients are more likely to be female, to have antecedent hypertension rather than coronary artery disease as the primary etiology, to have preserved left ventricular systolic function, and to have multiple comorbid conditions.
- Management of systolic HF is similar in older and younger patients, but limited data are available on the effects of most therapies in patients over 80 years of age, those with multiple comorbidities, and residents of long-term care facilities.
- Despite the fact that up to 50% of elderly HF patients have preserved left ventricular systolic function, few published randomized trials have addressed treatment of this condition, and to date no therapy has been shown to reduce mortality in patients with diastolic HF.
- Because of the complexity of managing HF in the elderly, the high prevalence of comorbid illnesses and polypharmacy, and the frequent coexistence of psychosocial and behavioral issues, older patients are best managed by utilizing a coordinated multidisciplinary team approach.

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Management of Acute Cardiac Emergencies and Cardiac Surgery

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CORONARY ARTERY BYPASS GRAFT SURGERY

The two indications for coronary revascularization in elderly persons with ischemic heart disease (IHD) (Table 1) are prolongation of life and relief of unacceptable symptoms despite optimal medical management (Eagle *et al.*, 1999; Braunwald *et al.*, 2000; Stemmer and Aronow, 2004; The TIME Investigators, 2001; Aronow, 2001; Aronow, 2003b; Woodworth *et al.*, 2002). The indications for coronary artery bypass graft surgery (CABGS) in elderly persons (Table 2) are

1. significant left main IHD;
2. significant left main equivalent IHD with proximal left anterior descending IHD plus proximal left circumflex IHD;
3. significant three-vessel IHD, especially in the presence of a decreased left ventricular (LV) ejection fraction and myocardial ischemia;
4. Significant two- or three-vessel IHD with a decreased LV ejection fraction and significant stenosis of the proximal left anterior descending coronary artery;
5. ST-segment depression in the resting electrocardiogram plus at least two of the following: New York Heart Association (NYHA) functional class III or 1V, history of myocardial infarction, history of hypertension, or all three without electrocardiographic changes;
6. significant two- or three-vessel IHD and exercise-induced ischemic ST-segment depression of 1.5 mm or greater;
7. clinical evidence of heart failure during ischemic episodes with ischemic but viable myocardium;
8. multivessel IHD in diabetics;
9. unacceptable symptoms despite optimal medical management.

Percutaneous transluminal coronary angioplasty or CABGS is recommended for (1) patients with one- or two-vessel IHD without significant proximal left anterior descending IHD and either a LV ejection fraction less than 50% or demonstrable myocardial ischemia on noninvasive testing; and (2) patients with one- or two-vessel IHD without significant proximal left anterior descending IHD but with a large area of viable myocardium and high-risk criteria on noninvasive testing (Braunwald *et al.*, 2000). Coronary angioplasty is also recommended for patients with multivessel IHD with a suitable coronary anatomy and with normal LV function and without diabetes mellitus (Braunwald *et al.*, 2000).

CABGS should be performed in elderly patients with life-threatening ventricular arrhythmias and left main IHD, three-vessel IHD, or bypassable one- or two-vessel IHD causing life-threatening ventricular arrhythmias (Eagle *et al.*, 1999). CABGS should also be performed in patients, after failed coronary angioplasty, who have ongoing myocardial ischemia or threatened occlusion with significant myocardium at risk or with hemodynamic compromise (Eagle *et al.*, 1999; Braunwald *et al.*, 2000).

The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease study reported adjusted 4-year survival rates for patients treated with medical management, coronary angioplasty, and CABGS (Graham *et al.*, 2002). Compared with medical therapy, the absolute risk reduction in 4-year mortality was 3.0% for coronary angioplasty and 4.2% for CABGS in patients younger than 70 years, 4.9% for coronary angioplasty and 8.2% for CABGS in patients aged 70–79 years, and 11.3% for coronary angioplasty and 17.0% for CABGS in patients aged 80 years and older (Graham *et al.*, 2002).

MECHANICAL COMPLICATIONS AFTER ACUTE MYOCARDIAL INFARCTION

Sudden or progressive hemodynamic deterioration with low cardiac output or pulmonary edema in patients with acute

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Table 1 Indications for coronary revascularization in older patients

1. Prolongation of life
2. Relief of unacceptable symptoms despite optimal medical management

Table 2 Indications for coronary artery bypass graft surgery in older patients

1. Significant left main IHD
2. Significant left main equivalent IHD with proximal left anterior descending IHD plus proximal left circumflex IHD
3. Significant three-vessel IHD, especially in the presence of a decreased LV ejection fraction and myocardial ischemia
4. Significant two- or three-vessel IHD with a decreased LV ejection fraction and significant stenosis of the proximal left anterior descending coronary artery
5. ST-segment depression in the resting electrocardiogram plus at least two of the following: NYHA functional class III or 1V, history of myocardial infarction, history of hypertension, or all three without electrocardiographic changes
6. Significant two- or three-vessel IHD and exercise-induced ischemic ST-segment depression of 1.5 mm or greater
7. Clinical evidence of heart failure during ischemic episodes with ischemic but viable myocardium
8. Multivessel IHD in diabetics
9. Unacceptable symptoms despite optimal medical management.

IHD, Ischemic Heart Disease; LV, Left Ventricular; NYHA, New York Heart Association.

myocardial infarction (MI) may be caused by acute mitral valve regurgitation, postinfarction ventricular septal defect, LV free wall rupture, or ventricular aneurysm (Bolooki, 1990; Labovitz *et al.*, 1984; Lemery *et al.*, 1992; Nunez *et al.*, 1983; Ryan *et al.*, 1996; Birnbaum *et al.*, 2002). Transthoracic or transesophageal echocardiography can usually establish the diagnosis. A balloon flotation catheter is helpful for the diagnosis and monitoring of therapy. Coronary angiography to detect the presence of surgically correctable IHD should be performed unless the patient is severely unstable hemodynamically because of the mechanical defect (Ryan *et al.*, 1996). Insertion of an intra-aortic balloon pump can help stabilize the patient.

Prompt surgical repair of these mechanical defects is usually indicated because medical treatment alone is associated with a 90% mortality (Labovitz *et al.*, 1984; Ryan *et al.*, 1996). The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines state that class I indications for emergent or urgent cardiac repair of mechanical defects caused by an acute MI are (1) papillary muscle rupture with severe acute mitral insufficiency (emergent); (2) postinfarction ventricular septal defect or free wall rupture and pulmonary edema or cardiogenic shock (emergent or urgent); and (3) postinfarction ventricular aneurysm associated with intractable ventricular tachyarrhythmias or pump failure (urgent) (Ryan *et al.*, 1996) (Table 3). Surgical repair may be deferred in patients with postinfarction ventricular septal defect if they are hemodynamically stable (Ryan *et al.*, 1996).

Table 3 Indications for emergent or urgent repair of mechanical defects caused by an acute myocardial infarction

1. Papillary muscle rupture with severe acute mitral regurgitation (emergent)
2. Postinfarction ventricular septal defect or free wall rupture and pulmonary edema or cardiogenic shock (emergent or urgent)
3. Postinfarction ventricular aneurysm associated with intractable ventricular tachyarrhythmias or pump failure (urgent)

CARDIOGENIC SHOCK

Cardiogenic shock is defined as the combination of markedly decreased cardiac output (cardiac index less than 1.8 liters/minute/meter), increased LV diastolic pressure or pulmonary wedge pressure (22 mm Hg or higher), hypotension (systolic blood pressure less than 80 mm Hg), and tissue hypoperfusion (e.g. impaired sensorium, prerenal azotemia) (Califf and Bengtson, 1994). This syndrome occurs twice as frequently in elderly patients with acute MI than in younger patients, and it accounts for most of the excess mortality associated with acute MI in the elderly (Leor *et al.*, 1993; Goldberg *et al.*, 1991; Berger *et al.*, 2002).

Since few patients survive cardiogenic shock in the absence of a treatable underlying disorder, immediate evaluation for a potentially correctable problem is critical. Emergent Doppler echocardiography should be performed to assess LV function and to rule out valvular lesions, pericardial disease, and septal perforation (Ryan *et al.*, 1996). Cardiac catheterization may be necessary if the diagnosis remains in doubt or as a prelude to coronary angioplasty or corrective surgery. Although emergent cardiac catheterization and coronary revascularization have been demonstrated to improve outcomes in patients up to age 75 years with cardiogenic shock complicating acute MI, patients older than 75 years may not benefit from these interventions (Hochman *et al.*, 1999).

In patients with a potentially reversible cause of shock, maximal aggressive therapy is indicated to stabilize the patient. In most cases, this will include assisted ventilation, an intra-aortic balloon pump (Anderson *et al.*, 1997), and intravenous vasoactive therapy. However, when cardiogenic shock is due to irreversible myocardial damage or other untreatable disorders, invasive interventions are unlikely to influence survival and should generally be avoided.

HEART FAILURE COMPLICATING MYOCARDIAL INFARCTION

Heart failure complicating acute MI is associated with a high mortality. Elderly patients with heart failure after MI had a 2.2 times higher mortality rate if they had an abnormal LV ejection fraction than if they had a normal LV ejection fraction (Aronow *et al.*, 2000).

Underlying causes and precipitating causes of heart failure should be treated when possible (Aronow, 2003a). Mechanical complications after MI must be ruled out with prompt surgical repair if present. Patients should be treated with supplemental oxygen, intravenous morphine, loop diuretics, intravenous nitroglycerin, angiotensin-converting enzyme

(ACE) inhibitors, and β-blockers (Aronow, 2003a). Calcium channel blockers, digoxin, and magnesium should not be used (Aronow, 2003a).

POSITIVE INOTROPIC DRUGS

If patients with acute MI have heart failure associated with severe LV systolic dysfunction and a low cardiac output with marked hypotension, intravenous norepinephrine should be given until the systolic arterial pressure increases to at least 80 mm Hg (Ryan *et al.*, 1996). These patients need balloon flotation right-heart catheter monitoring (Ryan *et al.*, 1996). Intravenous dopamine may then be given in a dose of 5–15 μg/kg/minute (Ryan *et al.*, 1996). After the systolic arterial pressure increases to 90 mm Hg, intravenous dobutamine may be given simultaneously to decrease the dosages of the norepinephrine and dopamine infusions (Ryan *et al.*, 1996). Intravenous milrinone given in a dose of 0.25–0.75 μg/kg/minute is reserved for patients who do not respond to catecholamines or who have significant arrhythmias, tachycardia, or myocardial ischemia induced by catecholamines (Ryan *et al.*, 1996).

Arrhythmic events are common in elderly patients with heart failure receiving intravenous dobutamine (Aronow, 2003b). Patients needing intravenous inotropic support should receive these drugs for as short a time as possible (Ryan *et al.*, 1996). Whenever possible, afterload-reducing drugs and intra-aortic balloon pumping should be substituted for positive inotropic drugs (Ryan *et al.*, 1996). Long-term intermittent therapy with intravenous dobutamine has been associated with increased ventricular arrhythmias and mortality (O'Connor *et al.*, 2000).

ARRHYTHMIAS COMPLICATING MYOCARDIAL INFARCTION

Patients with acute MI who develop ventricular fibrillation or sustained ventricular tachycardia should be treated with direct-current electric shock (Ryan *et al.*, 1996). β-blockers reduce mortality in postinfarction patients with complex ventricular arrhythmias and a LV ejection fraction of 40% or less (Kennedy *et al.*, 1994) or 40% and higher (Aronow *et al.*, 1994a; Aronow *et al.*, 1994b; Aronow *et al.*, 1994c) and should be administered to postinfarction patients with complex ventricular arrhythmias and no contraindications to β-blockers.

Patients with acute MI who develop bradyarrhythmias may need temporary pacing (Ryan *et al.*, 1996). The ACC/AHA recommendations for permanent pacing after acute MI are discussed elsewhere (Gregoratos *et al.*, 1998).

Direct-current cardioversion should be performed immediately in patients who have paroxysmal atrial fibrillation or atrial flutter with a very rapid ventricular rate associated with an acute MI, chest pain caused by myocardial ischemia, hypotension, severe heart failure, or syncope (Ryan *et al.*, 1996; Aronow, 2002). Heparin should be administered. Postinfarction patients with persistent atrial fibrillation should be treated with long-term warfarin to maintain an International Normalized Ratio (INR) of 2.0 to 3.0 plus ventricular rate control with a β-blocker plus digoxin, adding verapamil or diltiazem if necessary to slow the ventricular rate during exercise (Aronow, 2002; The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Investigators, 2002).

AORTIC STENOSIS

The frequency of aortic stenosis (AS) increases with age. Valvular AS diagnosed by Doppler echocardiography was present in 141 of 924 men (15%), mean age 80 years, and in 322 of 1881 women (17%), mean age 81 years (Aronow *et al.*, 2001). Severe valvular AS (peak gradient across aortic valve of $\geq$50 mm Hg or aortic valve area $<0.75\,cm^2$) was diagnosed in 62 of 2805 elderly patients (2%) (Aronow *et al.*, 2001).

Angina pectoris, syncope or near syncope, and CHF are the three classic manifestations of severe AS. CHF, syncope, or angina pectoris was present in 36 of 40 elderly patients (90%) with severe AS (Aronow *et al.*, 1998b). At 20-month follow-up of 40 elderly patients with severe AS, new coronary events developed in 93% of patients (Aronow *et al.*, 1998b).

In a prospective study, at 19-month follow-up (range 2 to 36 months), 90% of 30 patients with heart failure associated with unoperated severe AS and a normal LV ejection fraction were dead (Aronow *et al.*, 1993). At 13-month follow-up (range 2–24 months), 100% of 18 patients with heart failure associated with unoperated severe AS and an abnormal LV ejection fraction were dead (Aronow *et al.*, 1993).

Aortic valve replacement is the procedure of choice for symptomatic elderly patients with severe AS (Bonow *et al.*, 1998) (Table 4). Other Class I indications for aortic valve replacement in elderly patients with severe AS include patients undergoing CABGS or undergoing surgery on the aorta or other heart valves (Bonow *et al.*, 1998) (Table 4).

The bioprosthesis has less structural failure in elderly patients than in younger persons and may be preferable to the mechanical prosthetic valve for AS replacement in elderly persons because of the anticoagulation issue (Hammermeister *et al.*, 2000; Borkon *et al.*, 1988). Patients with mechanical prostheses need anticoagulant therapy indefinitely. Patients with porcine bioprostheses require anticoagulant therapy for 3 months after hospital discharge and then may be treated with antiplatelet therapy alone unless the patient has

Table 4 Indications for aortic valve replacement in older patients with severe aortic stenosis

1. Angina pectoris, syncope or near syncope, or congestive heart failure
2. Patients undergoing coronary artery bypass graft surgery
3. Patients undergoing surgery on the aorta or other heart valves

atrial fibrillation, abnormal LV ejection fraction, previous thromboembolism, or a hypercoagulable condition (Bonow *et al.*, 1998; Culliford *et al.*, 1991).

Arom *et al.* (1990) performed aortic valve replacement in 273 patients aged 70 to 89 years (mean age 75 years), 162 with aortic valve replacement alone, and 111 with aortic valve replacement plus CABGS. Operative mortality was 5%. Late mortality at 33-month follow-up was 18%. Actuarial analysis showed at 5-year follow-up that overall survival was 66% for patients with aortic valve replacement alone, 76% for patients with aortic valve replacement plus CABGS, and 74% for a similar age-group in the general population (Arom *et al.*, 1990).

A United Kingdom heart valve registry showed in 1100 patients aged 80 years and older (56% women) who underwent aortic valve replacement that the 30-day mortality was 6.6% (Asimakopoulos *et al.*, 1997). The actuarial survival was 89% at 1 year, 79% at 3 years, 69% at 5 years, and 46% at 8 years. The survival of patients with severe AS, a LV ejection fraction less than 35%, and a low transvalvular gradient at 1 year and at 4 years was 82% and 78% respectively in 39 patients, mean age 73 years, who underwent aortic valve replacement versus 41% and 15% respectively in 56 patients, mean age 75 years, in a control group (Pereira *et al.*, 2002).

If LV systolic dysfunction in patients with severe AS is associated with critical narrowing of the aortic valve rather than myocardial fibrosis, it often improves after successful aortic valve replacement (Connolly *et al.*, 1997). In 154 patients, mean age 73 years, with AS and a LV ejection fraction of 35% or lower who underwent aortic valve replacement, the 30-day mortality was 9%. The 5-year survival was 69% in patients without significant IHD and 39% in patients with significant IHD. NYHA functional class III or IV was present in 58% of patients before surgery versus 7% after surgery (Connolly *et al.*, 1997).

ACUTE AORTIC REGURGITATION

Acute aortic regurgitation (AR) in elderly patients may be due to infective endocarditis, rheumatic fever, aortic dissection, trauma following prosthetic valve surgery, or rupture of the sinus of Valsalva, and causes sudden severe LV failure. In patients with acute severe AR, the LV cannot adapt to the increased volume overload. Forward stroke volume falls, LV end-diastolic pressure increases rapidly to high levels (Welch *et al.*, 1957), and pulmonary hypertension and pulmonary edema result. The rapid rise of the LV end-diastolic pressure to exceed the left atrial pressure in early diastole causes premature closure of the mitral valve (Mann *et al.*, 1975). This prevents backward transmission of the elevated LV end-diastolic pressure to the pulmonary venous bed.

Patients with acute AR develop symptoms due to the sudden onset of heart failure with marked dyspnea and weakness. Patients with acute AR should have immediate aortic valve replacement because death may occur within hours to days.

CHRONIC AORTIC REGURGITATION

Chronic AR in elderly patients may be caused by valve leaflet disease or by aortic root disease. The prevalence of AR increases with age (Margonato *et al.*, 1989; Aronow and Kronzon, 1989). In a prospective study of 924 men, mean age 80 years, and 1881 women, mean age 82 years, valvular AR was diagnosed by pulsed Doppler recordings of the aortic valve in 282 of 924 men (31%) and in 542 of 1881 women (29%) (Aronow *et al.*, 2001). Severe or moderate AR was diagnosed in 16% of the elderly patients.

In a prospective study, at 24-month follow-up (range 7 to 55 months) of 17 patients, mean age 83 years, with heart failure associated with unoperated severe chronic AR and a normal LV ejection fraction, 15 patients (88%) were dead (Aronow *et al.*, 1994). At 15-month follow-up (range 8 to 21 months) of 8 patients, mean age 85 years, with heart failure associated with unoperated severe chronic AR and an abnormal LV ejection fraction, 8 patients (100%) were dead (Aronow *et al.*, 1994).

Patients with chronic severe AR should have aortic valve replacement if they develop symptoms of heart failure, angina pectoris, or syncope (Bonow *et al.*, 1991) (Table 5). Aortic valve replacement should also be performed in asymptomatic patients with chronic severe AR if they develop LV systolic dysfunction (Bonow *et al.*, 1991) (Table 5). Class I ACC/AHA indications for aortic valve replacement in patients with chronic severe AR include NYHA functional class III or IV symptoms and a LV ejection fraction of 50% or higher at rest; NYHA functional class II symptoms and a LV ejection fraction of 50% or higher at rest but with progressive LV dilatation or decreasing LV ejection fraction at rest on serial studies or decreasing effort tolerance on exercise testing; Canadian Heart Association functional class II or greater angina pectoris with or without IHD; asymptomatic or symptomatic patients with a resting LV ejection fraction of 25% to 49%; and patients undergoing CABGS or surgery on the aorta or other valves (Bonow *et al.*, 1998) (Table 5).

Elderly patients undergoing aortic valve replacement for severe AR have an excellent postoperative survival if the preoperative LV ejection fraction is normal (Bonow *et al.*,

Table 5 Indications for aortic valve replacement in older patients with severe chronic aortic regurgitation

1. Symptoms of heart failure, angina pectoris, or syncope
2. Asymptomatic patients who develop LV systolic dysfunction
3. NYHA functional class III or IV symptoms and a LV ejection fraction of 50% or higher at rest
4. NYHA functional class II symptoms and a LV ejection fraction of 50% or higher at rest but with progressive LV dilatation or decreasing LV ejection fraction at rest on serial studies or decreasing effort tolerance on exercise testing
5. Canadian Heart Association functional class II or greater angina pectoris with or without ischemic heart disease
6. Asymptomatic or symptomatic patients with a resting LV ejection fraction of 25% to 49%
7. Patients undergoing coronary artery bypass graft surgery or surgery on the aorta or other heart valves

LV, Left Ventricular; NYHA, New York Heart Association.

1985; Bonow, 1986; Turina *et al.*, 1998). If LV systolic dysfunction was present for less than 1 year, patients also did well postoperatively. However, if the patient with severe AR has an abnormal LV ejection fraction and impaired exercise tolerance and/or the presence of LV systolic dysfunction for longer than 1 year, the postoperative survival is poor (Bonow *et al.*, 1985; Bonow, 1986; Turina *et al.*, 1998). After aortic valve replacement, women exhibit an excess late mortality, suggesting that surgical correction of severe chronic AR should be considered at an earlier stage in women (Klodas *et al.*, 1996).

The operative mortality for aortic valve replacement in elderly patients with severe AR is similar to that in elderly patients with aortic valve replacement for valvular AS. The mortality rate is slightly increased in patients with infective endocarditis and in those patients needing replacement of the ascending aorta plus aortic valve replacement. The bioprosthesis is preferable to the mechanical prosthetic valve for aortic valve replacement in elderly patients as in elderly patients with valvular AS (Hammermeister *et al.*, 2000; Borkon *et al.*, 1988). Patients with porcine bioprostheses require anticoagulant therapy for 3 months after hospital discharge and then may be treated with antiplatelet therapy alone unless they have atrial fibrillation, abnormal LV ejection fraction, previous thromboembolism, or a hypercoagulable state (Bonow *et al.*, 1998; Borkon *et al.*, 1988).

ACUTE MITRAL REGURGITATION

Acute severe mitral regurgitation (MR) in older persons may be caused by ruptured *chordae tendineae* or development of a flail mitral valve leaflet due to acute MI, infective endocarditis, papillary muscle rupture, or mucoid degeneration of the mitral valve cusps. Acute severe MR usually causes biventricular failure with pulmonary edema and systemic venous engorgement.

Doppler echocardiography confirms the presence of severe MR. Transesophageal echocardiography provides an accurate anatomic assessment of the etiology of acute MR and assists in determining whether the mitral valve can be repaired or if it must be replaced (Enriquez-Sarano *et al.*, 1999). Heart failure often responds poorly or only transiently to medical therapy. In severe cases, an intra-aortic balloon pump may facilitate hemodynamic stabilization while awaiting surgery. Infective endocarditis should be treated with appropriate intravenous antibiotics. Mitral valve surgery should be performed urgently in persons who fail to respond to medical therapy.

CHRONIC MITRAL REGURGITATION

Valvular causes of chronic MR in older persons include mitral annular calcium, papillary muscle dysfunction after MI, rheumatic heart disease, myxomatous degeneration of the mitral valve leaflets and chordae tendineae with mitral valve prolapse, ruptured chordae tendineae, and prior endocarditis. MR may also result from alteration in the geometry of the LV and mitral apparatus due to dilated cardiomyopathy. In one study, chronic MR was present in 298 of 924 men (32%), mean age 80 years, and in 630 of 1881 women (33%), mean age 81 years (Aronow *et al.*, 2001). Moderate or severe MR was present in 10% of 2148 persons, mean age 81 years (Aronow *et al.*, 1998a).

Dyspnea on exertion develops with severe MR, progressing to orthopnea, paroxysmal nocturnal dyspnea, and dyspnea at rest caused by left-sided heart failure. Right-sided heart failure leads to ankle swelling, anorexia, and right upper abdominal tenderness due to hepatic congestion. The development of atrial fibrillation may cause palpitations and worsening symptoms of heart failure. In some older persons, acute pulmonary edema may be the initial manifestation of chronic severe MR. Doppler echocardiography can quantitate the severity of MR and assess LV size and function. Doppler echocardiography and especially transesophageal echocardiography may also aid in determining the etiology of MR.

ACC/AHA Class I indications for performing mitral valve surgery in persons with nonischemic severe MR include (1) acute symptomatic MR for which mitral valve repair is likely; (2) NYHA class II, III, or IV symptoms with normal LV function (LV ejection fraction $>60\%$ and LV end-systolic dimension <45 mm); (3) mild LV dysfunction (LV ejection fraction 50–60% and LV end-systolic dimension 45–50 mm), with or without symptoms; and 4) moderate LV dysfunction (LV ejection fraction 30–50% and/or LV end-systolic dimension 50–55 mm), with or without symptoms (Bonow *et al.*, 1998).

Older persons with symptomatic chronic severe MR and severely depressed LV function (LV ejection fraction $<30\%$ or LV end-systolic dimension >55 mm) should be treated medically (Bonow *et al.*, 1998). Older persons with chronic nonischemic MR and NYHA class I symptoms with normal LV function should be followed at 3–6 month intervals (Bonow *et al.*, 1998). If LV dysfunction, atrial fibrillation, or pulmonary hypertension develops, cardiac catheterization and possible mitral valve surgery should be considered, especially if it appears that mitral valve repair may be feasible (Bonow *et al.*, 1998).

The prognosis for ischemic MR, which is more common with advancing age, is worse than that for MR due to other causes. CABGS may improve LV function and reduce ischemic MR (Bonow *et al.*, 1998). However, the best operation for ischemic MR remains controversial (Bonow *et al.*, 1998). Mitral valve surgery for ischemic or cardiomyopathic MR is also controversial when MR is not severe (Borer and Bonow, 2003).

Warfarin should be administered to patients who have a mechanical mitral valve, indefinitely. The INR should be maintained between 2.5 and 3.5 (Bonow *et al.*, 1998). Patients with a bioprosthetic mitral valve should be treated with warfarin for the first 3 months after mitral valve replacement (Bonow *et al.*, 1998). Then aspirin 100 mg may be administered daily if the elderly patient has no risk factor (Bonow *et al.*, 1998). However, if the elderly patient

has either atrial fibrillation, LV systolic dysfunction, prior thromboembolism, or a hypercoagulable condition, long-term warfarin therapy needs to be administered with the INR maintained between 2.5 and 3.5 (Bonow *et al.*, 1998).

MITRAL STENOSIS

The most common cause of mitral stenosis (MS) in elderly persons is nonrheumatic MAC. Rheumatic MS diagnosed by Doppler echocardiography has been reported in 3 of 924 men (0.3%), mean age 80 years, and in 34 of 1881 women (2%), mean age 81 years (Aronow *et al.*, 2001). In a study of 1699 persons, mean age 81 years, the prevalence of rheumatic MS was 6% in older persons with atrial fibrillation and 0.4% in older persons with sinus rhythm (Aronow *et al.*, 1995).

Doppler echocardiography is the procedure of choice for diagnosing MS and assessing its severity. The cause of death in untreated persons with MS is progressive heart failure in 60–70%, systemic embolism in 20–30%, pulmonary embolism in 10%, and infection in 1–5% (Bonow *et al.*, 1998).

Percutaneous balloon valvotomy (PBV) carries a class I indication for use in persons with MS in the presence of class II, III, or IV symptoms; moderate or severe MS; and valve morphology favorable for PBV (flexible leaflets with limited calcification) in the absence of left atrial thrombus or moderate to severe MR (Bonow *et al.*, 1998). For the few older persons who meet these criteria, PBV is the procedure of choice (Iung *et al.*, 2000). Mitral valve repair should be performed in persons with class III or IV symptoms, moderate or severe MS, and valve morphology favorable for repair if PBV is not available or is contraindicated. In persons with a nonpliable or calcified mitral valve, the decision to proceed with valve repair or replacement is made at the time of surgery (Bonow *et al.*, 1998). In most older persons with symptomatic MS, valve replacement is required because the heavily calcified mitral valve is not amenable to open commissurotomy.

INFECTIVE ENDOCARDITIS

The incidence of infective endocarditis increases with age because of the increased prevalence of valvular abnormalities and potential sources of bacteremia (e.g. poor dentition, urinary tract infections, invasive procedures). The pathogens associated with endocarditis are similar in elderly and younger persons, with gram-positive cocci (streptococci, staphylococci, enterococci) being most common, followed by gram-negative bacilli. Up to 10% of infective endocarditis in older persons is culture-negative, usually due to initiation of antibiotic therapy prior to obtaining blood cultures.

Echocardiography is useful for detecting valvular vegetations, valvular regurgitation, ventricular dysfunction, abscesses, shunts, and ruptured *chordae tendineae*. Transesophageal echocardiography is more sensitive than transthoracic echocardiography in detecting vegetations. Echocardiography may be useful also in persons with culture-negative endocarditis and for the diagnosis of persistent bacteremia of unknown cause.

Surgery is indicated in persons with life-threatening heart failure or cardiogenic shock due to surgically treatable valvular heart disease with infective endocarditis. Class I indications for surgery for persons with native valve endocarditis, include (1) acute AR or MR associated with heart failure; (2) acute AR with tachycardia and premature closure of the mitral valve; (3) fungal endocarditis; (4) annular or aortic abscess; true or false aneurysm of the ascending aorta or sinus of Valsalva and (5) valve dysfunction and persistent infection after 7–10 days of appropriate antibiotic therapy, as evidenced by fever, leukocytosis, and bacteremia, provided there are no noncardiac causes for infection (Bonow *et al.*, 1998).

Class I indications for surgery for persons with prosthetic valve endocarditis include (1) 2 months or less after surgery; (2) heart failure with prosthetic valve dysfunction; (3) fungal endocarditis; (4) staphylococcal endocarditis not responding to antibiotic therapy; (5) paravalvular leak, annular or aortic abscess, true or false aneurysm of the ascending aorta or sinus of Valsalva, fistula formation, or new-onset conduction disturbances; and (6) infection with gram-negative organisms or organisms with a poor response to antibiotics (Bonow *et al.*, 1998).

KEY POINTS

- Significant left main IHD, significant left main equivalent IHD, and significant three-vessel IHD, especially in the presence of a decreased LV ejection fraction and myocardial ischemia are some of the indications for performing coronary artery bypass surgery to prolong life in elderly persons with IHD.
- Aortic valve replacement is the procedure of choice in symptomatic elderly persons with severe AS.
- Patients with chronic severe AR should have aortic valve replacement if they develop symptoms of heart failure, angina pectoris, or syncope.
- Older persons with symptomatic chronic severe MR and severely depressed LV function (LV ejection fraction $<30\%$ or LV end-systolic dimension >55 mm) should be treated medically.
- Surgery is indicated in persons with life-threatening heart failure or cardiogenic shock due to surgically treatable valvular heart disease with infective endocarditis.

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Cardiac Surgery in the Elderly

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INTRODUCTION

The first successful elective closed-heart operation, a mitral valvotomy, was done in 1923, because "there was no alternative and patients were already dying" (Harken, 1989). Advances in technology, pharmacology, and the science of medicine have since enabled physicians and surgeons to successfully treat a multitude of previously "terminal" conditions. The primary enabling technology that led to the exponential growth in modern cardiac surgery was the development of the heart-lung machine in 1953. In 1974, 50 open-heart operations per million population were performed in Europe, increasing to 450 per million in 1994, and in 2004, current western economies' estimated needs are 1000 to 1250 cardiac operations per million population.

Physicians today are no longer faced with the dilemma – "is there something we can do", but rather a multitude of choices from a menu of high-technology procedures. The question is no longer "what can we do" to relieve symptoms or improve prognosis but rather "what should we do", and this must be answered in terms of outcome, mortality and morbidity risk in relation to the expected improvement in quality of life. This philosophy is particularly important when assessing the elderly patient for possible cardiac surgery.

Life expectancy, especially in western economies, has increased significantly during the past 50 years, and in 2002, the average life expectancy in Europe was 82 years for women and 76 years for men (compared to 1980 at 77 and 71 years, respectively) (EUROSTAT, 2004). As a result, the elderly population is increasing and population age projections are that in 2020, 30% of the German, 25% of the United Kingdom, and 23% of the United States populations will be over the age of 60. Moreover, the number of people aged 75–84 will have increased by 50% from 1991 to 2031 in England and Wales (Pathy, 1999). The importance of these projections is that cardiovascular disease is the leading cause of morbidity and mortality in the elderly (Alexander *et al.*, 2000), and it is estimated that 25–40% of octogenarians have symptomatic cardiac disease (Kohl *et al.*, 2001).

Cardiac surgery epitomizes modern expensive high-technology medicine, and the elderly may be seen as less deserving of this expensive resource. However, the true cost of conservative medical therapy versus surgical options is not clearly known. Arguments of limited resources and costs of providing increasingly expensive therapeutic options should not be a major consideration in the decision making for the clinician. As physicians, we need to remain "the patient's advocate" and advise accordingly.

In a private health-care market, it is the individual patient's decision as to the level of health care he or she can afford. Whereas in socialized health-care systems, it is the elected politicians who must admit publicly what proportion and aspect of health care will be the State's responsibility as opposed to every citizen's individual responsibility, in the event that the State or National Health Service cannot afford everything that medical science has invented for every citizen. Politicians must dictate how, if unavoidable, rationing of free health care is to be implemented at the level of individual patients or health interventions. Clinicians working in socialized health-care systems must not allow themselves to be manipulated into assuming the role of health-care rationers by default.

The elderly increasingly continue to enjoy an active lifestyle and not unexpectedly want a good quality of life. Therefore, many feel that a high-operative risk, that is, death on the operating table is an acceptable alternative to increasing debilitating symptoms in the last few years of life. The decision when to offer or "deny" cardiac surgery cannot be based solely on age and a perceived excessive predicted mortality in the elderly, especially if one reflects on the aforementioned history of the beginnings of cardiac surgery and rapidity of improved recent outcomes.

Cardiac surgery outcome in terms of mortality has continually improved as a result of the development of less traumatic heart-lung machines, more effective myocardial protection strategies, and improved perioperative care. In the 1950s, the operative mortality for a mitral valvotomy approached 60%, (Alexander *et al.*, 2000) whereas today, the expected

Principles and Practice of Geriatric Medicine, 4th Edition. Edited by M.S. John Pathy, Alan J. Sinclair and John E. Morley.
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mortality for a mitral valvotomy is less than 0.5%. In the 1970s, cardiac surgery in the septuagenarian was considered a rarity worthwhile of a case report, but now, in the early twenty-first century, the mortality risks for selected octogenarians, nonagenarians, and even centenarians, who do not have significant comorbidities, undergoing cardiac surgery approaches that of younger patients (Alexander *et al.*, 2000; Bridges *et al.*, 2003). Careful preoperative patient selection based on comorbid risk factors should therefore be the primary determinant when advising surgery in the elderly.

The mean age of patients undergoing cardiac surgery is progressively increasing and many octogenarians are now successfully undergoing cardiac surgery (Peterson *et al.*, 1995). In the United Kingdom, the proportion of patients undergoing isolated coronary artery bypass graft (CABG) surgery over the age of 75 has increased from 2.2% to 10% over the last decade, and almost 30% of CABG patients are now over 70 years old (Figure 1) (Keogh & Kinsman, 2004). Similarly, 42% of patients undergoing heart valve surgery in the United Kingdom are now over 70 years old (Figure 2) (Keogh & Kinsman, 2004).

Age *per se* is not a contraindication for cardiac surgery provided the elderly patient can be discharged without significant disability and loss of independence.

CARDIAC SURGERY OUTCOMES IN THE ELDERLY

Mortality

The mortality of cardiac surgery increases with the complexity of the required procedure, which is usually grouped in terms of CABG alone, valve repair or replacement alone (Valve-only), and CABG with concomitant valve surgery (CABG + Valve; Figure 3) (Bridges *et al.*, 2003).

Operative mortality increases with age as do postoperative complications such as requirement for new hemodialysis

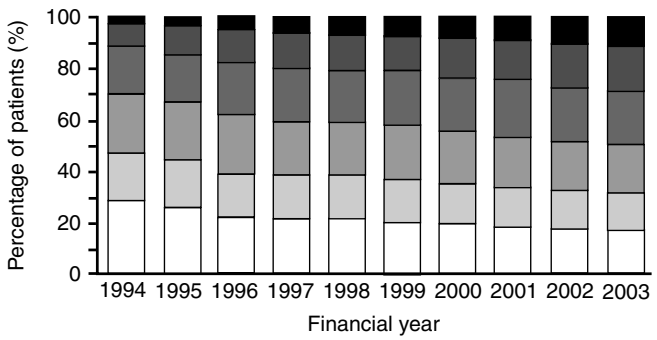

Figure 1 Age categories, by financial year, of 140 641 patients who underwent isolated coronary artery bypass graft surgery in the United Kingdom. Age categories are; <56 years (clear bar), in increasing shades 56–60 years, 61–65 years, 66–70 years, 71–75 years, and >75 years (solid bar) (Data derived from the UK National Adult Cardiac Surgical Database, and reprinted from Keogh & Kinsman (2004), with permission from Dendrite Clinical Systems Ltd and The Society of Cardiothoracic Surgeons of Great Britain and Ireland)

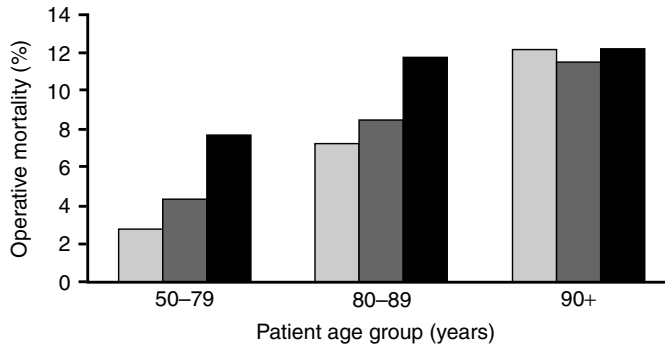

Figure 3 Unadjusted cardiac surgery mortality by patient age-group (50 to 79 years – 621 360 patients, 80 to 89 years – 59 576 patients, 90 to 99 years – 1092 patients, 100 years plus – 5 patients) undergoing isolated coronary artery bypass graft surgery (light shade bar), valve repair or replacement surgery alone (middle shade bar), or combined CABG, and valve surgery (solid bar). (Compiled from data published from the Society of Thoracic Surgeons National Cardiac Database (USA; 1997–2000) (Bridges *et al.*, 2003))

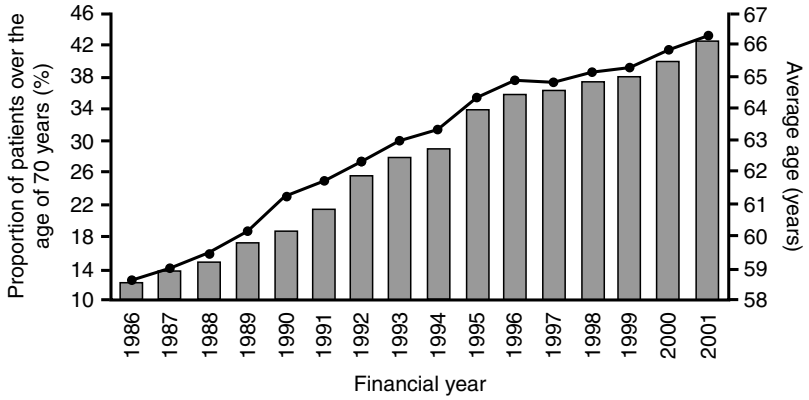

Figure 2 Age trends, by financial year, of patients who underwent heart valve surgery in the United Kingdom. The percentage of patients over the age of 70 is shown by the bar graph, and the average age by the solid line (Data derived from the UK Heart Valve Registry and reprinted from Keogh & Kinsman (2004), with permission from Dendrite Clinical Systems Ltd and The Society of Cardiothoracic Surgeons of Great Britain and Ireland)

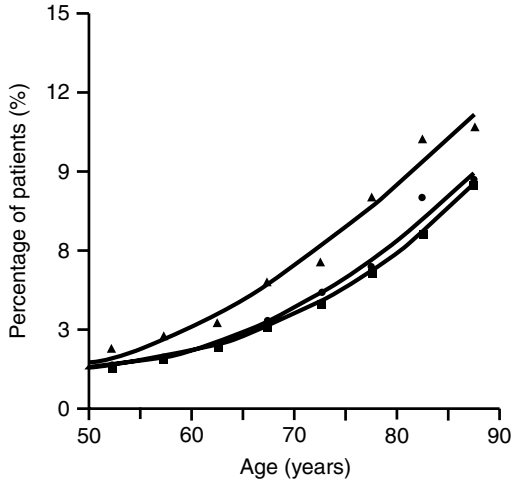

Figure 4 The rate of complications; in-hospital mortality (solid circles), neurological events (stroke, transient ischemic attacks, or coma; solid triangles), and renal failure (oliguria with a creatinine $>1\,\mathrm{mg\,dl^{-1}}$ or dialysis; solid boxes), by age in 64 467 patients following coronary artery bypass graft, with or without concomitant valve, surgery. (Reprinted with permission from the American College of Cardiology Foundation (Alexander *et al.*, 2000))

(usually temporary; nonagenarian 9.2%, octogenarian 7.7% versus 3.5% in younger age-groups), stroke, prolonged ventilation, and length of hospital stay (Figure 4) (Alexander *et al.*, 2000; Bridges *et al.*, 2003). Nevertheless, the crude mortality associated with cardiac surgery in the octogenarian has now decreased to less than 5–11%, with a postoperative actuarial 5-year survival of 60–75% (Akins *et al.*, 1997; Williams *et al.*, 1995).

Previous studies have identified several pre- and postoperative risk factors associated with increased mortality in octogenarians undergoing first-time open-heart operations. These comorbid risk factors include New York Heart Association (NYHA) dyspnea class III or IV, female gender, previous myocardial infarction, triple-vessel coronary artery disease, depressed left ventricular ejection fraction, chronic obstructive pulmonary disease, higher left ventricular end-diastolic pressure, preoperative intra-aortic balloon pump (IABP), congestive heart failure, mitral valve operation, urgency of operation, chronic renal disease, peripheral and cerebrovascular disease, postoperative stroke, and sternal wound infection (Akins *et al.*, 1997; Williams *et al.*, 1995; Peterson *et al.*, 1995).

Morbidity – Neurological Dysfunction (*see* Chapter 134, Rehabilitation; Chapter 72, Secondary Stroke)

The postoperative complication of greatest concern following cardiac surgery is a cerebrovascular accident (CVA), which is usually embolic in etiology. Preexisting comorbid risk factors for perioperative CVAs following cardiac surgery include surrogate markers for atheroembolic disease such as a history of peripheral vascular disease, previous CVA, transient ischemic attack (TIA), carotid bruits, diabetes mellitus, or renal failure as well as markers for thromboembolic disease such as poor left ventricular function and atrial fibrillation (Charlesworth *et al.*, 2003).

The risk of a perioperative stroke is higher in the elderly, primarily because the elderly tend to have more atheromatous plaque in the aorta as well as head and neck vessels (Figure 5) (Blauth *et al.*, 1992). Manipulation of the atherosclerotic ascending aorta increases the probability of atheroembolism and consequent stroke. It is therefore important to identify elderly patients who are at increased risk of sustaining a perioperative stroke preoperatively in order to institute additional intraoperative protective strategies.

Preoperative identification of patients with carotid artery disease is important, and the current guideline used at the University Hospital of Wales for patients undergoing cardiac surgery is to screen patients with carotid duplex imaging, if any of the aforementioned risk factors for atheroembolic disease are present. In addition, we screen patients with coronary artery disease who are over the age of 65 who have either left main stem disease, diabetes mellitus, or peripheral vascular disease, and patients under the age of 65 with any two of the aforementioned risk factors (Table 1). Carotid artery disease is uncommon in the cardiac surgical patient who does not have coronary artery disease.

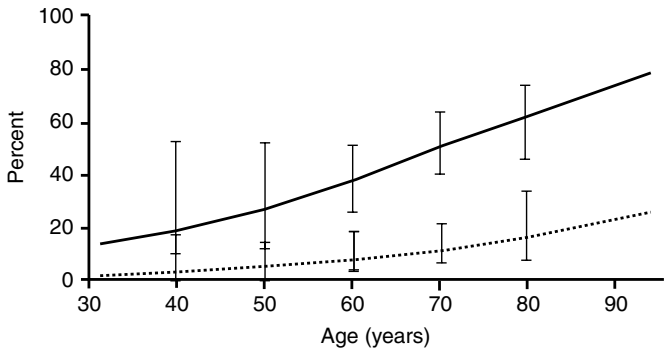

Figure 5 Probability of finding atheroemboli in organs, other than the heart or lungs, at 221 autopsies after cardiac operations for ischemic or valvular heart disease, according to age and the presence of a preoperative history of peripheral vascular disease (solid line) or no history thereof (dashed line) (Reprinted with permission from American Association for Thoracic Surgery (Blauth *et al.*, 1992))

Table 1 Risk factors for internal carotid artery atheromatous disease

Risk factors for internal carotid artery atheromatous disease
• Carotid bruit
• Previous cerebrovascular accident
• Previous transient ischemic attack
• Peripheral vascular disease
• Diabetes mellitus
• Left main stem coronary artery disease
– If age greater than 65 years

Patients scheduled for cardiac surgery who have coexisting symptomatic or asymptomatic carotid artery disease should then be assessed as to whether carotid artery endarterectomy is indicated either prior to or as a combined procedure with their cardiac surgery.

Intraoperative mechanisms of identifying ascending aortic atherosclerotic plaque are becoming essential in the elderly and include epiaortic Doppler ultrasound assessment of the ascending aorta. If significant atherosclerotic plaque is identified, then reducing ascending aortic manipulation such as off-pump surgery but without any manipulation of the ascending aorta, cardiopulmonary bypass using single cross-clamp techniques, and the use of ascending aortic filtration devices are available techniques that can potentially reduce the risk of intraoperative atheroembolism.

Not only does a stroke significantly reduce postoperative quality of life but is also associated with a high late mortality following hospital discharge.

More minor neurocognitive dysfunction such as memory loss and changes in visual acuity are also common after cardiac surgery and the etiology is multifactorial. Off-pump CABG and improvements in the management of cardiopulmonary bypass; use of membrane oxygenators as opposed to older bubble oxygenators; and routine use of arterial filters in the bypass circuit have assisted in reducing these complications. Nevertheless, preexisting comorbid neurological risk factors, especially confusional states of indeterminate origin, should be considered relative contraindications to cardiac surgery in the elderly, as undergoing open-heart surgery may aggravate them.

Long-term outcome following successful cardiac surgery in terms of both late neurological events and mortality is also strongly related to the presence of atherosclerosis of the ascending aorta (Dávila-Román *et al.*, 1999). The presence of severe ascending atherosclerosis at the time of cardiac surgery in patients aged 50 or more was associated with a 10% incidence of perioperative or late neurologic events, compared to 4% in patients with normal or only mild ascending aortic atherosclerosis (Dávila-Román *et al.*, 1999). Additional risk factors for late neurological events include hypertension and diabetes.

Morbidity – Renal Dysfunction

Predictors for postcardiac surgery renal dysfunction requiring hemofiltration or dialysis include atherosclerosis of the ascending aorta, advanced age, poor heart function, female gender, preexisting renal dysfunction (serum creatinine greater than $150\,\mu\mathrm{mol}\,\mathrm{l}^{-1}$), duration of cardiopulmonary bypass, and low postoperative cardiac output (Weerasinghe *et al.*, 2001). Postcardiac surgery renal support, although usually temporary, is associated with an increased mortality, and therefore, additional renal protective strategies such as reducing the inflammatory impact of cardiopulmonary bypass and metabolic mechanisms of improving renal blood flow are currently being investigated.

ASSESSMENT OF THE ELDERLY PATIENT FOR CARDIAC SURGERY

An improved longer-term prognosis is a frequent indication for cardiac surgery in younger patients; however, in the elderly, this is less of an issue. Patients must be assessed individually in terms of the natural history of their disease, symptoms thereof, current quality of life, and the risk (mortality and morbidity) versus benefit (improved quality of life) of any potential surgical intervention.

Operative Risk – Estimated Mortality for Cardiac Surgery

Mortality following cardiac surgery usually refers to either in-hospital, that is, deaths occurring within the base hospital during the same admission, or 30-day mortality, that is, deaths within 30 days of surgery. In the United Kingdom, the former definition is currently more commonly used. Crude mortality though fails as a comparative measure of quality between hospitals or surgeons, if there are major variations in case-mix comparisons. A mechanism of risk stratification based on preoperative factors that increase operative mortality risks, such as the elderly, is therefore essential if referral patterns, allocation of resources, and discouragement of the treatment of high-risk patients are to be avoided. Without risk stratification, surgeons and hospitals treating high-risk patients will appear, on the basis of crude mortality, to have worse results than others (Nashef *et al.*, 1999).

The estimated risk of undergoing a given cardiac procedure is therefore better determined from known preoperative risk factors and calculating the Euro Score (European System for Cardiac Operative Risk Evaluation Score), which is a weighted additive score that is used preoperatively to provide an estimated predicted operative mortality (Table 2) (Nashef *et al.*, 1999).

The Euro Score has been shown to provide a good correlation with actual observed mortality in the lower risk groups, but is less accurate and tends to underestimate actual operative morality when the predicted operative mortality risk exceeds 9%. In the higher-risk groups, the alternative logistic Euro Score mathematical model appears to slightly improve prediction; however, the original additive model remains a useful, simple, and user-friendlier clinical tool.

Predicted Euro Score operative mortality is a useful guideline of immediate risk, although in the future, procedural 1-year mortality or more will become additional useful assessments for predicting "true" outcome.

Benefit of Surgery – Intended Improved Quality of Life Following Surgery

Increased survival is no longer the primary benefit of cardiac surgery in the elderly and should therefore not necessarily be

Table 2 Weighted risk factors relevant to a specific individual patient are added and this then provides the Euro Score predicted mortality (%) for that patient to undergo the proposed cardiac surgical procedure (range 0–42%)

Risk Factors and Definitions	Weighted-score
Patient-related factors	
Age (Years)	
60–64	1
65–69	2
70–74	3
75–79	4
80–84	5
85–89	6
Equal to or greater than 90	7
Gender female	1
Chronic pulmonary disease	
Long-term use of bronchodilators or steroids for lung disease	1
Extracardiac arteriopathy (any or more of following)	
History of intermittent claudication, internal carotid occlusion greater than 50% stenosis, previous or planned abdominal aortic, limb or carotid vascular surgery	2
Neurologic dysfunction	
Severely affecting ambulation or day-to-day function	2
Previous cardiac surgery	
Requiring pericardial opening	3
Renal dysfunction	
Serum creatinine greater than 200 μmol l^{-1} prior to surgery	2
Active endocarditis	
Still under antibiotic treatment for endocarditis at time of surgery	3
Critical preoperative state (any or more of following)	
Ventricular tachycardia, ventricular fibrillation or aborted sudden death preoperative cardiac massage, preoperative inotropic or intra-aortic balloon pump support, preoperative ventilation before arrival in anesthetic room, preoperative acute renal failure (anuria or oliguria $<$10 ml/hour)	3
Cardiac-related factors	
Unstable angina	
Rest angina requiring intravenous nitrates preoperatively until theater	2
Left ventricular dysfunction	
Moderate (left ventricular ejection fraction 30–50%)	1
Poor (left ventricular ejection fraction $<$30%)	3
Recent myocardial infarct	
Within 90 days of surgery	2
Pulmonary hypertension	
Pulmonary artery systolic pressure $>$60 mmHg	2
Operation-related factors	
Emergency surgery	
Carried out on referral before the beginning of the next working day	2
Other than isolated CABG	
Major cardiac surgery other than or in addition to CABG	2
Surgery on thoracic aorta	
For disease of ascending, arch, or descending thoracic aorta	3
Postinfarction ischemic ventricular septal defect	4
Euro Score Predicted Mortality (%)	
Derived by the addition of the above relevant risk factor scores for each individual patient	

Source: Reprinted from (Nashef *et al.*, 1999) with permission from Elsevier.

the primary outcome indicator, but rather improvements in quality of life. Estimating improvements in quality of life intended by a proposed cardiac surgical procedure, although difficult, is essential to assess when making these critical decisions in the elderly.

A basic estimate of the perceived value of a cardiac procedure has been the perceived improvement in the NYHA dyspnea score, but this does not fully address the broader aspect of quality of life. The SF-36 health survey questionnaire assesses eight general health concepts: physical

functioning, bodily pain, role limitation because of personal or emotional problems, emotional well-being, social functioning, energy or fatigue, and general health perceptions (Brazier *et al.*, 1992). A study of octogenarians who had undergone cardiac surgery showed SF-36 scores equal or better than those of the general population of age greater than 65 (Fruitman *et al.*, 1999). Moreover, 84–94% of octogenarian operative survivors continue living on their own, and 83–98% indicate that they would in retrospect undergo cardiac surgery again because of the improvements in their lifestyle (Fruitman *et al.*, 1999; Hewitt *et al.*, 2003).

Elderly patients can undergo cardiac surgical procedures at a reasonable risk and show significant improvement in their symptoms, functional status and quality of life. The challenge facing physicians treating the geriatric population is in selecting those patients whose quality of life will be improved by cardiac surgery, when indicated. To date preoperative quality-of-life assessments such as the SF-36 questionnaire have not been used to guide preoperative decision making. An alternative simpler assessment is the EQ-5D or EuroQol, which assesses the level of mobility, self-care, usual activity, pain or discomfort, and anxiety or depression, and may well assist in preoperative decision making (Table 3) (Sollano *et al.*, 1998).

The perceived potential benefit of an intended surgical procedure must then be individualized in the elderly and be based on both preoperative symptoms as well as the perceived potential improvement in the level of independent lifestyle.

The elderly more frequently have additional coexistent medical conditions, which may frequently worsen, after cardiac surgery. Coexistent medical conditions must therefore be taken into account in terms of the patient's quality of life; however, in practice, they usually have a more minor impact on quality of life than the cardiac condition (Hewitt *et al.*, 2003).

A confounding factor though in the assessment of the elderly for cardiac surgery is that suboptimal timing of surgery, namely, excessively late referral for surgery, has a significant negative impact on both operative risk and late outcome (Lee *et al.*, 1997). The elderly are more sedentary, may not notice milder symptoms, or may attribute symptoms to increasing age and may thus present late. Mild symptoms in the elderly should therefore not preclude further investigations such as echocardiography and coronary angiography, in order to more accurately determine the presence and extent of any underlying cardiac disease.

Complete assessment on initial presentation is critical, because if an initial decision not to proceed with surgery is contemplated and symptoms progress, ongoing medical treatment is unlikely to be successful. The combined effect then of delay, deteriorating cardiac status, and exacerbating end organ dysfunction (i.e. renal, pulmonary) may render an otherwise operable candidate beyond salvage (Avery *et al.*, 2001; Hewitt *et al.*, 2003).

Table 3 EuroQol questionnaire, which assesses five quality-of-life dimensions and perception of general and present health state

EuroQol questionnaire
Mobility
I have no problem in walking about
I have some problems in walking about
I am confined to bed
Self-care
I have no problems with self-care
I have some problems washing or dressing myself
I am unable to wash or dress myself
Usual activities (work, study, housework, family, or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities
Pain or discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort
Anxiety or depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed
Compared with my general level of health over the past 12 months, my health state today is:
Better
Much the same
Worse

Source: Compiled from Kind, 1990.

CORONARY ARTERY BYPASS GRAFT SURGERY

Coronary artery bypass graft surgery forms the majority of cardiac surgery today and was introduced as a therapeutic option in the early 1960s once myocardial ischemia (angina pectoris or myocardial infarction) was shown to be due to narrowing of the coronary arteries from atherosclerotic plaque. Prospective randomized clinical trials, notably, the coronary artery surgery study (CASS) trial defined the indications for and benefits of CABG in both relieving symptoms and improving survival, but in a relatively young population (mean age 51 years) (CASS Principal Investigators and their Associates, 1983). These major trials showed that CABG increases survival in patients shown to have left main stem coronary artery stenosis, triple-vessel disease, or double vessel disease on coronary angiography and in those with impaired left ventricular function or with left ventricular aneurysms (Kaiser, 1986). CABG reduces the incidence of fatal myocardial infarction, relieves angina, and increases exercise capacity. However, isolated CABG does not improve symptoms of congestive heart failure, especially in the absence of proven hibernating or stunned myocardium.

Care though should be taken to not refer an elderly patient for coronary angiography only on the basis of symptoms

of angina, as there is a poor correlation of the degree of angina with the degree of coronary artery narrowing. Up to 42% of patients with left main stem stenosis (the cohort of ischemic heart disease patients at greatest risk of early death with continued medical therapy) will have only mild or no angina (Chaitman *et al.*, 1981). It is therefore important to make a distinction as to the indications of referral for further investigation as opposed to those for CABG surgery, which are not necessarily the same. Any recent change in angina symptoms should prompt a cardiologic assessment.

The demographics of the octogenarian or older patient undergoing cardiac surgery differs to that of the younger patient group (Bridges *et al.*, 2003; Craver *et al.*, 1999), in being more likely to be female (~45%), less likely to have diabetes (~20%), smoking (~35%) or chronic lung disease (~10%), and therefore possibly indicative that only in the absence of these risk factors is an individual likely to live long enough to become a nonagenarian.

In the elderly, improved survival, as previously mentioned, becomes less important in terms of being an indication for surgery and greater reliance is placed on relief of symptoms. Nevertheless, as previously mentioned, delays in referring for diagnostic coronary angiography should not occur, as this may partly account for the increased prevalence of left main stem disease in octogenarians or nonagenarians (~32%) undergoing CABG as well as need for emergent surgery (Bridges *et al.*, 2003). Left main stem stenosis of more than 50% remains an indication for CABG in the elderly even in the absence of severe symptoms, as less than 55% of medically treated patients 65 years or older with left main stem stenosis will survive for 3 years compared to an 87% survival for those undergoing CABG (Chaitman *et al.*, 1981).

The unadjusted operative mortality for CABG in the octogenarian is approximately 7.1% (Bridges *et al.*, 2003); however, in the absence of any significant comorbidity, it is only 2–4%, which approaches that of younger patient groups (Alexander *et al.*, 2000; Avery *et al.*, 2001). In the United Kingdom, the operative mortality for isolated CABG in the elderly (age > 75 years) has progressively decreased from 7.2% in 1999 to 4.7% in 2003, representing a reduction of 35% (Keogh & Kinsman, 2004). Preoperative risk factors associated with increased operative mortality in nonagenarians from the US Society of Thoracic Surgeons database are shown in Table 4 (Bridges *et al.*, 2003). Similarly, in Europe, potentially delayed surgery, that is, waiting until the patient requires emergent surgery or reaches NYHA dyspnea Class IV, are important risk factors for an increased operative mortality in octogenarians (Kohl *et al.*, 2001; Avery *et al.*, 2001). The decision to refer for further cardiac investigations and thereafter for possible surgery should be made timely and not seen as the "last option".

In an attempt to reduce operative risk in the elderly, it has been postulated that a less extensive surgical approach may be more prudent than complete revascularization. However, this is not so, as incomplete revascularization increases the risk of early death in elderly patients (Osswald *et al.*, 2001). Better outcomes occur with complete revascularization regardless of age.

Table 4 Risk factors for operative mortality in nonagenarians and centenarians undergoing CABG, listed in decreasing order of discriminatory importance

Risk factors for CABG in Nonagenarians	Operative mortality
• Emergent surgery	26.6%
• Preoperative need for an IABP	26.3%
• Renal failure (Creatinine >2.0 mg%) or dialysis	20.9%
• Peripheral or cerebrovascular disease	10.6%
• Mitral insufficiency	7.2%

Source: Data derived from the Society of Thoracic Surgeons National Cardiac Database (1997–2000) (Bridges *et al.*, 2003). IABP – intra-aortic balloon pump.

A retrospective study of CABG surgery in octogenarians showed CABG surgery to be more cost-effective than medical management; 3-year survival of 80% in the surgical group versus 64%, quality-of-life index of 84% in the surgical group (similar to an average 55 year old in the general population) versus 61%, and lower cost per quality-adjusted life year gained in patients managed surgically (Sollano *et al.*, 1998).

The overall outcome of CABG in the octogenarian can therefore be improved by avoiding excessive delay prior to referral, frequently based on misperceptions that age is a contraindication for cardiac surgery.

Is Percutaneous Coronary Angioplasty a Better Alternative in the Elderly?

Percutaneous coronary revascularization is also associated with a better survival than medical therapy in the octogenarian with significant ischemic heart disease (Figure 6).

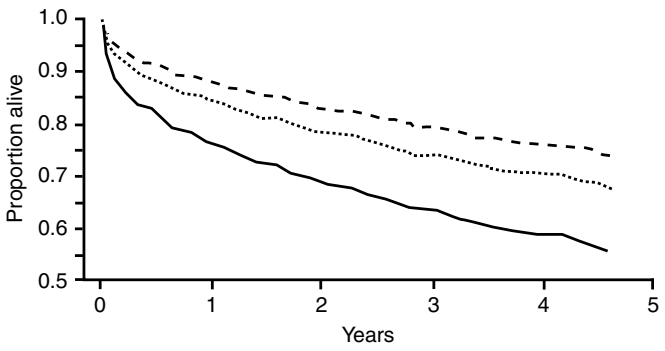

Figure 6 Risk-adjusted survival curves for 981 patients, 80 years of age or older, with ischemic heart disease who underwent either revascularization by coronary artery bypass graft surgery (dashed line) or percutaneous coronary intervention (dotted line) versus continued medical therapy (solid line) (Reprinted with permission from American Heart Association, Inc. (Graham *et al.*, 2002))

Perceived increased risks of surgery in the elderly should though not introduce a bias to opting for "less invasive" percutaneous coronary angioplasty as being a better option in the octogenarian. Complications of coronary angioplasty increase disproportionately in octogenarians and can be associated with a high in-hospital mortality of 8.2% (Batchelor *et al.*, 2000). Coronary anatomy is often more suitable for bypass surgery and incomplete revascularization is an independent predictor of both in-hospital and late mortality (Graham *et al.*, 2002).

Elective CABG surgery as opposed to percutaneous interventions is frequently a better option in nonagenarian patients, in the absence of significant associated comorbidity (Bridges *et al.*, 2003).

Use of the Internal Mammary Artery as a Conduit

CABG surgery was initially done using only reversed long saphenous vein as the bypass conduit between the ascending aorta and coronary artery, implanted distal to the flow-limiting atherosclerotic plaque. However, the conduit that provides the best long-term patency is the internal mammary artery, and is today the conduit of choice as a pedicled graft to the left coronary system. Use of the internal mammary artery also confers an immediate survival advantage by reducing operative mortality (Grover *et al.*, 1994).

Dissection of the internal mammary artery pedicle prolongs the operation time, is more technically demanding, and may be associated with increased postoperative bleeding, sternal infection in diabetics, and respiratory compromise. These reasons are therefore frequently cited to justify not using this conduit in higher-risk patients, such as the elderly. However, the use of an internal mammary artery has been shown to reduce mortality also in octogenarians undergoing CABG surgery (Figure 7) (Alexander *et al.*, 2000; Craver *et al.*, 1999; Morris *et al.*, 1996).

Newer techniques of harvesting the internal mammary artery by a skeletonized method can further reduce the risk of postoperative complications associated with its use. A high 71% use of internal mammary artery conduits in octogenarians as reported by Avery and coworkers, who also report one of the lowest operative mortalities of 2% in nonemergency octogenarian CABG, should be encouraged (Avery *et al.*, 2001).

The use of the internal mammary artery is beneficial in octogenarians by both reducing operative mortality and improving longer-term survival.

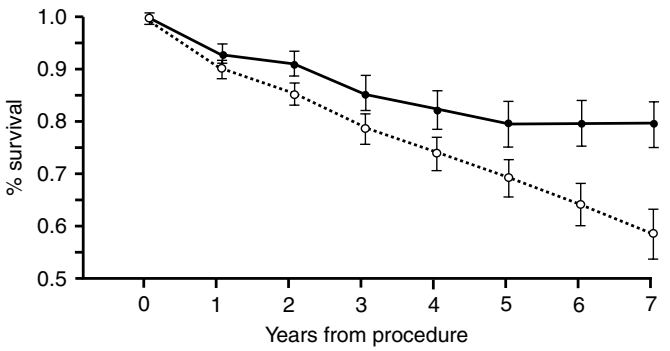

Figure 7 Actuarial survival rate of 487 patients 80 years of age or older who underwent coronary artery bypass graft surgery, and grouped according to whether they had received a left internal mammary artery graft to the left anterior descending coronary artery (solid line) versus those in whom only saphenous vein grafts (broken line) had been used (Reprinted with permission from Society of Thoracic Surgeons (Morris *et al.*, 1996))

Antithrombotic Therapy after Coronary Artery Bypass Graft Surgery

Graft closure after CABG surgery is largely related to platelet aggregation and intimal hyperplasia. The current recommendation is therefore lifelong aspirin therapy at a dose of $325\,\mathrm{mg\,day^{-1}}$ (Stein *et al.*, 2001). The use of lower doses of aspirin ($50-100\,\mathrm{mg\,day^{-1}}$) has not been conclusively shown to be as efficacious as the higher dose, but is nevertheless frequently prescribed. A lower dose of aspirin has though been associated with diminished risks of major bleeding in acute coronary syndrome trials (Peters *et al.*, 2003).

VALVE SURGERY

The first successful heart valve replacements were reported by Harken and Starr in 1960 (Harken, 1989). The insertion of a prosthetic heart valve, although correcting the functional or mechanical defect, is though tantamount to giving the patient another "iatrogenic" disease – the necessity for lifelong anticoagulation with Coumarin/Warfarin with mechanical prosthetic valves, or alternatively, the possibility of reoperation as a result of biological valve degeneration over time. No currently available prosthetic heart valve is as good as the normal human valve in either hemodynamic function or freedom from valve-related complications.

The proportion of patients undergoing cardiac surgery, requiring heart valve surgery (either Valve or Valve + CABG) as opposed to isolated CABG surgery increases with patient age and approaches 40% in nonagenarians in the United States (Figure 8) (Bridges *et al.*, 2003). In the elderly though, successful cardiac surgery leads to greater improvements in perceived health status in valvular than in coronary artery disease patients (Chocron *et al.*, 2000).

Aortic Valve Replacement in the Elderly

The predominant valve disease of the elderly is calcific degenerative aortic stenosis and accounts for 60–70% of the valve surgery caseload. Aortic valve cusps are calcified in 26% of adults older than 65 years and valve stenosis is observed in up to 5% of the population over the age of 75

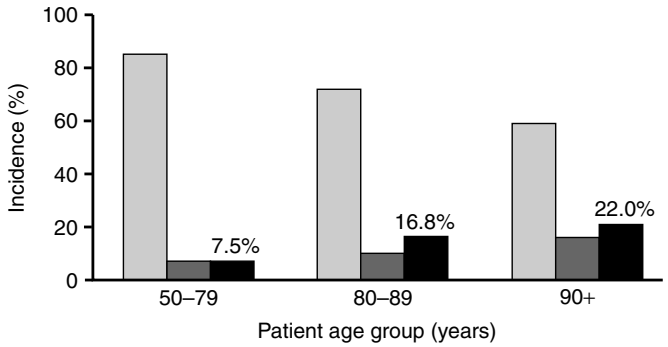

Figure 8 The incidence of the type of cardiac surgery by patient age-group, for coronary artery bypass graft surgery alone (light shade bar), valve repair or replacement surgery alone (medium shade bar), or combined CABG, and valve surgery (solid bar) (Compiled from data (662 033 patients) published from the Society of Thoracic Surgeons National Cardiac Database (USA; 1997–2000) (Bridges *et al.*, 2003))

(Mihaljevic *et al.*, 2003; Prètre and Turina, 2000; Lung *et al.*, 2003). The development of symptoms (angina, syncope, or heart failure) identifies a critical point in the natural history of aortic stenosis, and symptomatic aortic stenosis without surgery is associated with only a 20% 3-year survival (Bonow *et al.*, 1998). In contrast, survival of the elderly patient after successful aortic valve replacement (AVR) surgery is similar to that of the natural population (Figure 9), as well as enabling them to return to an independent active life.

Operative mortality for aortic valve surgery in the elderly approaches that obtained in younger patients and it is not until patients reach their 80s that age alone becomes a risk factor (Florath *et al.*, 2003). Early mortality in octogenarians undergoing aortic valve replacement with or without associated CABG can though be as high as 19%. This is primarily due to comorbid conditions, especially peripheral vascular disease, impaired renal function, and need for urgent surgery (Bonow *et al.*, 1998; Mistiaen *et al.*, 2004). Careful preoperative patient selection is therefore essential, but in addition, once aortic valve disease is diagnosed in patients aged 80 or more, early referral for surgery should lead to the avoidance of hazardous developments (the necessity for urgent surgery), and hence, to better postoperative outcomes (Mistiaen *et al.*, 2004). Successful aortic valve replacement surgery offers an excellent long-term outcome with long-term mortality being in most cases of non cardiac origin.

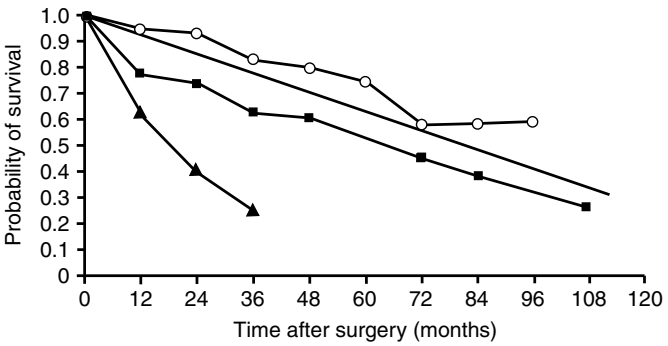

Figure 9 Comparative data between an unselected population of 80 year olds in the United States (solid line), patients over 80 years of age with symptomatic aortic stenosis who did not undergo aortic valve replacement surgery (solid triangles) and 103 octogenarians with aortic stenosis who underwent aortic valve replacement with or without concomitant coronary artery bypass grafts surgery (solid squares). The survival curve of the aforementioned octogenarian patients who survived more than 30 days after surgery (open circles) is also provided (Reprinted with permission from the BMJ publishing group (Gilbert *et al.*, 1999))

Asymptomatic Aortic Stenosis

The asymptomatic state is difficult to establish in practice, especially in the elderly, due to a gradual decrease in activity or sedentary lifestyle (Lung *et al.*, 2003). Asymptomatic elderly patients with severe aortic stenosis (effective orifice area $<1.0\,cm^2$) may pose a decision-making problem in terms of timing of referral for surgery; however, such patients are rarely truly asymptomatic. "Asymptomatic" aortic stenotic patients who should be referred for surgery include those with severe aortic stenosis (valve area $<1.0\,cm^2$ or an indexed aortic valve area $<0.6\,cm^2\ m^{-2}$ body surface area (BSA)), an abnormal response to exercise, left ventricular systolic dysfunction (left ventricular ejection fraction less than 50%), marked left ventricular hypertrophy ($\geq$15 mm wall thickness), the combination of moderate calcification and a peak jet velocity $>4\,m\,second^{-1}$ as well as a rapid increase in peak aortic jet velocity of $\geq 0.3\,m\,second^{-1}$ within 1 year or patients with severe ventricular arrhythmias for which no other cause other than severe aortic stenosis can be identified (Lung *et al.*, 2003).

Size of Implanted Prosthetic Aortic Valve

The size of the prosthetic aortic valve implanted by the cardiac surgeon in relation to the patient's body size is important for both early and late mortality as well as completeness of resolution of preoperative physical limitations (Rahimtoola, 2003). This is especially important in the small elderly obese female patient who has a higher potential risk of patient prosthesis mismatch if an inappropriately small prosthetic valve (in terms of the individual patient's BSA) is implanted by the cardiac surgeon. A prosthetic valve size whose manufacturer's predicted effective orifice area will be greater than the patient's BSA multiplied by 0.85 should be selected, and if necessary, the aortic root enlarged to achieve this.

"Prophylactic" AVR in Patients with Mild to Moderate Aortic Stenosis Undergoing CABG

A more difficult subset of patients includes those with moderate (effective orifice area of $1.0–1.5\,cm^2$) aortic stenosis but

requiring coronary artery or other valvular surgery. Progression of moderate aortic stenosis can be rapid in the elderly and quickly negate the benefits of isolated CABG surgery (Prètre and Turina, 2000). The presence of either aortic valve calcification or an aortic jet velocity of 3.0–4.0 m second^{-1} (Otto *et al.*, 1997) would suggest the likelihood of more rapid progression of aortic stenosis and therefore justification of a concomitant "prophylactic" aortic valve replacement at the time of the initial CABG referral. The alternative option of not doing a concomitant aortic valve replacement is the risk of a subsequent reoperative valve procedure in an octogenarian, which has a significant operative mortality of up to 32% (Kirsch *et al.*, 2004).

Aortic Valvuloplasty

Percutaneous balloon valvuloplasty has been a technique used to treat aortic valve stenosis, initially in neonates and infants. In the elderly, stenotic aortic valves are calcified with frequently no discernable commissures, and are probably the least suitable valve for dilatation. Not surprisingly, therefore, the results of percutaneous aortic valve dilatation in the elderly have been poor; mortality between 3–10%, morbidity – especially strokes in 10–25%, as well as a 25% incidence of restenosis within 72 hours, and 66% within 6 months (Bernard *et al.*, 1992). Less than 20% of aortic valvuloplasty patients will survive a year and most of them will not improve symptomatically.

Balloon valvotomy is therefore a poor alternative to surgery, and definitive aortic valve replacement should be considered in all elderly patients with symptomatic aortic stenosis. The results of aortic valve replacement in survivors after failed percutaneous valvuloplasty are also good; operative mortality of 12% and 2-year survival of 71%, suggesting that the reluctance to operate on aortic stenosis in the elderly is often exaggerated (Prètre and Turina, 2000).

Mitral Valve Surgery in the Elderly

Elderly patients are regarded as higher-risk patients for mitral valve surgery; however, higher early and late mortalities are in part due to elderly patients being referred late (more than 1 year after presenting with significant symptoms) and undergoing surgery later in the history of their mitral valve disease (Lee *et al.*, 1997). In this study, age greater than 70 years was not found to be a prognostic factor for operative mortality, which was 3.7%.

The predominant pathology in the elderly (developed economies) is either myxomatous degenerative or ischemic mitral valve regurgitation, and not unexpectedly in the former group, the elderly have significantly more associated coronary artery disease. The pathophysiology of degenerative mitral regurgitation is typically prolapse of the mitral leaflets as a result of elongated or ruptured chordae and mitral annular dilatation. In contrast, ischemic regurgitation is usually due to restricted motion of the mitral leaflets as a result of segmental or global ventricular dilatation.

Chronic severe mitral regurgitation results in progressive and eventual irreversible left ventricular dilatation and myocardial failure (NYHA Class III or IV) that is not reversed by eventual successful valve surgery. Hence, early surgery (NYHA Class I or II) is recommended for asymptomatic severe nonischemic mitral regurgitation regardless of age, if there are signs of left ventricular dysfunction (left ventricular ejection fraction less than 60%), atrial fibrillation, or pulmonary hypertension (pulmonary systolic pressure >50 mmHg), and preserved left ventricular function, and especially if there is a high likelihood of mitral valve repair (Lung *et al.*, 2003). The survival advantage of early surgery for severe mitral regurgitation is in fact greater in the elderly than in the younger population (Lee *et al.*, 1997). Seven-year freedom from complications-related death was 90% in elderly patients greater than 70 years of age versus 93% in younger patients if undergoing mitral valve surgery early (NYHA Class I or II). While, if undergoing surgery late (NYHA Class III or IV), 7-year complication free survival was only 51% in the elderly patient group versus 74% in the younger.

Mitral Valve Replacement or Repair

Conservative mitral valve repair rather than valve replacement should be done whenever feasible, as this is associated with both a lower operative mortality as well as improved long-term survival, regardless of presenting symptoms (Figure 10) (Tribouilloy *et al.*, 1999, Prètre and Turina, 2000). Valve repair preserves the subvalvar apparatus and left ventricular function, thereby reducing mortality from myocardial failure. In addition, thromboembolic and hemorrhagic complications are less frequent with mitral valve repair. The preference for mitral valve repair as opposed to mitral valve replacement applies equally to both the young and elderly patient populations.

Advances in surgical techniques including artificial Gore-Tex chordae have now made it possible for cardiac surgeons

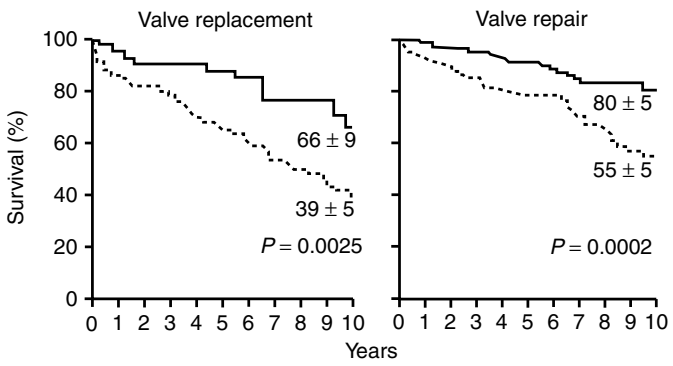

Figure 10 The long-term survival of 478 consecutive patients with organic nonischemic mitral valve regurgitation who underwent either mitral valve replacement (155 patients) or repair (323 patients) surgery, and grouped according to their preoperative NYHA dyspnea class; NYHA class I or II – solid line, NYHA Class III or IV – broken line. (Reprinted with permission from American Heart Association, Inc. (Tribouilloy *et al.*, 1999))

experienced in mitral valve repair to successfully repair more than 80% of degenerative and ischemic regurgitant mitral valves. If mitral valve repair is not feasible, then replacement with a prosthetic valve, but with preservation of the subvalvar apparatus, is the next best option.

Choice of Prosthetic Valve: Mechanical or Biological in the Elderly

A multitude of artificial mechanical heart valves have been developed, ranging from the initial obstructive "ball and cage" valves to "tilting disc" valves, and now "bi-leaflet" mechanical valves made from titanium steel and pyrolytic carbon. Mechanical heart valves though have an associated life-long thromboembolic risk from blood clots forming on the valve, which is the natural reaction of blood whenever it comes into contact with an artificial surface. This necessitates life-long anticoagulation with vitamin K antagonists (Coumarin/Warfarin), which in turn creates a risk of life-threatening major hemorrhage. A fine balance thus needs to be maintained for the rest of the patient's life, if mechanical prosthetic valves have been implanted, between too little anticoagulation which increases the risk of clot formation and thromboembolic ischemic stroke, and too much with its risk of anticoagulation-related hemorrhage and stroke (Figure 11).

Constant lifelong monitoring and maintenance of the patient's serum international normalized ratio (INR) in the recommended range, which is discussed in more detail later in this chapter, is therefore essential in all patients receiving mechanical prosthetic valves. Contraindications to warfarin use therefore preclude the implantation of mechanical prosthetic valves (Table 5).

Biological valves predominantly manufactured from bovine pericardium or porcine aortic valves have been developed as an alternative and do not require lifelong anticoagulation unless otherwise indicated. However, biological valves have a limited life span because of both calcium and non-calcium-related degeneration. Structural valve deterioration of bioprostheses is also higher in the mitral position than in the aortic position (Rahimtoola, 2003). Fifty percent of "first-generation" biological heart valves required replacement within 13 years of implantation (Starr and Grunkemeier, 1989). It has been thought that there is a reduced incidence of structural deterioration of bioprosthetic valves in the elderly; however, this has been shown to be not necessarily due to improved valve survival in the elderly but rather due to reduced patient survival from other causes (Grunkemeier and Wu, 2001). Nevertheless, current commercial, now improved "third-generation" biological prosthetic valves, based on animal studies, are thought to have significantly improved valve survival compared to these older "first-generation" bioprostheses. The major advantage of bioprosthetic valves in the elderly is that, unless otherwise indicated, lifelong anticoagulation with vitamin K antagonists is not required. The elderly (particularly >70 years) are at greater risk of thromboembolic and hemorrhagic complications secondary to Coumarin therapy (Rahimtoola, 2003).

The elderly patients would also benefit from implantation of a biological as opposed to mechanical prosthetic valve and, therefore, either not requiring anticoagulation or alternatively at a lower therapeutic INR range if other indications for anticoagulation exist, because of the increasing comorbid pathologies associated with the elderly.

In patients over the age of 69, the UK heart valve registry has shown no difference in patient survival between mechanical or bioprosthetic heart valve replacements. Nevertheless, other studies have shown biological valves to be associated with both a lower incidence of valve-related deaths and especially morbidity. Mortality from thromboembolic events and anticoagulation-related hemorrhage is three times higher in elderly patients over the age of 65 with mechanical prosthetic valves as compared to those with bioprostheses (Holper *et al.*, 1995).

The current recommendation is therefore to select a bioprosthetic heart valve for aortic valve replacements in patients equal or older than 60–65 years of age, and for mitral valve replacements in patients equal or older than 65 years (Figure 12) (Rahimtoola, 2003).

Table 5 Contraindications to Coumarin/Warfarin use

The patient
- Comorbidity; including comorbid medical conditions, falls, frailty, exposure to trauma
- Impaired cognitive function
- Possibly housebound
- Poor expected compliance

The doctor
- Poor appreciation of drug interactions
- Inefficient organization of INR monitoring

The system
- General practice versus Hospital facilities; for example, remote location, poor communication, and support
- Inadequate resources and facilities available.

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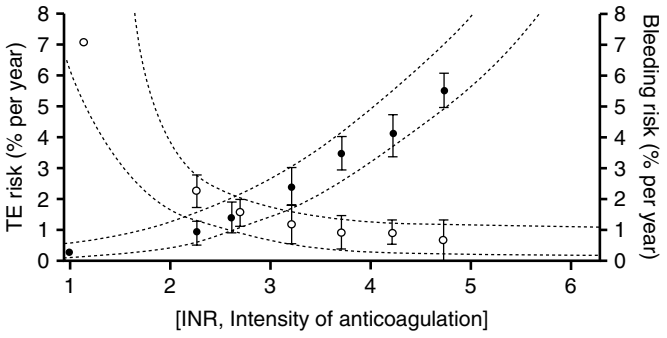

Figure 11 The incidence of thromboembolic (TE; open circles) and bleeding (solid circles) complications after 10-year follow-up, and grouped according to the average intensity of oral anticoagulation achieved by INR during the 10 years. The recommended target INR range was 3.0–4.5 in these patients with aortic mechanical St. Jude heart valve prostheses (Reprinted with permission from ICR publishers (Horstkotte *et al.*, 1993))

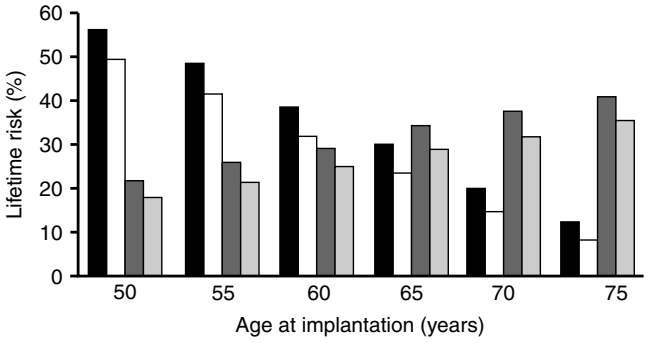

Figure 12 Microsimulation meta-analysis of the lifetime risk, according to the age at primary aortic valve implantation, of either structural valve degeneration of biological aortic valves without (solid bar) or with (open bar) concomitant coronary artery bypass graft surgery, or alternatively anticoagulation-related bleeding risks of mechanical aortic valves without (dark shaded bar) or with (light shaded bar) concomitant coronary artery bypass graft surgery (Reprinted with permission from Elsevier (Puvimanasinghe *et al.*, 2003))

COMBINED CORONARY ARTERY BYPASS GRAFT AND VALVE SURGERY IN THE ELDERLY

Previous unproven dictums such as "do as little as possible/only what is deemed essential" are slowly being disproved in terms of the extent of cardiac surgery undertaken. In CABG surgery, incomplete revascularization is an independent predictor of both in-hospital and late mortality (Graham *et al.*, 2002). The survival benefit of attending to coexistent moderate or more ischemic mitral regurgitation at the time of CABG surgery is well established. The supporting evidence for "prophylactic" additional aortic valve replacement for moderate aortic stenosis in patients already accepted for CABG surgery is becoming stronger, especially when considering the extremely high operative risk of subsequent reoperative valve procedures, should it become necessary in an octogenarian (Kirsch *et al.*, 2004). Hence, the incidence of combined CABG and Valve surgery is increasing, especially in the elderly.

Separating the influence of the comorbidity of the more complex underlying disease from the risk of the "complexity of the procedure" is difficult. Nevertheless, acceptable surgical results are being obtained with these more complex procedures in the elderly, and should not therefore be denied to the elderly. Careful individual preoperative assessment as previously discussed is though essential.

ANTICOAGULATION MANAGEMENT IN THE ELDERLY (*see* Chapter 40, Anticoagulants in the Elderly)

Bioprosthetic heart valves are currently the recommended prosthetic valve in the elderly, however, a number of patients may have had mechanical prosthetic valves implanted at a younger age and require continued anticoagulation management as they age. Furthermore, patients with bioprosthetic valves may have other coexistent medical conditions necessitating anticoagulation (Lip and Blann, 2003).

Patients at risk for cerebral thromboembolic events include patients with prosthetic heart valves, atrial fibrillation, reduced left ventricular function (less than 35% ejection fraction), history of previous thromboembolism or hypercoagulable states and these patients should receive anticoagulation with vitamin K antagonists and their INR should be maintained in a range between 2.0 and 5.0 (Hirsh *et al.*, 2003). Whether the target INR range is on the lower (INR 2.0–3.0), intermediate (INR 2.5–3.5), or upper (INR 3.0–4.5) side of this range will be dependant on the underlying thromboembolic risk, but will also influence the risk of anticoagulation-related hemorrhagic complications (Figure 11). The reason for providing a range is due to the difficulty of maintaining a "constant" INR in any individual patients.

Warfarin, the most commonly used coumarin derivative, results in anticoagulation by inhibiting the synthesis of factors dependant on vitamin K, and has a considerable variability in its effects due to considerable pharmacokinetic and pharmacodynamic factors (Table 6) (Lip and Blann, 2003). This therefore demands frequent laboratory measurements of each individual patient's INR, and audits have even still shown that only 50% of patients are within their target range at any specific time point. The half-lives of the vitamin K–dependant factors range from 6–60 hours, thus any specific warfarin dose takes 2–3 days to produce an effect and this needs to be taken into account when managing warfarin dosage. Warfarin dosing can also be separated into initial and maintenance phases, nevertheless the common practice

Table 6 This is only an illustrative list of interactions

Factors that influence the efficacy of warfarin
Patient factors
Enhanced anticoagulant effect
Weight loss, increased age (>80 years), acute illness, impaired liver function, heart failure, renal failure, excess alcohol ingestion
Reduced anticoagulant effect
Weight gain, diarrhea and vomiting, relative youth (<40 years), Asian or African-Caribbean background
Examples of some drug interactions with warfarin
Reduced protein binding
Aspirin, phenylbutazone, sulfinpyrazone, chlorpromazine
Inhibition of metabolism of warfarin
Cimetadine, erythromycin, sodium valproate
Enhanced metabolism of warfarin
Barbiturates, phenytoin, carbamazepine
Reduced synthesis of factors II, VII, IX, X
Phenytoin, salicylates
Reduced absorption of vitamin K
Broad-spectrum antibiotics, laxatives
Enhanced risk of peptic ulceration
Aspirin, nonsteroidal anti-inflammatory drugs, corticosteroids
Thrombolytics
Streptokinase, tissue plasminogen activator
Antiplatelet drugs
Aspirin, nonsteroidal anti-inflammatory drugs

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of initiating warfarin with a loading dose is no longer recommended (Hirsh *et al.*, 2003).

Patient self-management, especially in patients requiring life-long anticoagulation, using their own "point-of-care INR monitors" that are now available, may offer the potential for both simplifying and improving oral anticoagulation management. Recent trials have shown smaller mean deviations from the target INR range in self-managed patients (Hirsh *et al.*, 2003).

Anticoagulation for Biological Prosthetic Valves

The current guidelines recommend temporary (in patients with no other thromboembolic risk factors) use of warfarin for only the first 3 months after biological valve implantation (Bonow *et al.*, 1998). This may still be controversial in patients with biological aortic valves, and, thus, in these patients, either a temporary low-dose anticoagulation regimen (INR target range of 2.0–3.0), or antiplatelet therapy with aspirin (acetylsalicylic acid 75–100 mg day^{-1}) in patients not having reduced left ventricular ejection fraction (<35%), NYHA Class IV, preoperative atrial fibrillation, or a paced rhythm can be used (Gherli *et al.*, 2004; Orszulak *et al.*, 1995). After the first 3 postoperative months and provided there are no other thromboembolic risk factors, warfarin therapy can then be discontinued and replaced with aspirin 75–100 mg day^{-1} (Bonow *et al.*, 1998).

Anticoagulation for Mechanical Prosthetic Valves

Mechanical prosthetic valves in the aortic position (excluding first-generation Starr-Edwards, Lillehei Kaster, Omniscience, and Björk-Shiley valves) are considered to be less thrombogenic than in the mitral position (double the risk). Hence, patients with second- or third-generation mechanical prosthetic valves (St Jude Medical bileaflet, Medtronic-Hall tilting disc, CarboMedics bileaflet) can be maintained at an INR target range of 2.5–3.0 or 3.5 for the aortic position (Hirsh *et al.*, 2003; Bonow *et al.*, 1998; Lip and Blann, 2003), and at a slightly higher INR range of 3.0–3.5 or 4.5 for the mitral position (Hirsh *et al.*, 2003; Vink *et al.*, 2003; Lip and Blann, 2003). The higher top end point should probably be used if there are additional thromboembolic risk factors; an enlarged left atrium (>55 mm in diameter), reduced left ventricular ejection fraction (<35%), dilated left ventricle (left ventricular end-diastolic diameter greater than 70 mm), atrial fibrillation, or previous thromboembolic events.

Patients with mechanical prosthetic valves require lifelong constant monitoring of their INR (initially daily then at least every 1–2 weeks depending on individual variance), as diet, coexistent diseases, medication, etc interact with the efficacy of vitamin K antagonists (Table 6). Inadequate anticoagulation monitoring not only increases the risk of thrombosis, but also increases the risk of stroke (3–10%), major bleeding episodes (5%), nondisabling bleeding (14%), as well as recurrent thrombosis (11%). In the event that patients have evidence of prosthetic valve obstruction or thrombosis, they should be referred for emergent reoperation (Bonow *et al.*, 1998).

Anticoagulant Management of Patients with Mechanical Prosthetic Valves Undergoing Noncardiac Surgery

If it is necessary to interrupt oral anticoagulant therapy in patients with mechanical prosthetic heart valves, in preparation for elective surgical procedures, it is recommended to temporally stop oral vitamin K antagonist therapy for 4–5 days preoperatively, the INR normalized to <1.5, and either a continuous intravenous heparin infusion (prolonging the activated partial thromboplastin time (APTT) to twice normal) or subcutaneous low-molecular-weight heparin (100 U/kg every 12 hours) given to prevent thromboembolism (Hirsh *et al.*, 2003; Lip and Blann, 2003). The advantage of low-molecular-weight heparin is the ability to provide this therapy on an ambulatory basis. However, its effects are only partially neutralized by protamine because of its higher anti-Xa activity, and should therefore in turn be temporarily stopped 12–18 hours prior to surgery (Shapira *et al.*, 2001). Oral anticoagulation therapy is then recommenced the day after surgery or as soon as feasible in terms of intestinal function.

The aforementioned guidelines should also be used when patient's (requiring oral anticoagulation) INRs drop below their therapeutic range.

Parenteral vitamin K is not recommended in the treatment of non-life-threatening bleeding associated with warfarin use in patients with mechanical prosthetic valves because of the potential for induced hypercoagulable states.

Anticoagulation for Atrial Fibrillation (*see* Chapter 45, Arrhythmias in the Elderly)

The efficacy of oral anticoagulation with vitamin K antagonists for preventing stroke in patients with atrial fibrillation has been well documented. Targeting the lowest intensity of anticoagulation to minimize the risk of hemorrhagic complications is though particularly important for elderly patients with atrial fibrillation, and, in these patients, an INR target ranging between 2.0 and 3.0 is recommended (Hirsh *et al.*, 2003; Lip and Blann, 2003). The risk of anticoagulant-related hemorrhage increases with age (1–2% patients per year, if below 60 years old) (Bonow *et al.*, 1998). Hence, in patients more than 75 years old, a target INR range of 1.6–2.5 or albeit not as effective, only aspirin treatment (325 mg per day) may be considered in patients with atrial fibrillation and no other indications for Coumadin anticoagulation.

NONPHARMACOLOGICAL CURATIVE THERAPY FOR ATRIAL FIBRILLATION

Atrial fibrillation is the most common serious cardiac arrhythmia and is associated with a significant risk of cerebral thromboembolism. The prevalence of atrial fibrillation in

the general population is approximately 0.4%, however, the prevalence increases markedly with age to approximately 9% in the 80–89 year-old population group (Kannel *et al.*, 1998). Furthermore, the risk of stroke associated with atrial fibrillation also increases with age from a 1.5% risk at age 50–59 years to 23.5% risk at age 80–89 years. Anticoagulation with warfarin reduces this risk of stroke but imparts a risk of anticoagulation-related hemorrhage and reduces patients' quality of life.

The surgical Maze procedure developed by James L. Cox has been able to cure atrial fibrillation in up to 99% of carefully selected patients, and thereby has essentially abolished the risk of stroke associated with atrial fibrillation (Prasad *et al.*, 2003). Percutaneous transcatheter ablation of the pulmonary vein ostia, also in carefully selected patients, now offers a less invasive approach and a success rate of approximately 78% (Pappone *et al.*, 2003).

Newer hyperthermic ablation devices including radiofrequency, microwave, ultrasound, and laser, as well as cryoablation device have also now been developed to allow surgeons to do more rapid reproducible modified Maze procedures concomitant with other cardiac surgical procedures. Postoperative 5-year freedom from atrial fibrillation in "non-selected" patients with permanent atrial fibrillation of more than 1-year duration, undergoing concomitant cardiac surgery, can now be expected in 42%–87% of patients depending on underlying coexistent cardiac pathology (Sie *et al.*, 2004).

The nonpharmacological cure of atrial fibrillation is currently a rapidly developing field, and clear guidelines as to patient selection are slowly being developed. The elderly patient with atrial fibrillation who has the highest risk of stroke may though potentially stand to gain the most from this emerging therapeutic option.

THORACIC AORTIC SURGERY (*see* Chapter 86, Spinovascular Insufficiency)

The incidence of thoracic aortic aneurysms and aortic dissections increases in the elderly and is a lethal disease. The 5-year survival of patients not operated on is approximately 54%, and these patients have a 21–74% risk of acute rupture (Davies *et al.*, 2002; Clouse *et al.*, 1998).

The major factor influencing the risk of either acute rupture, dissection, or death is the diameter of the aneurysm at initial presentation; aneurysms greater than or equal to 6.0 cm in diameter have an annual risk of a negative outcome of 15.6% (Figure 13) (Davies *et al.*, 2002). The risk of rupture with time increases 11-fold with aortic aneurysm size of 5.0–5.9 cm, and 23-fold with size of 6.0 cm or greater (Davies *et al.*, 2002). This needs to be compared with the risk of surgery, which has an operative mortality of 5–9% for elective surgery, but as high as 57% for emergency operations in the elderly (Coady *et al.*, 1997).

The current accepted guidelines for asymptomatic aneurysms is to operate once an ascending aortic aneurysm

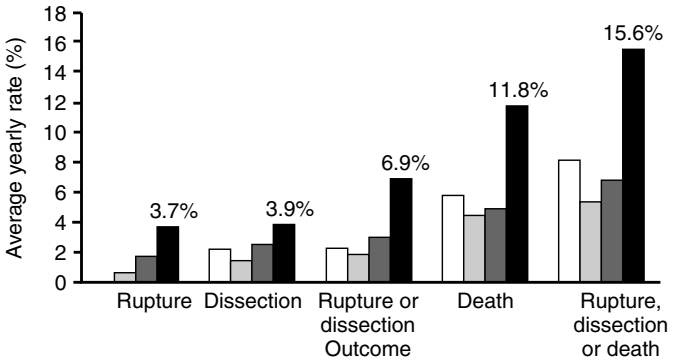

Figure 13 The average yearly rate (during the first 5 years after presentation), of negative outcomes (rupture, dissection, or death) as a function of the initial thoracic aortic aneurysm (ascending, arch, descending, or thoracoabdominal) size (maximal diameter); 3.5–3.9 cm (clear bar), 4.0–4.9 cm (light shade bar), 5.0–5.9 cm (medium shade bar), equal or greater than 6.0 cm (solid bar). (Reprinted with permission from Society of Thoracic Surgeons (Davies *et al.*, 2002))

diameter is 5.5 cm or more, or if a descending thoracic aortic aneurysm is 6.5 cm or more. However, a smaller diameter of 5.0 cm is used in patients with a Marfan's syndrome or a family history of aortic aneurysms because of the higher incidence of rupture in these subgroups. Additional operative risk factors that need to be taken into account when assessing a patient for surgery on the descending thoracic aorta are the risk of spinal cord injury and paraplegia of 2–8%, which is related to the extent of the aneurysm and is highest in Crawford type II thoracoabdominal aneurysms (LeMaire *et al.*, 2001).

In a large series (mean age 65 years), the risks of an adverse outcome (death, paraplegia, renal failure requiring hemodialysis or stroke) in elective thoracoabdominal aortic aneurysms was 13% and related to preoperative renal insufficiency, increasing age, type II extent, and symptomatic aneurysms (LeMaire *et al.*, 2001). An important conclusion of this study was that the development of any symptoms, no matter how mild or uncharacteristic, in patients with thoracoabdominal aneurysms requires immediate evaluation. The aneurysm must be considered the cause of the symptoms until proven otherwise as it indicates progression into a subacute phase. Once a symptomatic or asymptomatic aneurysm is diagnosed in an elderly patient, elective surgical correction should be considered and the risks thereof especially in terms of comorbid disease balanced against the risk of an adverse outcome, and a definitive decision in regard to treatment made.

Percutaneously inserted cloth-covered arterial stents are today becoming an alternative therapeutic intervention to open surgery. These cloth-covered stainless steel coils were initially developed in 1969 and can now be inserted retrograde via the femoral artery into the abdominal and descending thoracic aorta, to seal off some aortic aneurysms. Current trials in appropriately selected patients have shown a procedural mortality of approximately 9% and 5-year survival of 49% (Demers *et al.*, 2004). In "good surgical candidates" 5-year survival of 78% was similar to conventional open

surgical series, suggesting that cloth-covered stents are being increasingly used in patients possibly deemed unfit for conventional surgical interventions (Demers *et al.*, 2004). This technology is still developing and it is hoped that improved stent design will reduce the risk of distal migration of stents and perigraft leakage, and may become the preferred option in the elderly. The importance of the presence of an endoleak is that it implies that there is no protection against acute rupture. In patients judged to be poor conventional surgical candidates, 5-year survival at 31% was though bleak and mainly due to coexistent disease. Moreover, quality of life did not improve in patients asymptomatic in terms of their aneurysmal disease as opposed to their comorbid diseases (Demers *et al.*, 2004).

CARDIAC TRANSPLANTATION

The worldwide results of heart transplantation compiled by the International Society of Heart and Lung Transplantation Registry show that the current 1-year and 5-year survival following a heart transplant managed with modern immunosuppressive therapy is approximately 80 and 67%, respectively (Hosenpud *et al.*, 2001).

A heart transplant is technically a relatively simple operation, but replaces a patient's original terminal heart disease with another disease; the disease of immunosuppression, which though is expected to carry a slightly better chance of survival. Nevertheless, constantly having to take drugs to prevent the body from rejecting the new heart and balancing this against the risks of oversuppressing the body's defense mechanism, which makes the patient prone to infection or cancer, becomes even more of an issue in the elderly.

In the United Kingdom, there is no prescribed age limit for acceptance onto a heart transplant program; however, in practice, few patients above 65 years of age tend to be accepted. The international age distribution shows that less than 5% of heart transplants were in recipients aged 65 or more (Hosenpud *et al.*, 2001). Availability of donor organs is the primary limiting factor for heart transplantation worldwide. Improvements in road traffic safety amongst others have resulted in a 40% reduction in the availability of cadaveric cardiothoracic donors in the United Kingdom over the past 10 years (UK Transplant Activity Report 2003–2004, 2004). Equitable allocation of donor hearts, an increasingly restricted national resource, is therefore necessary. In 2002–2003, only 32% of patients on an active cardiothoracic transplant waiting list (heart, lung, or heart/lung) received an organ transplant (UK Transplant Activity Report 2003–2004, 2004).

An alternative option for patients with terminal heart disease not amenable to conventional cardiac surgery for whatever reason, which is now becoming available, is implantation of miniature blood pumps; totally implantable left ventricular assist devices. However, the current costs of these, what in the elderly will be "destination therapy" devices will probably preclude universal access.

CONCLUSIONS

The heart-lung machine developed in 1953 enabled previously "terminal" medical conditions to be successfully treated and resulted in an exponential growth in cardiac surgery such that the current need is for up to 1250 cardiac operations per million population. Concurrently, the elderly population has and will continue to increase and up to 40% of octogenarians have symptomatic cardiac disease. In the United Kingdom, almost 30% of patients undergoing CABG surgery and 42% undergoing heart valve surgery are currently over 70 years of age. Cardiac surgery mortality and morbidity outcomes have and will continue to improve and age itself is not a contraindication for cardiac surgery. The crude operative mortality for octogenarians undergoing cardiac surgery is currently less than 5–11% with postoperative 5-year survivals similar to the age matched natural population. The major morbidity risk is that of perioperative stroke because of the increased atherosclerotic vascular disease and can be as high as 10%.

Elderly patients must be individually assessed preoperatively in terms of the risk of the intended cardiac surgery; Euro Score predicted mortality, versus the perceived benefit in their quality of life; EuroQol, as well as the influence of other coexistent medical conditions. Although the prime indication for cardiac surgery in the elderly continues to be "relief of symptoms", excessively late referral has a significant negative impact on both operative risk and late outcome. Mild symptoms need to be promptly investigated, if necessary by echocardiography and angiography, in order to more accurately determine the true extent of any underlying cardiac condition.

The unadjusted operative mortality for CABG in the octogenarian is currently 7.1% but only 2–4% in the absence of other comorbidity when timeously referred, and continues to decrease especially with the use of the internal mammary artery as a conduit even in the octogenarian. Percutaneous coronary stenting or incomplete revascularization are not necessarily better alternatives in the elderly.

Aortic valve replacement accounts for the majority of valve surgery in the elderly, and operative mortality is primarily related to comorbid conditions. Once again more complete assessment of the "asymptomatic" patient is essential and early referral preferable. Replacement with a biological as opposed to mechanical prosthetic valve is recommended in the elderly because, unless otherwise indicated, lifelong anticoagulation is not required and the life span of current third-generation bioprostheses is greater than the elderly patient's projected life span. Percutaneous balloon aortic valvuloplasty is not currently considered to be a suitable alternative.

Chronic severe mitral valve regurgitation results in progressive irreversible left ventricular dysfunction and the survival advantage of early surgery (NYHA dyspnea class II) is even greater in the elderly population, especially if mitral valve reparative surgery can be confidently undertaken.

Atrial fibrillation is an increasing problem in the elderly with an associated high risk of stroke. Developments in the

nonpharmacological cure of atrial fibrillation are becoming an attractive option in the elderly, who potentially have the most to gain from this emerging therapeutic option, especially if concomitant cardiac surgery is already indicated.

Thoracic aortic dissections and aneurysms are more prevalent in the elderly, and untreated will rupture acutely in up to 74% of patients. In principal, patients who are symptomatic or with ascending aortic aneurysms greater than 5.5 cm or descending aneurysms greater than 6.5 cm should be referred for surgery. In appropriately selected patients, percutaneous inserted cloth-covered stents are becoming an alternative option.

Cardiac transplantation is not a realistic option in the elderly patient with terminal heart failure. New miniature fully implantable blood pumps may though become an option in the future.

KEY POINTS

- Age is not a contraindication for cardiac surgery in elderly patients provided that they can be discharged without significant disability and loss of independence.
- Elderly patients must be assessed individually in terms of the natural history of their disease, symptoms thereof, current quality of life, and the risk (mortality and morbidity) versus benefit (improved quality of life) of any potential surgical intervention.
- Referring elderly patients at an earlier stage of the disease process can improve the outcome of cardiac surgery in the elderly.
- The use of the internal mammary artery is beneficial even in octogenarians by both reducing operative mortality and improving longer-term survival.
- Aortic valve replacement surgery offers an excellent long-term outcome in selected elderly patients.
- Elderly patients benefit from implantation of a biological as opposed to mechanical prosthetic valve, if valve replacement is required, as bioprostheses do not require anticoagulation or, alternatively, at a lower therapeutic INR range, if other indications for anticoagulation exist.

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Pathogenesis of Atherosclerosis

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WHAT IS ATHEROSCLEROSIS?

Histological Appearance

Gross anatomy identifies atherosclerosis as a focal thickening of the wall of medium-sized and large arteries. In its advanced stages, it consists of a central core of yellowish toothpaste-like gruel surrounded by a leathery capsule – the fibrous cap. The normal vessel wall consists of an inner monolayer of lining cells – the endothelial cells (ECs), a thick middle layer of vascular smooth muscle cells (VSMCs) and connective tissue, and an outer layer of fibroblasts, small blood vessels (the "vasa vasorum"), and fat cells (Figure 1a). These three layers, referred to as the tunic intima, media, and adventitia, respectively, are separated by clearly defined internal and external elastic lamellae. As long ago as the 1850s, Rudolf Virchow using the light microscope described how cholesterol crystals and "foam cells" (FC) thicken the intima in atherosclerotic plaques (Hort, 1994). Virchow's conclusion that cholesterol and foam cells insuded from the blood is supported by observing blood leucocytes adhering to the surface of plaques. Light micrographs also demonstrate the fibrous cap, which has a continuous connection to the underlying connective tissue. These simple histological findings illustrate the three defining components of atherosclerosis: cholesterol-rich gruel, inflammatory leucocytes, and expanded connective tissue (Figure 1b).

Application of immunohistochemistry identifies some foam cells as α-smooth-muscle-actin-positive VSMCs, but the majority are CD68-positive macrophages, derived from circulating monocytes. Although not foamy, T lymphocytes are found at all stages of atherosclerosis progression, and there are also less frequent B cells and mast cells (Libby *et al.*, 2002; Hansson *et al.*, 2002). Many, but not all, of the mesenchymal cells in the fibrous cap are α-smooth-muscle-actin-positive. There is frequently wasting of the normal media at the base of the plaque, suggesting that normal medial VSMC migrate into the intima, proliferate, and elaborate extracellular matrix (ECM) to form the fibrous cap. However, recent work suggests that clones of circulating hemopoietic stem cells can also enter the intima from the circulation and differentiate into smooth-muscle-like cells (Sata *et al.*, 2002). This would neatly account for the histological and molecular evidence that intimal VSMCs are frequently monoclonal in origin (Murry *et al.*, 1997). Similarly, endothelial cells on the surface of atherosclerotic plaques undergo increased turnover and may be replaced not only by expansion of neighboring cells but also by circulating endothelial precursors (Rabelink *et al.*, 2004).

Histological analysis of coronary arteries from accident victims provides evidence for the natural history of atherosclerosis and also informs a consensus classification of early lesions (Stary, 1990). In babies and young children, there is focal thickening of the intima in sites prone to later atherosclerosis (type I lesion). The earliest stages of lipid accumulation are evident as foam-cell-rich "fatty streaks" or dots (type II). With onset of puberty, however, there is increasing prevalence of "preatheroma" with small extracellular lipid accumulations (type III). These may coalesce into a lipid pool, which is the defining feature of "atherosclerosis" (type IV). Later on in life, lesions with an expanded fibrous cap, "fibroatheromas", become more frequent (type V). Autopsy specimens from patients who died as a result of myocardial infarction or sudden cardiac death refine the definition of later stages of atherosclerosis evolution (Virmani *et al.*, 2000). There is increasing prevalence of "complex atheromas" with evidence of incorporated mural thrombus, where the cap has ruptured and become repaired, and even where the artery has become occluded by thrombus and then recanalized (type IV). The media and intima may also have become calcified (type VII). Type VIII lesions are largely fibrous and show little lipid deposition. Whether they represent a fully healed stage of atherosclerosis or follow a separate path of evolution is not clear.

Recent intravascular ultrasound (IVUS) data suggests that lipid-rich atherosclerotic plaques are very common in the coronary arteries of western adults, particularly men, although particular lesions may remain clinically silent

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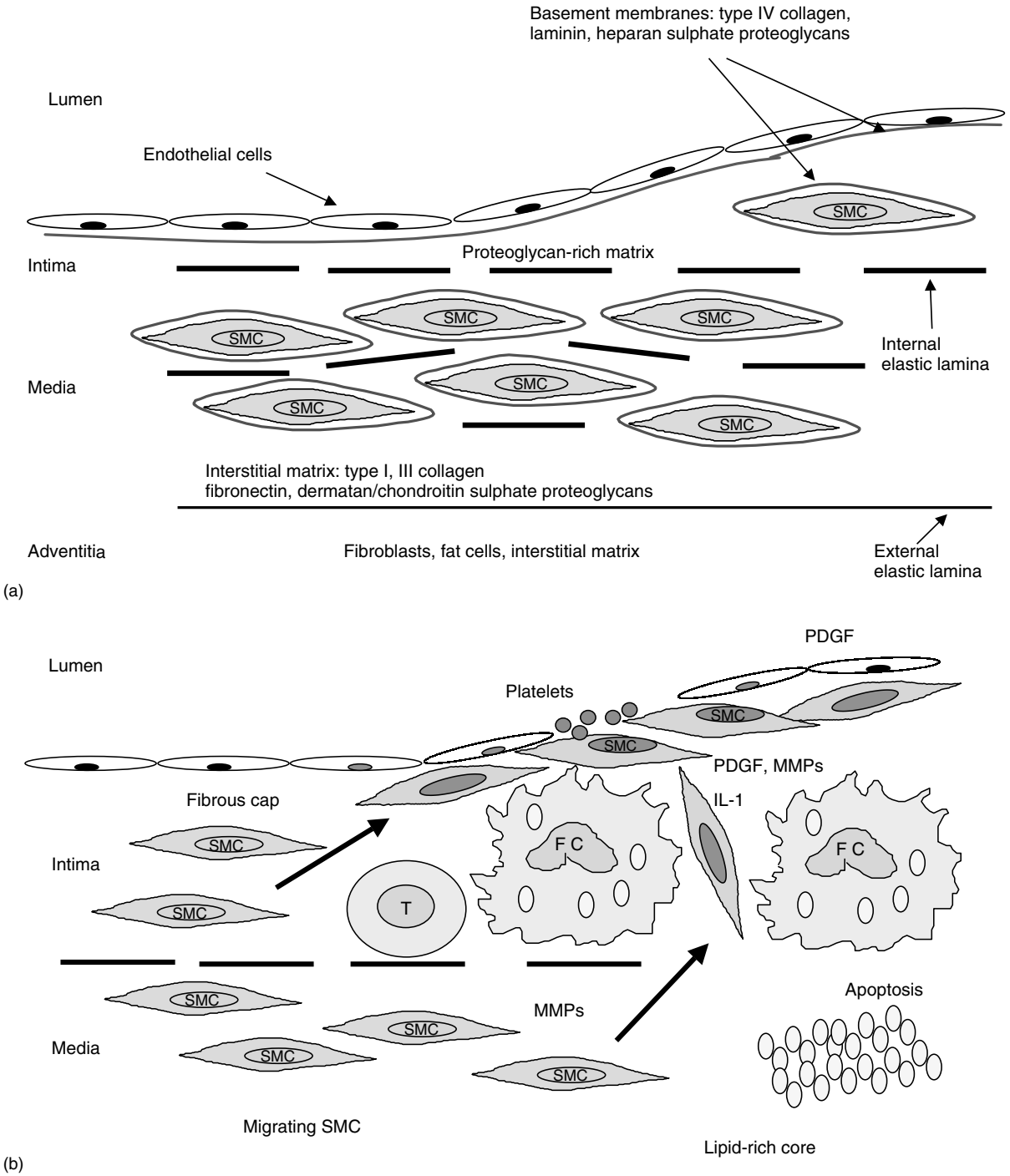

Figure 1 Structure of normal and atherosclerotic arteries. (a) Normal artery. Cellular and extracellular matrix components of the tunica intima, media, and adventitia are shown. (b) Atherosclerosis. T lymphocytes and macrophage foam cells thicken the intima. Secretion of the growth factor, PDGF, the inflammatory cytokine IL-1 and proteases including MMPs mediates the migration of smooth muscle cells from the media to make up the fibrous cap. Apoptosis of macrophages leads to formation of the lipid core. Loss of endothelial cells in late lesions causes platelet adhesion, another source of PDGF. FC, foam cell; IL-1, interleukin-1; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; SMC, smooth muscle cells; T, T-lymphocyte

(Schoenhagen *et al.*, 2003). Presentation, for example, as stable angina pectoris (in the coronary arteries) or intermittent claudication (in the legs) requires that plaques should have occluded the original artery lumen by more than approximately 70%. Ischemic symptoms from the carotid and other vascular beds are also observed. This eventuality is avoided or delayed in many cases by expansion of the media and adventitia, in a process known as *positive* or *compensatory remodeling* (Glagov *et al.*, 1987). In other arterial segments there may be shrinkage, that is, negative or adverse

remodeling, that would hasten symptoms of ischemia. Alternatively, patients may present with an acute event (e.g. unstable angina pectoris, myocardial infarction, or sudden cardiac death). In as many as 85% of men who die from an acute coronary event, the plaque cap has suffered a rupture, which exposes the strongly thrombogenic lipid core (Davies, 2000). This promotes mural thrombus formation and may progress to complete lumen occlusion resulting in infarction. In the minority of men and in about half of women with fatal infarcts, there is evidence of mural thrombus formation at the site of a surface "erosion" rather than plaque rupture (Davies, 2000).

Biochemical Analysis

Atherosclerotic plaques contain an abundance of cholesterol esters and free cholesterol, which forms crystalline deposits. Another difference from normal tissue is the presence of oxidized lipids and ceroid, which is the insoluble residue of extensive lipid oxidation. Oxidation of low-density lipoprotein (LDL) depletes concentrations of the natural antioxidant, vitamin E, and produces oxidized phospholipids that can act as antigens. Extensive lipid oxidation leads to fragmentation of the fatty acid side chains of phospholipids to yield highly reactive species such as malondialdehyde, which then react with the lysine side chains of proteins to generate further neoantigens. There is biochemical and immunological evidence for these products in atherosclerotic plaques (Chisolm and Steinberg, 2000; Navab *et al.*, 2004b), which together suggest a strongly pro-oxidant environment.

MECHANISMS RESPONSIBLE FOR THE GENESIS OF THE LIPID, FIBROUS, AND INFLAMMATORY COMPONENTS OF ATHEROSCLEROTIC PLAQUES

Lipid Deposition – "The Cholesterol Hypothesis"

Feeding susceptible animals such as rabbits with diets rich in cholesterol and saturated fats provokes accelerated atherosclerosis. Literally hundreds of epidemiological studies identify plasma cholesterol concentration as a risk factor for coronary heart disease (CHD) and other consequences of atherosclerosis in man. Perhaps the most striking data is obtained by comparing the incidence of CHD in populations with different average levels of cholesterol (Feher and Richmond, 1997). There seems an almost linear relationship between CHD risk and cholesterol concentration, despite the varied prevalence of other major risk factors such as smoking and hypertension. For this reason, hypercholesterolemia is often thought of as a dominant risk factor. Hence, there has been a major interest in understanding the regulation of lipid metabolism in the body and how it influences atherosclerosis. However, more than 300 other risk factors have been identified, including age, male sex, hypertension, smoking status, the presence or absence of diabetes (De Backer *et al.*, 2003) and, amongst others, the fasting levels of trigylcerides (TGs) (Feher and Richmond, 1997).

TGs are the main storage form of dietary fats and also transport fatty acids mainly to muscles where they are metabolized to produce energy. Phospholipids are essential components of all cell membrane lipid bilayers, but these would not be fluid at body temperature without cholesterol. The rigid cholesterol molecules intercalate among the more flexible fatty acid side chains of phospholipids and lower their melting temperature. Since ion channel opening and receptor signaling, for example, require a fluid lipid membrane, all cells require a carefully titrated amount of cholesterol in their membranes to ensure normal function. Elegant mechanisms have evolved to distribute lipids around the body (Figure 2). The insolubility of lipids in plasma has been overcome by packaging them up as lipoprotein particles. Lipoproteins (LPs) all contain at least one scaffolding protein (apolipoprotein, Apo), an oily core of TGs and cholesterol esters, and an envelope formed by monolayer of phospholipids and free cholesterol. Loosely adsorbed to the surface are other apolipoproteins which act as addresses, telling the LPs where to go. Chylomicrons are constructed in the intestine around ApoB48 (Figure 2). They have some cholesterol ester and large quantities of TGs and, hence, have the lowest buoyant density among the LPs. They carry on their surface Apo CII, which activates lipoprotein lipase in the capillaries of muscle and adipose tissue. As a result, in a matter of tens of minutes, most of the TGs are removed and delivered to muscle and fat in the form of free fatty acids and glycerol. Chylomicrons also contain surface attached ApoE, which addresses the TG poor remnants to the liver for recycling. In the liver, recycled cholesterol from the diet enters a common pool with that derived from *de novo* synthesis. Although variable, in the typical person only 1/3 of cholesterol comes from the diet (extrinsic pathway) and 2/3 from *de novo* synthesis (intrinsic pathway). As with all fats, *de novo* synthesis occurs by sequential 2-carbon addition from acetyl-CoA (Figure 2). The regulated step in the pathway is the conversion of hydroxymethyglutarylcoenzymeA (HMGCoA) to mevalonic acid by HMGCoA reductase. This is subject to feedback inhibition by the ultimate product of the pathway, cholesterol. The activity of HMGCoA reductase is increased by saturated fatty acids and reduced by polyunsaturated fats, which explains their positive and negative influence, respectively, on plasma cholesterol levels.

Liver cholesterol is constructed into very low density lipoprotein (VLDL) (Figure 2) around the scaffold protein ApoB100 (as its name implies, a longer version of ApoB48). VLDL also has large amounts of TGs and both ApoCII and ApoE. Hence, VLDL also serves as a source of fatty acids for muscle and adipose tissue and its remnants are rapidly recycled to the liver. Further lipolysis by hepatic lipase converts some VLDL remnants to intermediate density lipoprotein (IDL). This can lose ApoE and CII by transfer to high-density lipoprotein (HDL) and other LPs, and becomes the cholesterol-rich particle containing only ApoB100 that we call LDL. Since LDL lacks ApoE, it binds only to the relatively low affinity classical LDL receptor (LDLr)

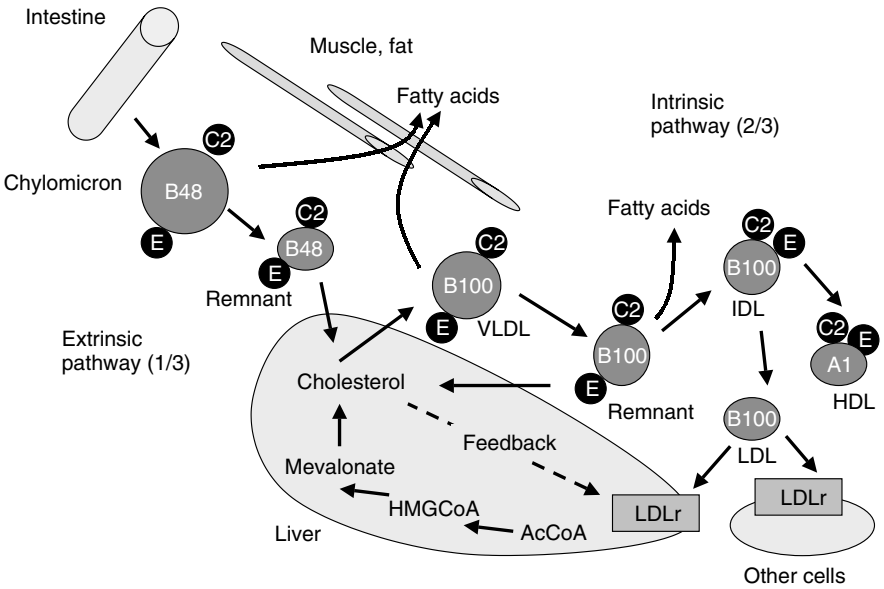

Figure 2 Cholesterol metabolism. A1, apolipoprotein A1; AcCoA, acetylcoenzymeA; C2, apolipoprotein CII; B48(100), apolipoprotein B48(100); E, apolipoprotein E; HDL, high-density lipoprotein; HMGCoA, hydroxymethyglutarylcoenzymeA; IDL, intermediate density lipoprotein; LDL(r), low-density lipoprotein (receptor); VLDL, very low density lipoprotein

and has a halftime in plasma of several days. LDLrs are found on almost all cells in the body, although not on macrophages. After binding, LDL is internalized by clathrin-coated pits to the lysosomes, where it is broken up by proteolysis and lipolysis and the free cholesterol is distributed to cell and mitochondrial membranes. Free cytoplasmic cholesterol plays a key regulatory role by downregulating production of LDL receptors (Anderson, 2003). Using this mechanism, a cell replete with cholesterol prevents further uptake.

Up until now, this describes a mechanism by which cholesterol can flow from the liver to peripheral tissues. However, in a steady state, this must be balanced by reverse cholesterol transport to the liver (Figure 3). HDL is specialized for this function, and in epidemiological studies, high concentrations of plasma HDL protect against atherosclerosis. A lipid-poor form of HDL known as *pre-βHDL* acts as an acceptor for free cholesterol, which becomes esterified by lecithin cholesterol acyl-transferase (LCAT) and is then passed on by cholesterol ester transfer protein (CETP) to other LPs, eventually reaching LDL. LDL is finally taken up by the liver and the resulting cholesterol is either repackaged into VLDL or further metabolized to bile acids that are secreted as emulsifiers in the small

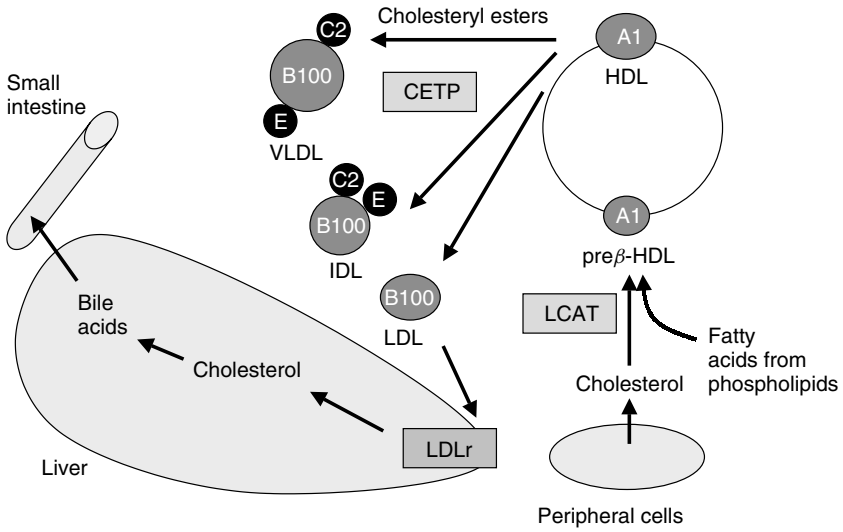

Figure 3 Reverse cholesterol transport. A1, apolipoprotein A1; C2, apolipoprotein CII; HDL, high-density lipoprotein; B100, apolipoprotein B100; E, apolipoprotein E; IDL, intermediate density lipoprotein; LDL(r), low density lipoprotein (receptor); VLDL, very low density lipoprotein

intestine (Figure 3). Despite reuptake in the large intestine, a proportion (around 15%) of bile acids are secreted in the feces and this constitutes the only mechanisms for net loss of cholesterol from the body.

On balance, therefore, there is dietary uptake and *de novo* cholesterol synthesis matched by excretion of bile acids (Figure 4). Given its relative lesser importance (perhaps 1/3), variation in dietary uptake has a relatively small effect and, hence, uptake inhibitors only reduce plasma concentrations by 15–20%. Inhibiting *de novo* synthesis with HMGCoA reductase inhibitors (i.e. statins), however, can reduce plasma cholesterol by 30–50%. Bile-acid sequestrants increase the proportion of cholesterol secreted in feces and reduce blood cholesterol levels by around 15–20%. Other drugs such as niacin and fibrates reduce cholesterol concentrations by more complex mechanisms. Fibrates, in particular, bind to a class of nuclear hormone receptors called *PPARα* that have multiple effects on lipid metabolism and, in particular, raise HDL concentrations (Barbier *et al.*, 2002; Marx *et al.*, 2004). The ultimate mechanism for the reduction in plasma LDL cholesterol concentrations appears to be by lowering the free cholesterol concentration in the liver cytoplasm and, hence, upregulating transcription of LDL receptors.

The reciprocal relationship between plasma cholesterol and LDL receptor numbers is most clearly illustrated in patients with familial hypercholesterolemia (FH), which leads to deletion or loss of function of the classic LDL receptor (Figure 4). In heterozygous FH, LDL receptor numbers are halved, cholesterol levels increase on average by more than 50% (from around 5 to more than 8 mM) and risk of atherosclerosis is increased. In homozygous FH plasma, LDL receptors are lacking or greatly dysfunctional, plasma cholesterol concentrations are around 15 mM, when other low affinity pathways appear to take over, and atherosclerosis risk is increased further. Mutations in several other genes, including ApoB100, also impair liver uptake of LDL, increase plasma cholesterol concentrations and predispose affected individuals to atherosclerosis (Soutar *et al.*, 2003). Genetics therefore provide some of the strongest evidence that high blood cholesterol levels actually cause atherosclerosis – the so-called "cholesterol hypothesis". Exactly the same increased propensity is observed in rabbits lacking LDL receptors (Watanabe rabbits) or LDL receptor knockout mice. Knockout of ApoE also raises plasma cholesterol in mice (albeit mainly VLDL) and provokes atherosclerosis, while transgenic overexpression of HDL ameliorates it.

In summary, the following evidence supports the cholesterol hypothesis: plaques contain cholesterol, feeding cholesterol to rabbits or primates accelerates atherosclerosis, epidemiological studies clearly link plasma cholesterol to atherosclerosis incidence and mutations that lead to raised plasma cholesterol levels increase risk of diseases related to atherosclerosis. Finally, large controlled clinical trials with statins and other drugs establish an apparently linear relationship between the extent of cholesterol lowering and reduction in coronary events and strokes (Rabbani and Topol, 1999). The only remaining task therefore is to explain how plasma cholesterol accumulates in the artery wall (Figure 5).

Arterial cells, like all cells in the body, need cholesterol in their membranes. LPs together with other large solutes pass from the plasma to the vessel wall through a specialized reticular system in ECs. There is therefore a fluid flux carrying LDL through the artery wall that is driven by arterial blood pressure and is therefore increased by hypertension. Most LDL passes through the vessel wall, but resistance to fluid flux will obviously be greatest in the thicker walled arteries where atherosclerosis is known to occur. Indeed, a small proportion of LDL is retained in thicker walled arteries. Several runs of basic amino acids in the ApoB100 protein sequence are believed to form "sticky patches" that interact strongly with the acidic glycosaminoglycan side chains of the proteoglycan components of the arterial ECM (Camejo *et al.*, 1998).

Retained LDL becomes aggregated and then modified by hydrolytic enzymes (Camejo *et al.*, 1998) and oxidation (Chisolm and Steinberg, 2000; Navab *et al.*, 2004b).

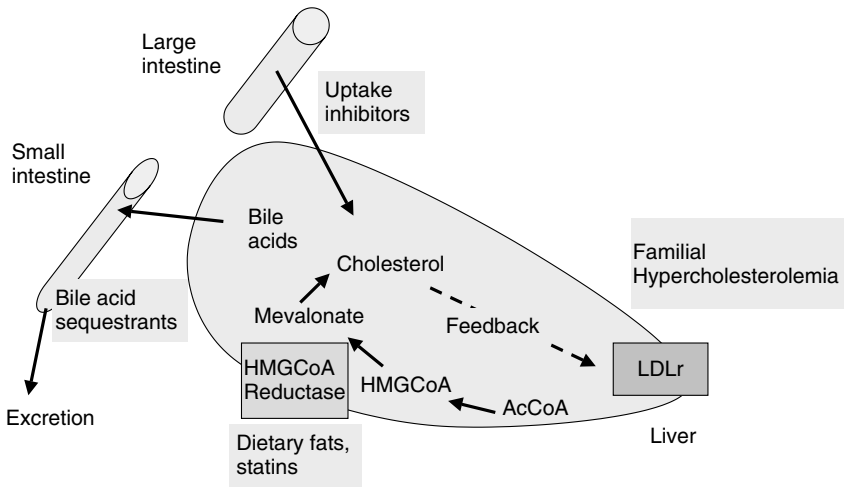

Figure 4 Physiological and pharmacological control of cholesterol metabolism. AcCoA, acetylcoenzymeA; HMGCoA, hydroxymethyglutarylcoenzymeA; LDLr, low density lipoprotein receptor; VLDL, very low density lipoprotein

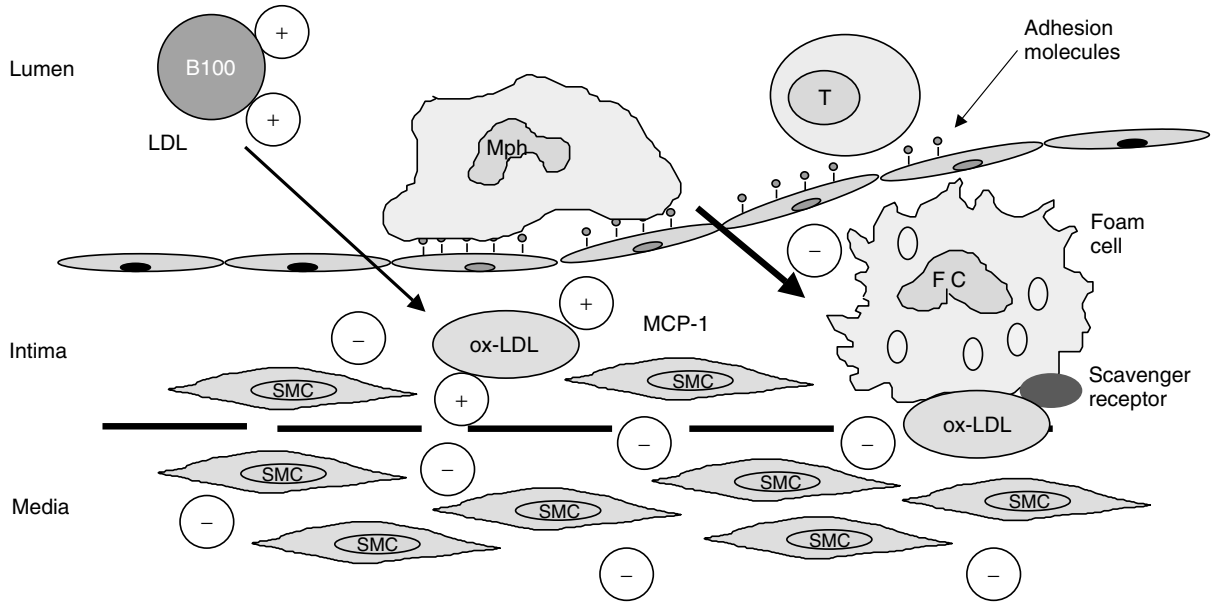

Figure 5 How cholesterol insudation provokes atherosclerosis. B100, apolipoprotein B100; FC, foam cell; (ox-)LDL, (oxidized-)low-density lipoprotein; MCP-1, monocyte chemotactic protein-1, Mph, macrophage; SMC, smooth muscle cells; T, T-lymphocyte

Plasma LPs are protected from oxidation by carrying vitamin E, which reacts preferentially with reactive oxygen species (ROS). Nevertheless, a small proportion of fatty acids in phospholipids can become peroxidated even in plasma LDL. Oxidized phospholipids can be exchanged with HDL and then reduced by paraoxonase. However, once trapped in the vascular ECM, LDL is rapidly oxidized by the surrounding ECs, VSMCs, and macrophages, which contain multiple oxidase enzymes, including NADPH (reduced nicotine adenine dinucleotide phosphate) oxidase and lipoxygenases. Firstly, vitamin E becomes depleted and then a chain reaction of radical-induced oxidation is set in motion. This ultimately gives rise to highly reactive fatty acid fragments such as malondialdehyde, which bind covalently to the surface lysines of ApoB100 and change its net charge from positive to neutral. Such damaged proteins are recognized and cleared by so-called "scavenger" receptors on macrophages. Scavenger receptors are in fact a diverse group of proteins (Chisolm and Steinberg, 2000). Since scavenger receptors are not specialized for clearance of LDL, they are not downregulated by free cholesterol like the classic LDL receptor. As a result, macrophages can become engorged with cholesterol, which is esterified and stored in vesicles leading to the typical foam cell appearance.

Considerable uncertainty surrounds the eventual fate of foam cells. The observation that fatty streaks can regress after weaning in infants or after withdrawal of cholesterol-rich diets in animals suggests that foam cells can migrate away, unload cholesterol by reverse transport, or both. Foam cells might also disappear by programmed cell death. Migration of foam cells and release of cholesterol from them can be observed *in vitro* but are hard to track *in vivo* by histological methods. However, death of macrophages is clearly observed histologically in atherosclerotic plaques (Geng and Libby, 2002). Dying macrophage tends to be found bordering the lipid core, which suggests that extracellular lipid pools accumulate as a consequence of macrophage apoptosis. Moreover, the lipid core contains abundant cell debris, including matrix vesicles, one of the hallmarks of apoptosis. Hence, there are plausible mechanisms to explain the accumulation of cholesterol in foam cells and the formation of the atheromatous gruel in plaques.

Localization of Atherosclerosis – "The Endothelial Activation Hypothesis"

One of the greatest challenges to the "cholesterol hypothesis" is the fact that atherosclerosis is a focal disease, while all parts of the artery are exposed to the same cholesterol concentration. Additional factors must be responsible, therefore, for localizing atherosclerosis. Atherosclerosis tends to occur just downstream of arterial branch points, which suggests that it is influenced either by the microanatomy at these sites (e.g. presence of intimal cushions) or by fluid dynamics. Most attention has been focused on fluid dynamics because it may be responsible for intimal cushion formation in the first place and because atherosclerosis has a similar distribution in experimental animals, which, unlike humans, do not have prominent preexisting intimal cushions. Blood flow through arteries produces two main forces, tangential wall stress and fluid shear stress. Tangential wall stress is caused by the pressure wave during the cardiac cycle. Depending on arterial compliance, this will cause more or less strain (distension) to both ECs and VSMCs. Tangential strain is of major importance for plaque rupture (see section 3) but its relationship to atherosclerosis progression is unclear (*see* **Chapter 86, Spinovascular Insufficiency**). Greater strain of

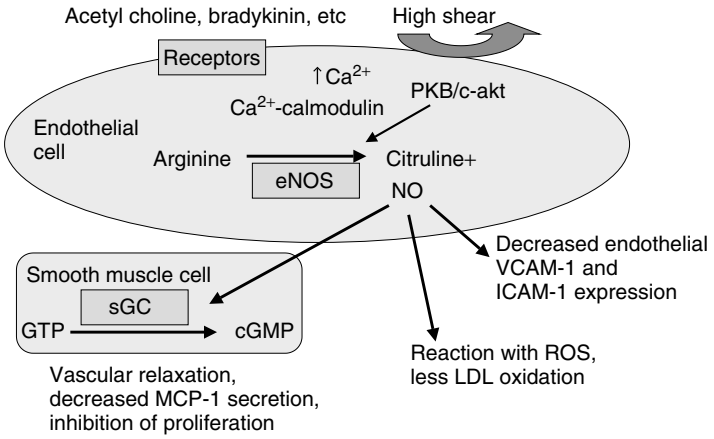

Figure 6 Production and some actions of nitric oxide (NO). c-akt, oncogene c-akt synonymous with PKB; cGMP, guanosine 3′-5′cyclic monophosphate; eNOS, endothelial nitric oxide synthase; GTP, guanosine trisphosphate; PKB, protein kinase B; sGC, soluble guanylate cyclase

unsupported epicardial coronary arteries might explain the preferential occurrence of atherosclerosis there. On the other hand, atherosclerosis is associated with greater arterial stiffness, which will exaggerate the pressure wave, increase stress but reduce strain. In segmental disease, normal arterial segments will experience increased strain, while sclerotic and calcified segments will experience less strain overall. There is, therefore, little evidence to support a connection between greater strain and atherosclerosis progression.

Shear stress is caused as the blood drags over the surface of the artery wall and is clearly experienced only by the lining ECs. Fluid dynamic modeling and flow imaging concur that atherosclerosis predominates in areas with low average shear stress, where there is reversal of flow during the cardiac cycle, and where there is least wash out from one cycle to the next (Landmesser *et al.*, 2004). Fluid shear (as well as vasodilator agents including acetyl choline) increases intracellular free Ca^{2+} concentrations in ECs and activates nitric oxide synthase (NOS) through its calmodulin subunit (Figure 6). This leads to an acute increase in production of NO, which diffuses to VSMCs and activates soluble guanylate cyclase (sGC). The end result is vasodilatation and greater compliance. Increased shear also upregulates transcription of the NOS gene, in part by activating the PI3-kinase/Akt pathway. This leads to a longer term, adaptive increase in NO production. Arterial vasodilatation reduces resistance to the flux of solutes including LDL across the artery wall. NO is also an antioxidant and these two mechanisms might therefore reduce trapping and oxidation of LDL. NO also has a potent anti-inflammatory effect (*see* **Chapter 9, The Demography of Aging**) that may be even more important to explain its role in decreasing atherosclerosis (see Section Atherosclerosis as an Inflammatory Disease).

This "endothelial activation" hypothesis of atherosclerosis progression gains support from other experimental and clinical data (Landmesser *et al.*, 2004). For example, inhibition of NOS increases, and gene transfer of NOS decreases, atherosclerosis in diet-induced and genetic models of hypercholesterolemia. Moreover, hypercholesterolemia conversely impairs NO-mediated vasodilatation, although, surprisingly, not principally by inhibiting NOS. Instead, hypercholesterolemia decreases NO availability by stimulating production of ROS, principally superoxide radicals (Figure 7). These react chemically with NO to produce peroxynitrite, which can nitrosylate proteins and cause tissue injury in its own right. Several oxidases might contribute to superoxide production but most experiments implicated NADPH oxidase. This is upregulated by hypercholesterolemia and several other risk factors for atherosclerosis, including smoking, diabetes, hypertension, hyperhomocysteinemia, and angiotensin II. Another consequence of ROS production is consumption of the tetrahydrobiopterin cofactor of NOS, which can convert NOS itself to an oxidase.

Clinical studies indicate that atherosclerosis and risk factors again including smoking, diabetes, hypertension,

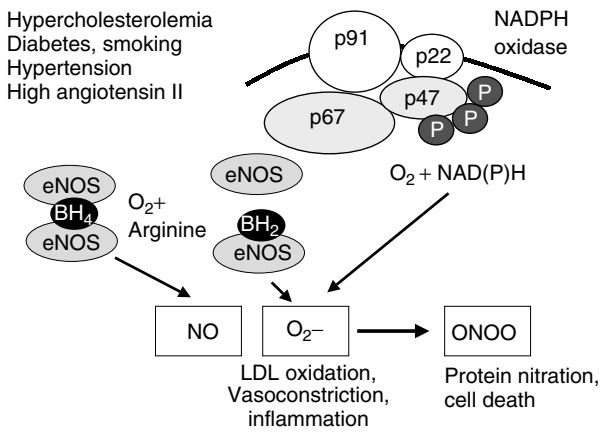

Figure 7 Causes and consequences of reactive oxygen species (ROS) formation. BH_2, dihydrobiopterin; BH_4, tetrahydrobiopterin; eNOS, endothelial nitric oxide synthase; NADPH, reduced nicotine adenine dinucleotide phosphate, NO, nitric oxide, O_2^-, superoxide anion, ONOO, peroxinitrite, P; phosphate; p22, 47, 67, 91, subunits of NADPH oxidase of the corresponding relative molecular mass in kDa

hyperhomocysteinemia, and angiotensin II can reduce NO-mediated vasodilatation. This can be measured directly in the coronary arteries using angiography, in the coronary resistance vessels by measuring flow, or noninvasively in the brachial or femoral arteries using ultrasound imaging. Consistent with experimental data, vasodilatation can be provoked using acetylcholine or flow shear (e.g. reactive hyperemia). Vasodilatation is abolished by pharmacological inhibitors of NOS and potentiated by the NOS substrate L-arginine or by the antioxidant, ascorbic acid. Most interestingly, impaired NO-mediated vasodilatation is a good prognostic indicator for coronary atherosclerosis and its associated clinical events. This not only strongly supports the clinical relevance of the "endothelial activation" hypothesis but also suggests that a simple test of endothelial function might have a future role in risk stratification in populations and perhaps even individual patients.

Atherosclerosis as an Inflammatory Disease

The presence of macrophage foam cells most clearly demonstrates the inflammatory component of atherosclerosis. There are also a few polymorphonuclear leukocytes and a large number of other mononuclear cells associated with immune-inflammatory mechanisms. These include dendritic cells, various populations of T lymphocytes, B lymphocytes, and mast cells (Hansson *et al.*, 2002; Libby *et al.*, 2002).

Recruitment of leukocytes to foci of inflammation requires initial capture (so-called "rolling"), firm adhesion, and then exit, "diapedesis", from the circulation (Weber, 2003) (Figure 8). Rolling requires interaction between the selectin class of adhesion molecules and their counterreceptor glycoproteins. Consistent with this, knockout of P-selectin, which occurs on platelets and ECs, reduces atherosclerosis in mice. Firm adhesion depends on immunoglobulin-family member adhesion proteins, including vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1). These dock with $\beta 2$ integrin receptors on leucocytes, provided the leucocytes are concomitantly activated by a chemokine such as monocyte chemotactic peptide-1 (MCP-1). Knockout or knockdown of VCAM-1, ICAM-1 and MCP-1 decreases atherosclerosis in mice. Interestingly, nitric oxide potently inhibits the upregulation of VCAM-1 and ICAM-1 in ECs and MCP-1 in VSMC. Together with its antioxidant function, it suggests that NO is a natural antiatherosclerotic defense mechanism. Conversely, impairment of endothelial NO by risk factors for atherosclerosis and in areas of low shear explains both the development and location of inflammation associated with atherosclerotic plaques.

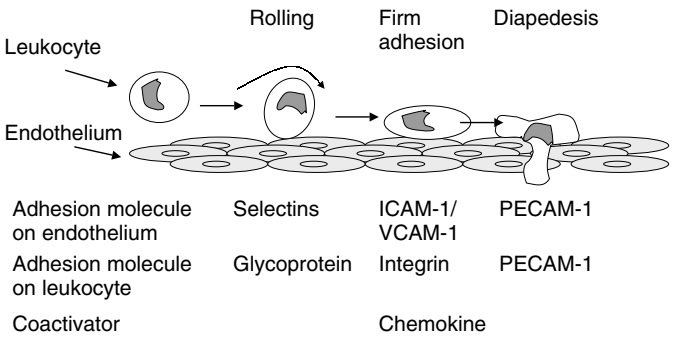

Figure 8 Leukocyte adhesion to and migration across the endothelium. ICAM-1, intracellular adhesion molecule-1, PECAM-1, platelet endothelial cell adhesion molecule-1, VCAM-1, vascular cell adhesion molecule-1

Diapedesis of leucocytes is mediated by a complex of adhesion molecules that are present in the junctional region between endothelial cells, including, importantly, platelet endothelial cell adhesion molecule-1 (PECAM-1) (Weber, 2003). Entry of other inflammatory cells may be mediated by similar adhesion molecules but probably in response to a wider range of chemokines. Chemokines not only activate leucocyte adhesion but also promote chemotaxis into the intima.

Oxidation of LDL may be the initial stimulus for recruitment of circulating monocytes (Navab *et al.*, 2004b). Partial oxidation of phospholipids is sufficient, certainly not enough for recognition of LDL by the scavenger receptor. This "minimally modified LDL" (MM-LDL) stimulates overexpression of adhesion molecules. Moreover, MM-LDL increases MCP-1 secretion from VSMCs and therefore satisfies both requirements for firm adherence. The role of oxidized LDL in this process is supported by recent studies showing that HDL or an HDL-mimetic peptide can scavenge oxidized lipids from LDL, decrease mouse monocyte activation *in vitro* and atherosclerosis formation *in vivo*. In mice, endothelial VCAM-1 expression is evident even before frank lesion formation. However, VCAM-1 expression is hard to detect in human atherosclerotic arteries, and its function may be substituted by ICAM-1.

Fully oxidized LDL inhibits migration of monocytes, possibly mediating their retention within lesions. High concentrations of oxidized LDL can also promote death of ECs, VSMCs, and macrophages by apoptosis. Increased proliferation of ECs is noted in areas prone to atherosclerosis, indicative of replacement of dead cells. During mitosis, the endothelium shows increased permeability to large solutes such as LDL, which could perpetuate a vicious circle. There are also reduced numbers of circulating endothelial precursor cells with age and risk factors for atherosclerosis, which may therefore retard endothelial repair (Rabelink *et al.*, 2004).

Immune deficiency reduces atherosclerosis in susceptible mice, and this can be reconstituted by transplanting T- but not B lymphocytes (Hansson *et al.*, 2002). Although T-suppressor cells, and natural killer lymphocytes are found in human atherosclerotic lesions, T-helper (Th) cells predominate. These are polarized into proinflammatory Th1 or anti-inflammatory Th2 cells, by the interleukins (ILs) and other cytokines that they secrete and respond to. Th1 cells mature in response to IL-12 and IL-18; they produce IL-2 and interferon γ (IFNγ), which inhibits Th2 development. Conversely, Th2 cells mature in response to IL-2 and IFNγ; they produce IL-4 and IL-10, which block Th1 development. Th1 lymphocytes appear to promote atherosclerosis since lesion formation is decreased in mice by blockade

of IL-18 or knockout of IFNγ or its receptors (Hansson *et al.*, 2002). Conversely, injection of IL-12, IL-18 or IFNγ, enhances atherosclerosis in mice. Furthermore, IL-10 deficiency increases and IL-10 overexpression reduces atherosclerosis in mouse models. The presence in human atherosclerotic lesions of high levels of IL-12 and lower levels of IL-10, also implicates Th1 rather than Th2 lymphocytes.

Human lesions contain clones of T cells that respond to a variety of antigens that includes human heat shock proteins (HSPs). HSPs from bacterial pathogens, most plausibly *Chlamidia pneumoniae*, could trigger an autoimmune response to human HSPs (Xu, 2002). Early work showed that immunizing rabbits with HSP-47 provoked atherosclerosis in cholesterol-fed rabbits. More recently, however, mucosal immunization with HSP-65 (Maron *et al.*, 2002) was shown to decrease atherosclerosis in mice. These apparently conflicting results could be explained if antigen challenge caused a stimulatory Th1 response in one experiment but a Th2/B cell response that induced tolerance in the other. Interestingly, other T-cell clones respond to oxidized-LDL (ox-LDL), which also provokes a B cell response since antibodies are frequently observed in humans. Titers of anti-ox-LDL increase with age, with risk factors for atherosclerosis and with incidence of CHD. Immunization of mice or rabbits with ox-LDL produces a B cell response and decreases atherosclerosis. Taken together, these studies raise the exciting prospect of immunization against atherosclerosis (Hansson, 2002).

Fibrous Tissue Expansion – "Sclerosis"

The fibrous ECM consists of collagens, elastin, proteoglycans, and multiadhesive glycoproteins (Newby, 2002; Wight and Merrilees, 2004). Ultrastructural examination demonstrates that ECs sit upon and VSMCs are surrounded by a thin basement membrane that is rich in the network forming type IV collagen, in heparin sulphate containing proteoglycans (e.g. perlecan, syndecans), and in the glycoprotein, laminin (Figure 1a). In contrast, the interstitial matrix between VSMCs consists mainly of fibrillar types I and III collagen, elastin, dermatan sulphate containing proteoglycans, such as versican, and the glycoprotein, fibronectin. In the atherosclerotic intima, there is a generalized overexpression of ECM. VSMCs surrounded by multiple layers of basement membrane are present. Areas of acellular connective tissue are frequently observed, which suggests that the cells once present have emigrated or died. There is upregulation of unusual collagens (e.g. type VII) and several additional glycoproteins become abundant, including osteopontin, tenascin C, vitronectin, and thrombospondin. These changes not only influence the mechanical properties of the ECM but also regulate processes such as calcification and VSMC proliferation, migration, and death (Newby, 2002).

VSMC normally contain mainly contractile fibers and have a very low rate of new messenger RNA and protein synthesis. Nevertheless, VSMC can modulate in culture, in injured arteries and to a degree in atherosclerotic plaques into a phenotype that actively produces all components of the ECM. Phenotypic modulation is actually a continuous spectrum with purely "contractile" and "synthetic" VSMC as its two poles (Owens *et al.*, 2004). This plasticity suggests that intimal VSMC could indeed derive from migration and proliferation of normal medial VSMCs. However, other sources of cells could contribute or even predominate. Firstly, there is much evidence in animals and some in humans for a preexisting SMC phenotype, with altered morphology and greater synthetic and replicative capacity (Hao *et al.*, 2003). Secondly, some intimal VSMC may be differentiated from circulating precursors or transdifferentiated from ECs. Fibroblasts from the adventitia might also migrate across the media to the intima (Zalewski *et al.*, 2002). These uncertainties have to be borne in mind when describing the relevant properties of VSMC.

A variety of growth factors stimulate VSMC proliferation in tissue culture, and a lesser number also act as chemoattractants (Newby and George, 1993; Ross, 1999). These include peptide growth factors and vasoconstrictor agents (e.g. angiotensin II, 5-hydroxytryptamine and thrombin) that stimulate VSMC proliferation in part by transactivating epidermal growth factor receptors. Conversely, vasodilator agents including NO and prostacyclin inhibit VSMC proliferation by interfering with the signaling pathways downstream of growth factor receptors (Newby *et al.*, 1992). Among the peptide growth factors, intervention studies in balloon injury models establish a role for platelet-derived growth factor (PDGF) in intimal migration of VSMC, and for fibroblast growth factor-2 in VSMC proliferation. Insulin-like growth factor-1 is an ancillary growth factor and an important survival factor for intimal VSMC. The role of PDGF may translate into human atherosclerosis, since PDGF is detected at elevated levels in plaques. PDGF can be produced from EC, phenotypically modulated VSMC and macrophages all of which are localized to the atherosclerotic intima (Figure 1b). PDGF could establish a chemotactic gradient that attracts VSMC from the media to make up the fibrous cap of plaques (Figure 1b).

In the vessel wall, as opposed to in culture, responses to growth factors are clearly suppressed by the need to overcome physical and biochemical restraints. Matrix metalloproteinases (MMPs) are a group of more than 20 zinc-containing proteases that together remodel the ECM. Induction of MMP activity requires a combination of inflammatory cytokines, such as IL-1 (Figure 1b), as well as growth factors. MMP activity is essential for migration of VSMCs (Galis and Khatri, 2002; Newby, 2005) because proteolysis disrupts the physical interactions, for example, between VSMC and basement membrane components. Indeed MMPs mediate disappearance of basement membranes in migrating VSMCs (Newby, 2005). MMPs also facilitate VSMC proliferation, probably in combination with other proteases (Newby, 2005). These could include plasmin, a serine protease, and cathepsins, which are thiol proteases (Liu *et al.*, 2004). VSMC proliferation requires not only the presence of growth factors but also the correct engagement of cell surface integrins and ECM components (Assoian and Marcantonio, 1996).

Signals from these pathways come together to downregulate cyclin-dependent kinase inhibitors and permit cells to progress round the cell cycle (Bond *et al.*, 2004). Remodeling of the existing ECM by proteases and synthesis of new cellular and ECM proteins are all necessary to relieve the constraints on VSMC proliferation. These mechanisms appear designed to avoid excessive fibrous proliferation.

THE TRANSITION FROM STABLE TO UNSTABLE ATHEROSCLEROTIC PLAQUES

The final collapse of a plaque cap is likely to involve the chance interplay of acute hemodynamic factors superimposed on a chronic process of plaque destabilization (Figure 9). Consistent with this idea, plaques with ruptured caps contain a thinner fibrous cap with less collagen and a larger lipid core than stable plaques (Davies, 2000; Virmani *et al.*, 2000). Plaque rupture is therefore the consequence of mechanical failure of a thin, weak cap that is greatly deformed each cardiac cycle by being stretched over the surface of a large lipid core. Hence, acutely increased heart rate and blood pressure will add to the likelihood of rupture. Moreover, plaques tend to rupture at the shoulder regions, where the calculated strain is greatest (Lee *et al.*, 1996). There is no correlation with percentage of occlusion; indeed most plaque ruptures occur on hemodynamically insignificant plaques (Davies, 2000). Ruptured plaques, particularly the shoulder regions where the plaque is growing, have a greater proportion of macrophages, and fewer VSMCs. Hence the cap may be chronically weakened by the presence of macrophages and by the unavailability of VSMCs to secrete strength giving collagens. Plaque rupture is also more likely in outwardly remodeled plaques, which may imply that the same or similar processes to those that weaken the plaque cap also allow the expansive remodeling of the media.

Macrophages secrete a broad range of MMPs (Galis and Khatri, 2002) and cathepsins (Liu *et al.*, 2004) that are capable in principle of degrading the entire ECM. Decreases in MMP levels closely parallel reduction of macrophage numbers after cessation of cholesterol feeding or use of cholesterol-lowering drugs. On the other hand, MMPs promote vascular repair by permitting entry of inflammatory cells and freeing VSMC to migrate, change phenotype, and proliferate (as mentioned earlier). This suggests that some deregulation of the factors that stimulate MMP secretion, which include oxidative stress, soluble inflammatory mediators, and T lymphocytes acting through the CD40/CD40 ligand system, provokes plaque instability (Newby, 2005). This link via T lymphocytes to immune activation suggests that the presence of pathogens such as *C. pneumoniae* might not only provoke plaque growth but also trigger unstable events.

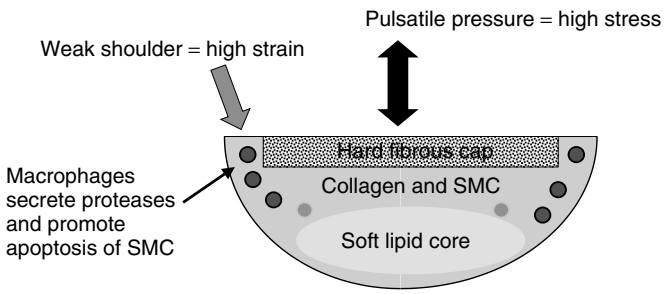

Figure 9 Plaque rupture – an unhappy combination of adverse physical forces and unfavorable cell biology. SMC, smooth muscle cell

Cell death is also likely to play a key role in plaque destabilization (Bennett, 1999; Geng and Libby, 2002). Apoptosis of ECs, VSMCs, and macrophages is observed in human and experimental plaques. It occurs together with VSMC proliferation during vascular repair, where it presumably helps to prevent or reverse excessive intimal thickening. On the other hand, apoptosis, triggered by oxidative stress and inflammatory cells acting through cytokines and engagement of cell surface Fas ligand, is believed to underlie development of the lipid core. Apoptosis of VSMC may leave acellular areas of ECM, which could be vulnerable to degradation by proteases, without the possibility of being resynthesized.

Not all plaque ruptures or erosions result in myocardial infarction and many are completely asymptomatic (Davies, 2000). The decisive factor is the extent of thrombus formation, which is influenced by the interaction of tissue factor present in the plaque with cellular and protein components in the plasma. A small mural thrombus may not give rise to symptoms but can become incorporated into and rapidly expand the plaque. A larger waxing and waning thrombus underlies unstable angina, while an occlusive thrombus causes infarction. The important concept is that both plaque and blood characteristics determine the final outcome.

PROSPECTS FOR THERAPY

The "cholesterol" hypothesis has motivated the development of several classes of cholesterol-lowering drugs including, bile-acid sequestrants, HMGCoA reductase inhibitors, and cholesterol uptake inhibitors. Cholesterol lowering stops atherosclerosis progression and reduces unstable events by around a third, which prolongs life both in primary and secondary prevention (Rabbani and Topol, 1999). This tremendous success story prompts a search for even more effective single or adjunctive therapies based on inhibiting steps in the accumulation of cholesterol or other facets of atherosclerosis.

While studies with antioxidant vitamins proved at best equivocal, promising experimental studies examine the possibility of preventing LDL oxidation using a stabilized HDL-mimetic peptide (Navab *et al.*, 2002; Navab *et al.*, 2004a). The "endothelial dysfunction" hypothesis provides new prognostic indicators (Landmesser *et al.*, 2004). It may also explain the atheroprotective effect of angiotensin-II converting enzyme inhibitors. These decrease local angiotensin-II levels and could block the upregulation of NADPH oxidase,

reduce oxidative stress and preserve NO. The inflammatory component of atherosclerosis is an attractive target for intervention. PPARγ agonists (e.g. the thiazolidinediones), have an anti-inflammatory effect, and are undergoing large-scale trials that will monitor cardiovascular endpoints in diabetic patients (Barbier *et al.*, 2002; Marx *et al.*, 2004). Involvement of immune activation led to antibiotic trials, which were ultimately disappointing, but also raises the tantalizing prospect of immunization against atherosclerosis (Hansson, 2002). Finally, knowledge of the roles of matrix remodeling in the processes of plaque growth and destabilization suggest new protease inhibitor therapies. These are examples of the exciting prospects for developing new therapies based, as in the past, on sound knowledge of the pathogenesis of atherosclerosis.

KEY POINTS

- Atherosclerotic plaques contain cholesterol-rich gruel, inflammatory leucocytes, and expanded connective tissue. They develop over many years before provoking ischemia or thrombosis.
- The lipid insudation hypothesis accounts for the following facts: plaques contain cholesterol; feeding cholesterol to rabbits or primates accelerates atherosclerosis; epidemiological studies link plasma cholesterol to atherosclerosis incidence; mutations causing raised plasma cholesterol levels increase risk of atherosclerosis and that large controlled clinical trials with statins and other drugs reduce coronary events and strokes.
- Early endothelial dysfunction occurs in atherosclerosis and explains the focal localization of atherosclerosis and many nonlipid risk factors
- Response to injury (including that caused by oxidized lipids) explains the inflammatory nature of atherosclerosis and accounts for fibrous cap formation through the production of growth factors and extracellular proteases
- Increased mechanical stress together with weakening of the fibrous cap by cell death and proteolysis of the ECM probably account for plaque rupture, which triggers myocardial infarction. New drug therapies are being developed based on this concept.

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Peripheral Vascular Disease in Elderly Persons

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INTRODUCTION

Peripheral vascular disease (PVD) is a chronic arterial occlusive disease of the lower extremities caused by atherosclerosis. PVD may cause intermittent claudication, which is pain or weakness with walking that is relieved with rest. The muscle pain or weakness after exercise occurs distal to the arterial obstruction. Since the superficial femoral and popliteal arteries are most commonly affected by atherosclerosis, the pain of intermittent claudication is most commonly localized to the calf. Atherosclerotic obstruction of the distal aorta and its bifurcation into the two iliac arteries may cause pain in the buttocks, hips, thighs, or the inferior back muscles as well as the legs.

Only one-half of elderly persons with documented PVD are symptomatic. Persons with PVD may not walk far or fast enough to induce muscle ischemic symptoms because of comorbidities such as pulmonary disease or arthritis, may have atypical symptoms unrecognized as intermittent claudication (McDermott *et al.*, 2001), may fail to mention their symptoms to their physician, or may have sufficient collateral arterial channels to tolerate their arterial obstruction. Women with PVD have a higher prevalence of leg pain on exertion and at rest, poorer functioning, and greater walking impairment from leg symptoms than men with PVD (McDermott *et al.*, 2003). Poorer leg strength in women contributes to poorer lower extremity functioning in women with PVD than in men with PVD (McDermott *et al.*, 2003).

If the arterial flow to the lower extremities cannot meet the needs of resting tissue metabolism, critical lower extremity ischemia occurs with pain at rest or tissue loss. Critical ischemia causes rest pain in the toes or foot with progression to ulceration or gangrene. Chronic arterial insufficiency ulcers commonly develop at the ankle, heel, or leg. Mummified, dry, black toes, or devitalized soft tissue covered by a crust is gangrene caused by ischemic infarction. Suppuration often develops with time, and dry gangrene changes to wet gangrene.

NONINVASIVE DIAGNOSIS

Persons with PVD of the lower extremities have decreased or absent arterial pulses. Noninvasive tests used to assess lower extremity arterial blood flow include measurement of ankle and brachial artery systolic blood pressures, characterization of velocity waveform, and duplex ultrasonography. Measurement of ankle and brachial artery systolic blood pressures using a Doppler stethoscope and blood pressure cuffs allows calculation of the ankle-brachial index (ABI), which is normally 0.9 to 1.2. An ABI of less than 0.90 is 95% sensitive and 99% specific for the diagnosis of PVD (McDermott *et al.*, 2002). The lower the ABI, the more severe the restriction of arterial blood flow, and the more serious the ischemia. ABIs of 0.6 to 0.9 usually correlate with mild-to-moderate intermittent claudication. ABIs of 0.4 to 0.6 usually correlate with severe intermittent claudication. With ABIs between 0.25 and 0.4, rest pain and tissue loss are often found. Patients with calcified arteries from diabetes mellitus or renal failure occasionally have relatively noncompressible arteries leading to falsely elevated ABI values in the normal range.

In addition to measuring arterial pressure in nonpalpable arteries, Doppler ultrasound methods allow characterization of the flow versus time velocity waveform. Finding biphasic flow at the groin or monophasic flow more distally is evidence of arterial obstruction even when ABI measurements are falsely increased to normal levels because of calcification.

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Duplex ultrasonography combines Doppler frequency measurements with two-dimensional images of blood vessels. The severity of flow restriction caused by an arterial stenosis can be accurately assessed by this most comprehensive noninvasive method (Kohler *et al.*, 1987).

PREVALENCE

The prevalence of PVD increases with age. (Schroll and Munck (1981) found that the prevalence of peripheral arterial disease (PAD) was 16% in men and 13% in women aged 60 years (Table 1). (Criqui *et al.* (1985) reported that the prevalence of PVD was 5.6% in persons aged 38 to 59 years old, 15.9% in persons aged 60 to 69 years old, and 33.8% in persons aged 70 to 82 years old (Table 1). In the Cardiovascular Health Study, PVD was present in 13.9% of 2214 men aged ≥65 years and in 11.4% of 2870 women aged ≥65 years without cardiovascular disease (Newman *et al.*, 1993) (Table 1). Symptomatic PVD was present in 20% of 467 men, mean age 80 years, and in 13% of 1444 women, mean age 81 years, living in the community and being seen in a geriatrics clinic (Ness *et al.*, 2000) (Table 1). In the Rotterdam Study, PVD was present in 16.9% of 2589 men aged ≥55 years and in 20.5% of 3861 women aged ≥55 years (Meijer *et al.*, 1998) (Table 1). The prevalence of symptomatic PVD was 32% in 1160 men, mean age 80 years, and 26% in 2464 women, mean age 81 year, living in a nursing home (Aronow *et al.*, 2002a) (Table 1). The prevalence of symptomatic PVD in persons living in a nursing home was also 29% in 268 blacks, mean age 81 years, 24% in 71 Hispanics, mean age 81 years, and 23% in 1310 whites, mean age 82 years (Aronow, 1992). (Table 1). The prevalence of symptomatic PVD was 26.7% in 386 men, mean age 72 years, and 17.1% in 620 women, mean age 72 years, living in the community and seen in a university general medicine clinic (Ness *et al.*, 2005) (Table 1).

Table 1 Prevalence of peripheral vascular disease

Study	Prevalence (%)
360 men aged 60 years (Schroll and Munck, 1981)	16
306 women aged 60 years (Schroll and Munck, 1981)	13
158 persons aged 38–59 years (Criqui *et al.*, 1985)	5.6
161 persons aged 60–69 years (Criqui *et al.*, 1985)	15.9
294 persons aged 70–82 years (Criqui *et al.*, 1985)	33.8
2214 women aged ≥65 years (Newman *et al.*, 1993)	13.9
2870 women aged ≥65 years (Newman *et al.*, 1993)	11.4
467 men, mean age 80 years (Ness *et al.*, 2000)	20[a]
1444 women, mean age 81 years (Ness *et al.*, 2000)	13[a]
2589 men aged ≥55 years (Meijer *et al.*, 1998)	16.9
3861 women aged ≥55 years (Meijer *et al.*, 1998)	20.5
1160 men, mean age 80 years (Aronow *et al.*, 2002a)	32[a]
2464 women, mean age 81 years (Aronow *et al.*, 2002a)	26[a]
268 blacks, mean age 81 years (Aronow, 1992)	29[a]
71 Hispanics, mean age 81 years (Aronow, 1992)	24[a]
1310 whites, mean age 82 years (Aronow, 1992)	23[a]
386 men, mean age 72 years (Ness *et al.*, 2005)	26.7[a]
620 women, mean age 72 years (Ness *et al.*, 2005)	17.1[a]

[a]Symptomatic peripheral vascular disease.

RISK FACTORS

Modifiable risk factors that predispose to PVD include cigarette smoking (Schroll and Munck, 1981; Ness *et al.*, 2000, 2005; Hughson *et al.*, 1978; Beach *et al.*, 1982; Reunanen *et al.*, 1982; Pomrehn *et al.*, 1986; Stokes *et al.*, 1987; Aronow *et al.*, 1988; Murabito *et al.*, 2002; Sukhija *et al.*, 2003), diabetes mellitus (Schroll and Munck, 1981; Ness *et al.*, 2000, 2005; Hughson *et al.*, 1978; Beach *et al.*, 1982; Reunanen *et al.*, 1982; Pomrehn *et al.*, 1986; Stokes *et al.*, 1987; Aronow *et al.*, 1988; Murabito *et al.*, 2002; Sukhija *et al.*, 2003; Beach *et al.*, 1979), hypertension (Schroll and Munck, 1981; Ness *et al.*, 2000, 2005; Hughson *et al.*, 1978; Stokes *et al.*, 1987; Aronow *et al.*, 1988; Murabito *et al.*, 2002; Sukhija *et al.*, 2003; Aronow, 2002a, 2003), dyslipidemia (Schroll and Munck, 1981; Ness *et al.*, 2000, 2005; Hughson *et al.*, 1978; Reunanen *et al.*, 1982; Pomrehn *et al.*, 1986; Stokes *et al.*, 1987; Aronow *et al.*, 1988; Murabito *et al.*, 2002; Sukhija *et al.*, 2003; Beach *et al.*, 1979; Aronow and Ahn, 1994a; Aronow, 2001, 2002b), increased plasma homocysteine levels (Boushey *et al.*, 1995; Malinow *et al.*, 1989; Clarke *et al.*, 1991; Aronow and Ahn, 1998), and hypothyroidism (Mya and Aronow, 2003). Significant independent risk factors for PVD in 467 men, mean age 80 years, and in 1444 women, mean age 81 years, living in the community and seen in an academic geriatrics practice were age (odds ratio = 1.05 for each 1-year increase in age in men and 1.03 for each 1-year increase in age in women); current cigarette smoking (odds ratio = 2.6 for men and 4.6 for women); systolic or diastolic hypertension (odds ratio = 2.2 for men and 2.8 for women); diabetes mellitus (odds ratio = 6.1 for men and 3.6 for women); serum high-density lipoprotein cholesterol (odds ratio = 0.95 for each 1 mg dl^{-1} increase in men and 0.97 for each 1 mg dl^{-1} increase in women); and serum low-density lipoprotein cholesterol (odds ratio = 1.02 for each 1 mg dl^{-1} increase in men and in women) (Ness *et al.*, 2000).

In a study of 1006 persons, mean age 72 years, seen in a university general medicine clinic, symptomatic PVD was present in 209 of 1006 persons (20.8%) (Ness *et al.*, 2005). In this study, the prevalence of symptomatic PVD was increased 1.4 times by male gender, 2.6 times by cigarette smoking, 1.2 times by hypertension, 2.1 times by diabetes mellitus, and 1.5 times by dyslipidemia (Ness *et al.*, 2005).

In 147 men and women with PVD and 373 men and women without PVD, mean age 81 years, plasma homocysteine was a significant independent risk factor for PVD with an odds ratio of 1.13 for each 1 μmol l^{-1} increase (Aronow and Ahn, 1998). In 249 men and women, mean age 79 years, the prevalence of PVD was significantly higher in persons with subclinical hypothyroidism (14 of 18 persons or 78%) than in persons with euthyroidism (40 of 231 persons or 17%) (Mya and Aronow, 2003).

COEXISTENCE OF OTHER ATHEROSCLEROTIC DISORDERS

PVD coexists with other atherosclerotic disorders (Table 2) (Ness *et al.*, 2005; Sukhija *et al.*, 2003; Aronow and Ahn, 1994b; Ness and Aronow, 1999; Aronow *et al.*, 2001a,b). In a study of 1886 men and women, mean age 81 years, 270 of 468 persons (58%) with PVD had coexistent coronary artery disease (CAD) and 159 of 468 persons (34%) with PVD had prior ischemic stroke (Aronow and Ahn, 1994b) (Table 2). In a study of 1802 men and women, mean age 80 years, living in the community and seen in an academic geriatrics practice, 161 of 236 persons (68%) with PVD had coexistent CAD and 100 of 236 persons (42%) with PVD had coexistent prior ischemic stroke (Ness and Aronow, 1999) (Table 2). In a study of 1006 men and women, mean age 72 years, living in the community and seen in a university general medicine clinic, 131 of 209 persons (63%) with PVD had coexistent CAD and 75 of 209 persons (36%) with PVD had prior ischemic stroke (Ness *et al.*, 2005).

In 924 men, mean age 80 years, the prevalence of PVD was 1.5 times significantly higher in 336 men with mitral annular calcium than in 588 men without mitral annular calcium (43% versus 28%) (Aronow *et al.*, 2001a) (Table 2). In 1881 women, mean age 81 years, the prevalence of PVD was 1.6 times significantly higher in 985 women with mitral annular calcium than in 896 women without mitral annular calcium (31% versus 19%) (Aronow *et al.*, 2001a) (Table 2).

In 989 men, mean age 80 years, the prevalence of PVD was 1.6 times significantly higher in 141 men with valvular aortic stenosis than in 848 men without valvular aortic stenosis (48% versus 30%) (Aronow *et al.*, 2001b) (Table 2). In 1998 women, mean age 81 years, the prevalence of PVD was 1.7 times significantly higher in 321 women with valvular aortic stenosis than in 1677 women without valvular aortic stenosis (39 versus 23%) (Aronow *et al.*, 2001b) (Table 2).

In 279 men and women, mean age 71 years, with documented PVD, and in 218 men and women, mean age 70 years, without PVD with normal ABIs undergoing coronary angiography for suspected CAD, the prevalence of obstructive CAD was significantly higher in persons with PVD (98%) than in persons without PVD (81%) (Sukhija *et al.*, 2003) (Table 2). The prevalence of left main CAD was significantly higher in persons with PVD (18%) than in persons without PVD (<1%) (Sukhija *et al.*, 2003) (Table 2). The prevalence of three-vessel or four-vessel CAD was significantly higher in persons with PVD (63%) than in persons without PVD (11%) (Sukhija *et al.*, 2003) (Table 2).

Table 2 Coexistence of peripheral vascular disease with other atherosclerotic disorders in older persons

Study	Result
1886 persons, mean age 81 years (Aronow and Ahn, 1994b)	If PVD was present, 58% had coexistent CAD and 34% had prior ischemic stroke
1802 persons, mean 80 years (Ness and Aronow, 1999)	If PVD was present, 68% had coexistent CAD and 42% had prior ischemic stroke
1006 persons, mean 72 years (Ness *et al.*, 2005)	If PVD was present, 63% had coexistent CAD and 36% had prior ischemic stroke
924 men, mean age 80 years (Aronow *et al.*, 2001a)	PVD was 1.5 times higher in men with mitral annular calcium than in men without mitral annular calcium
1881 women, mean age 81 years (Aronow *et al.*, 2001a)	PVD was 1.6 times higher in women with mitral annular calcium than in women without mitral annular calcium
989 men, mean age 80 years (Aronow *et al.*, 2001b)	PVD was 1.6 times higher in men with aortic stenosis than in men without aortic stenosis
1998 women, mean age 81 years (Aronow *et al.*, 2001b)	PVD was 1.7 times higher in women with aortic stenosis than in women without aortic stenosis
279 persons with PVD, mean age 71 years, undergoing coronary angiography for suspected CAD (Sukhija *et al.*, 2003)	Obstructive CAD was present in 98% of persons, left main CAD in 18% of persons, and three- or four-vessel CAD in 63% of persons
218 persons without PVD, mean age 70 years, undergoing coronary angiography for suspected CAD (Sukhija *et al.*, 2003)	Obstructive CAD was present in 82% of persons, left main CAD in <1% of persons, and three- or four-vessel CAD in 11% of persons

PVD, peripheral vascular disease; CAD, coronary artery disease.

CARDIOVASCULAR MORTALITY AND MORBIDITY

Persons with PVD are at increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events (Reunanen *et al.*, 1982; Criqui *et al.*, 1992; Smith *et al.*, 1990; Aronow *et al.*, 1992; Vogt *et al.*, 1993; Eagle *et al.*, 1994; Farkouh *et al.*, 1994; Simonsick *et al.*, 1995; Newman *et al.*, 1997). At 10-year follow-up of 565 men and women, mean age 66 years, PVD significantly increased the risk of all-cause mortality (relative risk = 3.1), of mortality from cardiovascular disease (relative risk = 5.9), and of mortality from CAD (relative risk = 6.6) (Criqui *et al.*, 1992). At 4-year follow-up of 1492 women, mean age 71 years, an ABI of 0.9 or less was associated with a relative risk of 3.1 for all-cause mortality after adjustment for age, smoking, and other risk factors (Vogt *et al.*, 1993).

In a prospective study of 291 men and women, mean age 82 years, with PVD, CAD was present in 160 persons (55%) (Aronow *et al.*, 1992). Silent myocardial ischemia detected by 24-hour ambulatory electrocardiography was present in 60 of 160 persons (38%) with PVD and CAD and in 26 of 131 persons (20%) with PVD and no clinically evident CAD (Aronow *et al.*, 1992). At 43-month follow-up, new coronary events developed in 54 of 60 persons (90%) with PVD, CAD, and silent myocardial ischemia and in 59 of 100 persons (59%) with PVD, CAD, and no silent myocardial ischemia (Aronow *et al.*, 1992). New coronary events also developed in 18 of 26 persons (69%) with PVD, no CAD, and silent myocardial ischemia and in 34 of 105 persons (32%) with PVD, no CAD, and no silent myocardial ischemia (Aronow

et al., 1992). Dipyridamole thallium scintigraphy also has prognostic value in the preoperative assessment of patients with PVD undergoing vascular surgery (Hendel *et al.*, 1992).

RISK FACTOR MODIFICATION

Continuing smoking increases the risk of amputation in patients with intermittent claudication (Juergens *et al.*, 1960). Patency in lower extremity bypass grafts is also worse in smokers than in nonsmokers (Myers *et al.*, 1978). Smoking cessation decreases the progression of PVD to critical leg ischemia and decreases the risk of myocardial infarction and death from vascular causes (Quick and Cotton, 1982). Smoking cessation programs should be strongly encouraged in persons with PVD.

There are no good data showing that drug treatment of hypertension or diabetes mellitus will favorably affect the progression of PVD. However, hypertension should be adequately controlled to reduce cardiovascular mortality and morbidity in persons with PVD (Aronow, 2002a, 2003; Adler *et al.*, 2000). Diabetes mellitus should also be controlled with the hemoglobin A_{1c} level reduced to less than 7% to reduce the incidence of myocardial infarction (Stratton *et al.*, 2000).

Treatment of dyslipidemia with statins has been documented to reduce the incidence of mortality, cardiovascular events, and stroke in persons with PVD with and without CAD (Aronow, 2001, 2002b; Pedersen *et al.*, 1998; Heart Protection Study Collaborative Group, 2002; Aronow and Ahn, 2002a; Aronow *et al.*, 2002b; Aronow and Ahn, 2002b,c; Aronow *et al.*, 2002c; Aronow and Ahn, 2003). At 5-year follow-up of 4444 men and women with CAD and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin significantly decreased the incidence of intermittent claudication by 38% (Pedersen *et al.*, 1998).

In a study of 264 men and 396 women, mean age 80 years, with symptomatic PVD and a serum low-density lipoprotein cholesterol of 125 mg dl^{-1} or higher, 318 of 660 persons (48%) were treated with a statin and 342 of 660 persons (52%) with no lipid-lowering drug (Aronow and Ahn, 2002c). At 39-month follow-up, treatment with statins caused a significant independent decrease in the incidence of new coronary events of 58%, of 52% in persons with prior myocardial infarction, and of 59% in persons with no prior myocardial infarction (Aronow and Ahn, 2002c).

In a prospective study of 69 patients, mean age 75 years, with intermittent claudication, a mean ABI of 0.63, and a serum low-density lipoprotein cholesterol of 125 mg dl^{-1} or higher, 34 persons were randomized to simvastatin 40 mg daily and 35 persons to placebo after baseline treadmill exercise tests until the onset of intermittent claudication (Aronow *et al.*, 2003). Three of 34 persons (9%) treated with simvastatin and 6 of 35 persons (17%) treated with placebo died before the 1-year study was completed (Aronow *et al.*, 2003). Compared with placebo, simvastatin significantly increased the treadmill exercise time until the onset of intermittent claudication by 24% at 6 months and by 42% at 1 year after therapy (Aronow *et al.*, 2003). Two other studies have also demonstrated that statins improve walking distance in persons with intermittent claudication due to PVD (Mohler *et al.*, 2003a; Mondillo *et al.*, 2003).

On the basis of the available data, persons with PVD and hypercholesterolemia should be treated with statins to decrease cardiovascular mortality and morbidity and progression of PVD, and to improve exercise time until intermittent claudication in persons with PVD. Since lipid-lowering therapy is underutilized in persons with PAD (Ghosh *et al.*, 2002; Ghosh and Aronow, 2003), intensive educational programs are needed to educate physicians to use lipid-lowering therapy in older persons with cardiovascular disease and dyslipidemia (Ghosh and Aronow, 2003; Sanal and Aronow, 2003; Nayak and Aronow, 2004). On the basis of data from the Heart Protection Study, persons with PAD should be treated with statins regardless of age, gender, or initial serum lipids levels (Heart Protection Study Collaborative Group, 2002).

ANTIPLATELET DRUGS

If one combines the 42 randomized studies of 9706 patients with intermittent claudication, peripheral arterial grafting, or peripheral angioplasty, the incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke at follow-up were significantly decreased (23%) by antiplatelet drugs, with similar benefits among patients with intermittent claudication, those having peripheral arterial grafting, and those having peripheral angioplasty (Antithrombotic Trialists' Collaboration, 2002). These data favor the use of aspirin 160 to 325 mg daily in elderly men and women with PVD (Antithrombotic Trialists' Collaboration, 2002).

Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation by inhibiting the binding of adenosine 5′-diphosphate to its platelet receptor (Mills *et al.*, 1992). In the Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial, 5795 persons with PVD were randomized to clopidogrel 75 mg daily and 5797 persons with PVD were randomized to aspirin 325 mg daily (CAPRIE Steering Committee, 1996). At 1.9-year follow-up, the annual incidence of vascular death, nonfatal myocardial infarction, and nonfatal stroke was 3.7% in persons randomized to clopidogrel versus 4.9% in persons randomized to aspirin, a 24% significant reduction with the use of clopidogrel (CAPRIE Steering Committee, 1996).

On the basis of these data, it is reasonable to conclude that clopidogrel is superior to aspirin in the therapy of elderly persons with PVD. On the basis of these data, the author also recommends the use of clopidogrel 75 mg daily in the treatment of persons with PVD. However, clopidogrel is much more expensive than is aspirin. In a vascular surgery clinic, 501 of 506 persons (83%) with PVD were treated with aspirin or clopidogrel (Sukhija *et al.*, 2005).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The American College of Cardiology/American Heart Association guidelines recommend treating all persons with atherosclerotic vascular disease with angiotensin-converting enzyme inhibitors, unless there are contraindications to the use of these drugs, to decrease cardiovascular mortality and morbidity (Smith *et al.*, 2001).

β-BLOCKERS

Elderly persons with PVD are at increased risk for developing new coronary events (Reunanen *et al.*, 1982; Ness and Aronow, 1999; Aronow *et al.*, 2001a,b; Criqui *et al.*, 1992; Smith *et al.*, 1990; Aronow *et al.*, 1992; Vogt *et al.*, 1993; Eagle *et al.*, 1994). Many physicians have been reluctant to use β-blockers in persons with PVD because of concerns that β-blockers will aggravate intermittent claudication. However, a meta-analysis of 11 randomized controlled studies found that β-blockers do not adversely effect walking capacity or the symptoms of intermittent claudication in persons with mild-to-moderate PVD (Radack and Deck, 1991).

An observational study was performed in 575 men and women, mean age 80 years, with symptomatic PVD and prior myocardial infarction (Aronow and Ahn, 2001). Of the 575 persons, 85 persons (15%) had contraindications to the use of β-blockers. Of the 490 persons without contraindications to the use of β-blockers, 257 persons (52%) were treated with β-blockers. Adverse effects causing cessation of β-blockers occurred in 31 of the 257 persons (12%). At 32-month follow-up, use of β-blockers caused a 53% significant independent reduction in the incidence of new coronary events in elderly persons with PVD and prior myocardial infarction (Aronow and Ahn, 2001). In a vascular surgery clinic, 301 of 364 persons (83%) with PVD and CAD were treated with β-blockers (Sukhija *et al.*, 2005).

DRUGS TO INCREASE WALKING DISTANCE

Chelation therapy has been shown to be ineffective in the therapy of PAD (Ernst, 1997). Numerous drugs have been demonstrated to be ineffective in improving walking distance in persons with intermittent claudication (Hiatt, 2001; Eberhardt and Coffman, 2000). Most recently, beraprost sodium, an orally active prostaglandin I_2 analogue, was shown to be no more effective than placebo in persons with intermittent claudication (Mohler *et al.*, 2003b). Naftidrofuryl (Lehert *et al.*, 1994) and propionyl levocarnitine (Brevetti *et al.*, 1999) have been reported to improve exercise walking distance in persons with intermittent claudication but have not been approved for use in the United States (Hiatt, 2001).

Two drugs, pentoxifylline and cilostazol, have been approved by the United States Food and Drug Administration for symptomatic treatment of intermittent claudication. However, many studies have found no consistent improvement with pentoxifylline in patients with intermittent claudication in comparison with placebo (Radack and Wyderski, 1990; Porter *et al.*, 1982; Eberhardt and Coffman, 2003). In a vascular surgery clinic, 301 of 301 persons (100%) with intermittent claudication were treated with cilostazol or pentoxifylline (Sukhija *et al.*, 2005).

Cilostazol inhibits phosphodiesterase type 3, increasing intracellular concentration of cyclic adenosine monophosphate. Cilostazol suppresses platelet aggregation and also acts as a direct arterial vasodilator. Cilostazol has been demonstrated in numerous trials to improve exercise capacity in persons with intermittent claudication (Dawson *et al.*, 1998; Thompson *et al.*, 2002; Dawson *et al.*, 2000), and in a dose of 100 mg twice daily, was found to be superior to both placebo and pentoxifylline (Dawson *et al.*, 2000). However, cilostazol should not be administered to persons with PVD who also have heart failure.

EXERCISE REHABILITATION

Exercise rehabilitation programs have been documented to increase walking distance in persons with intermittent claudication through improvements in peripheral circulation, walking economy, and cardiopulmonary function (Gardner *et al.*, 2000). The optimal exercise program for improving claudication pain distance in persons with PVD uses intermittent walking to near-maximal pain during a program of at least 6 months (Gardner and Poehlman, 1995). Strength training is less effective than treadmill walking (Hiatt *et al.*, 1994).

FOOT CARE

Elderly persons with PVD must wear properly fitted shoes. Careless nail clipping or injury from walking barefoot must be avoided. Feet should be washed daily and the skin kept moist with topical emollients to prevent cracks and fissures, which may have portals for bacterial infection. Fungal infection of the feet must be treated. Socks should be wool or other thick fabrics, and padding or shoe inserts may be used to prevent pressure sores. When a wound of the foot develops, specialized foot gear, including casts, boots, and ankle foot orthoses may be helpful in unweighting the affected area.

Table 3 shows the approach to the medical management of PVD.

LOWER EXTREMITY ANGIOPLASTY AND BYPASS SURGERY

Indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are (1) incapacitating

Table 3 Medical management of peripheral vascular disease

1. Smoking cessation program
2. Treatment of hypertension
3. Control diabetes mellitus with the hemoglobin A_{1c} level reduced to <7%
4. Reduce serum low-density lipoprotein cholesterol to $<70\,mg\,dl^{-1}$
5. Antiplatelet drug therapy with aspirin or preferably clopidogrel
6. Treatment with an angiotensin-converting enzyme inhibitor
7. Treatment with β-blockers in patients with coronary artery disease in the absence of contraindications to these drugs
8. Treatment with cilostazol in patients with intermittent claudication
9. Exercise rehabilitation program
10. Foot care

claudication in persons, interfering with work or lifestyle; (2) limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; and (3) vasculogenic impotence (Weitz *et al.*, 1996). Percutaneous transluminal angioplasty can be performed if there is a skilled vascular interventionalist and the arterial disease is localized to a vessel segment less than 10 cm in length (Weitz *et al.*, 1996). Compared to percutaneous transluminal angioplasty alone, stenting improves 3-year patency by 26% (Palmaz *et al.*, 1990). After infrainguinal bypass surgery, oral anticoagulant therapy is preferable in persons with venous grafts, whereas aspirin is preferable in persons with nonvenous grafts (Dutch Bypass Oral Anticoagulants or Aspirin (BOA) Study Group, 2000).

AMPUTATION

Nonrandomized studies have found that both immediate and long-term survival are higher in patients having revascularization rather than amputation for limb-threatening ischemia (Ouriel *et al.*, 1988; DeFrang *et al.*, 1991). However, amputation of lower extremities should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations reduce the benefit of limb salvage (Fujitani *et al.*, 2003).

KEY POINTS

- PVD may be asymptomatic, may be associated with intermittent claudication, or may be associated with critical limb ischemia.
- Modifiable risk factors such as cessation of cigarette smoking and control of dyslipidemia, hypertension, and diabetes mellitus should be treated in elderly persons with PVD.
- Antiplatelet drugs such as aspirin or clopidogrel, especially clopidogrel, and angiotensin-converting enzyme inhibitors should be given to elderly persons with PVD and β-blockers also if there is coexistent CAD.
- Exercise rehabilitation programs and cilostazol improve exercise time until intermittent claudication in elderly persons with PVD.
- Indications for lower extremity angioplasty, preferably with stenting, or bypass surgery in elderly persons with PVD are (1) incapacitating claudication in persons, interfering with work or lifestyle; (2) limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; and (3) vasculogenic impotence.

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Venous Thromboembolism

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EPIDEMIOLOGY AND PATHOGENESIS

Thromboembolism (venous, cardiac, or arterial) is the commonest cause of death, and a major cause of morbidity, in later life. Like cardiac and arterial thromboembolism, the incidence of venous thromboembolism increases exponentially with age (Anderson *et al.*, 1991; Heit *et al.*, 2002). This may reflect age-related increases in activation of inflammation, endothelium, platelets, and coagulation (Lowe *et al.*, 1997; Woodward *et al.*, 1999, 2003); combined with age-related decreases in coagulation inhibition (Lowe *et al.*, 1997, 1999b), fibrinolytic activity, and in general mobility.

The median age for objectively diagnosed cases of deep vein thrombosis (DVT) of the lower limb or pulmonary thromboembolism (PE) in the United States population is about 65–69 years, the annual incidence in this age-group being about 3 per 1000 (Anderson *et al.*, 1991; Heit *et al.*, 2002; Kniffin *et al.*, 1994). In the 85–89-year age-group, the annual incidence rises to about 6 per 1000 (Kniffin *et al.*, 1994). Risk factors for venous thromboembolism in older patients (Kniffin *et al.*, 1994) are similar to those in younger patients (Anderson *et al.*, 1991; Heit *et al.*, 2002), with the obvious exception of pregnancy and the puerperium (Tables 1 and 2). There is increasing evidence that the pathogenesis of DVT involves a "multiple hit model" (Koster, 1995; Rosendaal, 1999), which starts at conception with multiple, interacting, genetic predispositions (thrombophilias) which thereafter interact throughout life with acquired risk factors which may precipitate thrombosis (Figure 1). Once thrombosis has occurred, it acts as a strong predictor of the risk of recurrence, especially if idiopathic.

Genetic Thrombophilias

Genetic thrombophilias should be suspected clinically if there is a past history, or a family history in blood relatives, of "premature" (e.g. onset before 40–45 years) DVT, PE, or recurrent fetal loss (spontaneous abortion or stillbirth); if there is recurrent venous thromboembolism or thrombophlebitis; or if thromboembolism occurs at an unusual site (upper limb veins, retina, cerebral venous sinuses, mesenteric, portal, or hepatic veins (Walker *et al.*, 2001). Protein C or protein S deficiency may also present with coumarin-induced skin necrosis (Walker *et al.*, 2001). Congenital deficiencies of the three coagulation inhibitors (antithrombin, protein C, or protein S) are usually due to heterozygosity for autosomal dominant gene defects. In the population-based Leiden study of 474 persons with a first, objectively confirmed DVT (excluding patients over 70 years with malignancy) and 474 controls aged 16–73 years (mean 47), such functional deficiencies were found in 8% of patients and 3% of controls; the population attributable risk was 0.05 (Table 2). In other words, about 5% of DVT in the population is attributable to the presence of these "classical thrombophilias". The prevalence of a mutation in coagulation factor V (factor V Leiden, which confers resistance to its inactivation by activated protein C (Walker *et al.*, 2001)) was 19% in patients and 3% in controls: the population attributable risk was 0.17 (Table 2). The low prevalence of this mutation in non-Western countries may explain their low incidence of DVT and PE. The combination of the factor V Leiden mutation with a deficiency of antithrombin, protein C, or protein S increases the risk of thrombosis (Walker *et al.*, 2001). Unlike other thrombophilias, the impact of the V Leiden mutation on risk of DVT appears to *increase* with age (Ridker *et al.*, 1997).

DVT in the population is also associated with increased plasma levels of coagulation factor VIII (Walker *et al.*, 2001). The population-attributable risk for high factor VIII ($\geq 150\,\mathrm{IU\,dl^{-1}}$) was 0.16 (Table 2). The interrelationships between factor VIII, ABO blood group, and thrombosis await clarification. Homozygous homocystinuria has long been recognized as a risk factor for premature arterial and venous thrombosis. More recently, hyperhomocysteinemia has also been associated with increased risk of both venous and arterial thrombosis: this is partly due to heterozygosity

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Table 1 Risk factors for venous thromboembolism

Patient factors	Disease or surgical procedure
Age	Trauma or surgery, especially of pelvis, hip, lower limb
Obesity	Malignancy, especially pelvic, abdominal, metastatic
Varicose veins	Heart failure
Immobility (bed rest over 4 days)	Recent myocardial infarction
Pregnancy	Paralysis of lower limb (e.g. stroke)
Puerperium	Infection
Estrogen therapy	Inflammatory bowel disease
Previous deep vein thrombosis or pulmonary embolism	Nephrotic syndrome
Thrombophilias	Polycythemia
Activated protein C resistance	Paraproteinemia
Factor V Leiden	Paroxysmal nocturnal hemoglobinuria
Other	Bechet's disease
Increased factor VIII	
Deficiency of antithrombin, protein C or protein S	
Antiphospholipid antibodies± lupus anticoagulant	
Homocystinemia	

Table 2 Risk factors for DVT: Leiden thrombophilia study

Risk factor	Cases ($n = 474$)	Controls ($n = 474$)	Odds ratio[a] (95% confidence intervals)
1) Acquired risk situations			
Surgery	18%	3.6%	6 (4–10)
Hospitalization without surgery	12%	1.3%	12 (6–24)
Prolonged immobilization at home	3.6%	0.2%	16 (3–72)
Pregnancy	5.0%	1.3%	4 (1–17)
Puerperium	8.2%	0.6%	14 (2–107)
Total	33%	5.9%	11 (6.2–19)
2) Thrombophilias			
Factor V Leiden	19%	3.0%	8 (4–15)
High factor VIII (150 IU dl^{-1} or over)	24%	10%	3 (2–4.5)
Antithrombin or protein C deficiency	8%	3%	2.5 (1.5–4.5)
3) Population attributable risks			
Acquired risk situation	0.30		
Factor V Leiden	0.17		
High factor VIII	0.16		
Antithrombin or protein C deficiency	0.05		
Total	0.55		

Source: Data from Koster (1995).
[a]Adjusted for age and sex.

for cystein synthase or methylene-tetrahydrofolate reductase (MTHRF) deficiency (whose cumulative prevalence in the general population is 0.4–1.5%) and partly due to deficiencies of vitamins (folate, cobalamine, and pyridoxine) especially in the elderly (Boushey *et al.*, 1995). Drugs interfering with folate metabolism (methotrexate, anticonvulsants) cobalamine (nitrous oxide) or pyridoxine (theophylline) can also cause moderate homocysteinemia. There is much current interest in the possibility that dietary supplementation of these vitamins could have a major impact on venous as well as arterial thrombosis, especially in the elderly: however, randomized trials are required (Boushey *et al.*, 1995).

Acquired Risk Factors

As noted above, increasing age, and (potentially) vitamin deficiencies, increases the risk of DVT. Obesity (body mass index of 30 $kg\,m^{-2}$ or over) also increases the risk of DVT and PE, especially in women (Goldhaber *et al.*, 1983); possibly due to concomitant changes in coagulation factors or activated protein-C resistance (Lowe *et al.*, 1999b; Woodward *et al.*, 1997). Smoking has no effect on risk of DVT or PE (Goldhaber *et al.*, 1983). Varicose veins increase the risk of postoperative DVT (Lowe *et al.*, 1999a), possibly because they may be a marker of previous (often asymptomatic) DVT in older persons. The increased risks of DVT and PE with increased estrogens – in pregnancy and the puerperium (Rosendaal *et al.*, 2003), combined oral contraceptives (Rosendaal *et al.*, 2003), and hormone replacement therapy (Rosendaal *et al.*, 2003; Lowe, 2004) suggest common mechanisms, including activated protein-C resistance, low levels of antithrombin and protein S, and high levels of factor IX (Lowe, 2004). These risks are increased in women with thrombophilias (Rosendaal *et al.*, 2003; Lowe, 2004).

In the population-based Leiden Study, the impact of acquired risk situations on a first objectively confirmed DVT in persons aged under 70 and without malignancy was studied. These situations included pregnancy at time of DVT; puerperium (within 30 days of DVT); or surgery, hospitalization without surgery or prolonged ($\geq$2 weeks) immobilization at home (including plaster casts) within the year preceding the DVT (Table 2). An acquired risk situation was recorded in 33% of cases and 6% of controls; and the population attributable risk was 0.30 (Koster, 1995) (Table 2). When these acquired risk situations were combined with thrombophilias (e.g. antithrombin or protein-C deficiency, factor V Leiden, high factor VIII) the combined population attributable risk was 0.55 (Koster, 1995) (Table 2).

Immobilization (at home or in hospital) and surgery are usually due to trauma or illness (e.g. infection, malignancy, heart failure, myocardial infarction, and stroke). The cumulative risk of DVT and PE increases with the duration of immobility, suggesting a role for venous stasis in the inactive leg in the pathogenesis of DVT. Venous stasis also increases in patients with paralyzed legs, heart failure, or polycythemia, which are also risk factors for DVT (SIGN, 2002). Activation of blood coagulation also occurs following trauma, surgery and immobilizing illnesses including infection, malignancy, infarction, and hemorrhage. The hypothesis that the combination of immobility and coagulation activation predisposes to DVT formation is supported by the prophylactic efficacy of both mechanical measures which increase leg vein blood flow, and antithrombotic drugs especially anticoagulants, and by the increased efficacy of combinations of mechanical with anticoagulant prophylaxis (SIGN, 2002).

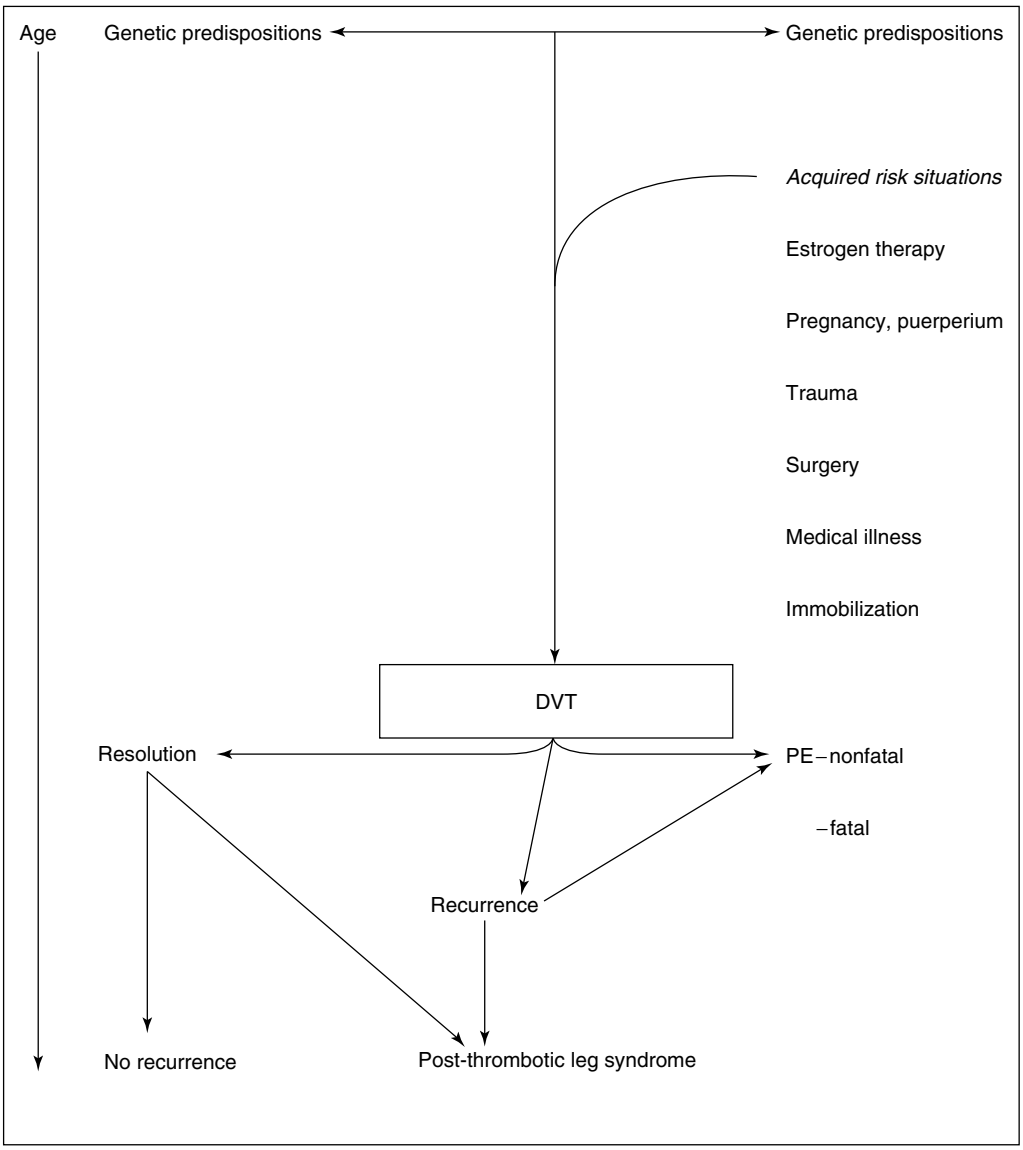

Figure 1 Multiple hit model for DVT

The population impact of immobilizing trauma, surgery or illness on risk of DVT, and PE in the elderly is probably greater than that observed in the Leiden study of persons aged under 70 years (Koster, 1995), given their higher incidence and prevalence. Furthermore, the elderly have a high prevalence of malignant disease, which activates blood coagulation and increases the frequency of both "spontaneous" and recurrent venous thromboembolism (Edwards and Rickles, 1996). Less common acquired conditions which are associated with increased risk of venous thromboembolism include lupus anticoagulants, which are antiphospholipid antibodies and which usually occur in persons without systemic lupus erythematosis (SLE) (Walker *et al.*, 2001); inflammatory bowel disease, nephrotic syndrome, Bechet's disease, hyperviscosity (polycythemias, paraproteinemias), and paroxysmal nocturnal hemoglobinuria (SIGN, 2002).

PRIMARY PROPHYLAXIS

Necropsy studies in the United Kingdom and Sweden during the 1980s continued to show a high incidence of PE, which was estimated to be the main cause of death in about 10% of necropsies (Karwinski and Svendson, 1989; Sandler and Martin, 1989). Because inpatient mortality in general hospitals is about 10%, it is estimated that about 1% of patients admitted to hospital die from PE. The National Confidential Enquiry into postoperative deaths has highlighted the continuing frequency of fatal postoperative PE (HMSO, 1993). However, for every patient who dies from PE in a surgical ward, three die in nonsurgical wards (Karwinski and Svendson, 1989; Sandler and Martin, 1989). In the great majority of patients dying from PE, previous venous thromboembolism was not diagnosed or treated. DVT

is often nonocclusive and hence clinically silent prior to embolization; while nonfatal PE occurring prior to fatal PE may not be recognized clinically, especially in older patients who frequently have preexisting cardiorespiratory symptoms, for example, from heart failure or chronic obstructive airways disease (Goldhaber *et al.*, 1982).

The clinical nonrecognition of venous thromboembolism prior to fatal PE implies that its detection and treatment cannot have a major impact on its mortality: hence, identification of, and primary prophylaxis in, hospitalized patients (medical and surgical) at high absolute risk of DVT is required for its prevention (SIGN, 2002). Subcutaneous or low molecular weight (LMW) heparin prevents about 2 in 3 cases of DVT and of PE; mechanical methods such as compression stockings are effective in prophylaxis of DVT but their effect on PE is unknown; while aspirin reduces the risk of clinical postoperative DVT and PE by one-third (Pulmonary Embolism Prevention (PEP) Trial Collaborative Group, 2000). Evidence-based guidelines for identification of high-risk patients and prophylaxis have been recently produced in Scotland (SIGN, 2002), North America (Geerts *et al.*, 2004) and by an International Consensus Group (International Consensus Statement, 2002). It has been recommended that each hospital, service, or unit should develop its own local protocol, based on national guidelines (SIGN, 2002). Such protocols can then be used to develop local clinical standards which can be audited (SIGN, 2002).

MANAGEMENT OF SUSPECTED DVT OR PE

As with prophylaxis of venous thromboembolism, evidence-based guidelines for diagnosis and management have been published recently (SIGN, 1999; Buller *et al.*, 2004) from which local protocols, standards, and audit should be developed. There is good evidence from randomized trials that full-dose anticoagulation (with heparins, followed by oral anticoagulants such as warfarin) is effective in secondary prophylaxis of recurrent thromboembolism, reducing morbidity and mortality. In patients for whom full-dose anticoagulants are contraindicated (usually due to high risk of bleeding), insertion of an inferior vena caval (IVC) filter should be considered to reduce PE risk. However, the costs and morbidity risks of both long-term anticoagulants and IVC filters require that they should be prescribed only to the minority of patients with clinically suspected DVT or PE in whom venous thromboembolism is confirmed by objective tests (Ginsberg, 1996).

Venous thromboembolism should be suspected in patients with

1. congenital or acquired risk factors (Table 1) and
2. clinical symptoms or signs suggestive of either DVT – leg (usually calf, usually unilateral) pain, tenderness, swelling, edema, warmth, distended superficial veins and/or PE – breathlessness, chest pain, cough, hemoptysis, wheeze, tachycardia, tachypnea, syncope, shock, or cardiac arrest.

Formal clinical scoring should be performed in the Accident and Emergency Department, and a rapid test for fibrin D-dimer performed. In patients with a low clinical score and normal D-dimer, DVT and PE can be excluded. Other patients should receive heparin therapy (unless strongly contraindicated, e.g. by high risk of bleeding) until diagnostic imaging is performed.

Objective tests for DVT include *contrast venography* (which is sensitive and specific but invasive) and noninvasive tests such as *compression ultrasound* or *Duplex ultrasound scanning* (which are noninvasive, specific, and sensitive to proximal DVT but less sensitive to calf DVT). The increasing availability of routine ultrasound in UK radiology departments has led many departments to perform this as the first diagnostic test for DVT. A negative ultrasound test does not exclude the presence of calf DVT, which in about 20% of patients may extend proximally over the subsequent few days and increase the risk of PE. Hence, a negative ultrasound test in patients with clinically suspected DVT should either be repeated (usually after 5–7 days), or followed immediately by venography to exclude calf DVT.

Diagnosis of clinically suspected PE includes

1. *chest X ray and ECG* to exclude alternative diagnoses such as myocardial infarction, pneumothorax, or pneumonia;

2. *ventilation perfusion isotope lung scanning* which may be exclusive (normal) or diagnostic (high probability – "mismatched" major lung segments that are ventilated but not perfused); but which in about 50% of cases is nondiagnostic (intermediate probability);

3. *further diagnostic approaches* in the latter category of patients include computerized tomographic pulmonary angiography, contrast pulmonary angiography (invasive and not widely available), echocardiography (suspected massive PE), leg ultrasound or venography to detect underlying DVT, and a decision to anticoagulate or not, depending on the overall probability of DVT and PE.

Unfractionated heparin is the historical initial treatment for DVT or PE. An initial intravenous bolus dose (5000 IU or 75 IU kg^{-1} body weight) is given over 5 minutes, followed by maintenance intravenous infusion (initial rate 14 000 IU $hour^{-1}$) or (in the case of DVT) 12-hourly subcutaneous injections (initially 175 000 IU). Regardless of the route of administration, unfractionated heparin should be monitored at least daily by the activated partial thromboplastin time (APTT) and the heparin dose adjusted to achieve the therapeutic target range (APTT ratio 1.5–2.5) (Buller *et al.*, 2004). Problems with such APTT monitoring (Buller *et al.*, 2004) include lack of APTT standardization; practical difficulties in achieving the target APTT, even with use of nomograms; and the lack of venous access, for example, in intravenous drug users. For all these reasons, subcutaneous LMW heparins (which do not require coagulation test monitoring) are now preferred to APTT-monitored unfractionated heparin. They are usually given 12–24 hourly subcutaneously.

LMW heparins do not require coagulation monitoring and have been shown in meta-analyses of randomized trials to have greater efficacy (lower rates of DVT extension, recurrence, and mortality) and lesser risk of major bleeding than unfractionated heparin in the initial treatment of DVT (Siragusa *et al.*, 1996). Their efficacy as daily, unmonitored subcutaneous injections allows the possibility of outpatient treatment of acute DVT in many cases, provided this is acceptable to patients and their hospital and general practitioners.

Oral anticoagulants (usually warfarin) are required as maintenance treatment following initial heparin treatment of DVT or PE, to reduce the risk of recurrence (SIGN, 1999; Buller *et al.*, 2004; Ginsberg, 1996). They can be started (according to a nomogram (Fennerty *et al.*, 1988)) as soon as objective diagnosis is obtained; concomitant heparin treatment should be continued until the target therapeutic range of the International Normalized Ratio (INR) (2.0–3.0) has been achieved for 2 consecutive days (SIGN, 1999; Buller *et al.*, 2004). The routine recommended duration of oral anticoagulant therapy following a first episode of DVT is at least 3 months. A recent, large prospective observational study showed that the risk of recurrent DVT after 3 months of warfarin is higher than previously suspected: 17.5% after 2 years, 25% after 5 years, and 30% after 8 years (Prandoni *et al.*, 1996). The cumulative incidence of the postthrombotic leg syndrome was 23, 28, and 29% respectively; and was strongly associated with ipsilateral recurrent DVT (Prandoni *et al.*, 1996). Recurrence was associated positively with thrombophilias, malignant disease, and an "idiopathic" presentation (e.g. no recent trauma, fracture, or surgery) (Prandoni *et al.*, 1996). Continued oral anticoagulant prophylaxis after 3 months should therefore be considered in such patients (Goldhaber, 2004).

Compression Stockings

These should be prescribed routinely to be worn on the affected leg(s) during the day, long term, to reduce the risk of the post-thrombotic leg syndrome (SIGN, 1999; Buller *et al.*, 2004).

Considerations in Elderly Patients

Overall, the literature suggests that any association of age with risk of bleeding on heparin or warfarin is weak, and contrasts with the strong, consistent finding of an exponential increase in thromboembolic risk with age (Lowe and Stott, 1996). However, geriatricians should consider several practical considerations when prescribing oral anticoagulants to the elderly (Lowe and Stott, 1996):

1. Sensitivity to the anticoagulant effect of a given dose increases with age: for example, an average warfarin dose of 4 mg day^{-1} was required in patients 74–90 years old to achieve the same target INR as an average dose of 8 mg day^{-1} in patients aged 19–35 (Lowe and Stott, 1996; Routledge *et al.*, 1979).
2. Polypharmacy (including self-medications) increases the risk of drug interactions which alter oral anticoagulant effect, or which increase the risk of bleeding (e.g. aspirin and other nonsteroidal antiinflammatory drugs).
3. Increased prevalence of concurrent or intercurrent illness also increases risk of bleeding (e.g. severe anemia, renal failure, gastrointestinal bleeding, hemorrhagic stroke, bleeding disorder).
4. Decreased compliance or decreased access to monitoring – whether performed by the general practitioner or hospital anticoagulant clinic – also increases risk of bleeding.

KEY POINTS

- Venous thromboembolism is common in elderly patients, especially with obesity, malignancy, heart failure, immobility, trauma, surgery, and acute medical illness.
- Consider primary prophylaxis (low-dose heparin, aspirin, or stockings) in acutely immobilized patients, especially those with other risk factors, previous DVT or PE, or known thrombophilia.
- Diagnosis of suspected nonmassive DVT or PE involves a formal clinical score and rapid D-dimer in outpatients; proceeding to initial heparin therapy and diagnostic imaging.
- If diagnosis is confirmed, oral anticoagulation with warfarin (target INR 2.0–3.0) is usually given for at least 3 months.
- Older patients are at increased risk of bleeding on oral anticoagulants.

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Cardiac Cachexia

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DEFINITION OF CARDIAC CACHEXIA

Cachexia has long been recognized as a feature of chronic disease and as a prognostic marker. Reports on cachexia date back to the time of Hippocrates (about 460–370 B.C.): "The flesh is consumed and becomes water, . . . , the shoulders, clavicles, chest and thighs melt away. This illness is fatal, . . ." (Katz and Katz, 1962). However, despite being known since ancient times, there is no generally accepted definition of cachexia.

Different definitions have been suggested for cardiac cachexia, using parameters of body composition (fat and lean tissue measurements) or skeletal protein turnover (using labeled amino acids), calculations based on reference values for ideal body mass (matched for gender, age, and height, usually derived from life insurance tables) or scoring systems including serum albumin concentrations, cell-mediated immunity changes, body mass index (BMI) (BMI = weight/height^2) and the history of weight loss (Anker and Coats, 1996).

A body fat content <22% in women and <15% in men or a body weight <90% of the ideal body weight was previously used to classify CHF (chronic heart failure) patients as being cachectic (Carr *et al.*, 1989). Alternatively, a body fat content <29% in females and <27% in males (McMurray *et al.*, 1991), or a body weight <85% (Levine *et al.*, 1990) or <80% respectively (Otaki, 1994) of the ideal body weight has been suggested by other groups to define cardiac cachexia. Freeman and Roubenoff (1994) defined cardiac cachexia as a loss of at least 10% of lean tissue. All these definitions, however, require access to facilities for body composition measurement (such as dual energy X-ray absorptiometry scanning or magnetic resonance imaging), which are not widely available and cause additional costs. A definition of "clinical cachexia" should be simple, widely applicable, and account for the dynamic character of cardiac cachexia. Therefore, cardiac cachexia should be proven by a documented weight loss measured in a nonedematous state. We, accordingly have suggested a non-intentional weight loss >6% of the premorbid weight occurring over a time period of >6 months as a definition of "clinical cardiac cachexia". If significant weight loss occurs over a shorter time period, other potential causes of wasting (like malignancies or infective diseases) need to be excluded. This definition is simple and easily applicable, requiring only taking a careful weight history. Theoretically, the degree of weight loss most accurately predicting impaired survival should be considered the clinically most relevant cutoff value. A weight loss of ≥6% has been demonstrated to be a strong predictor of impaired prognosis in 1929 patients enrolled in the Studies of left ventricular dysfunction (SOLVD) study (Anker *et al.*, 2003). This finding has been validated on 619 patients from the V-HeFT-II study (Anker *et al.*, 2003).

EPIDEMIOLOGY AND PROGNOSIS OF CARDIAC CACHEXIA

CHF is a leading cause of death and associated with high morbidity as well as a substantial socioeconomic burden (Jessup and Brozena, 2003; Steward *et al.*, 2002). Its prevalence is still rising due to aging of the population and improved survival of acute ischemic events. CHF is predominantly a disease of the elderly, reaching a prevalence of up to 30% in the over-80 year olds (Kannel and Belanger, 1991). The exact prevalence of cachexia among CHF patients is unknown. It has been suggested that up to 50% of CHF patients suffer from some degree of malnutrition (Carr *et al.*, 1989). One decade ago, we performed the first prospective study on the prevalence and prognostic impact of cachexia in CHF patients, defining cachexia as a weight loss >7.5% of the premorbid weight over a time period >6 months. Assessing 171 consecutive CHF patients, we demonstrated that 16% had cardiac cachexia (Anker *et al.*, 1997c). In

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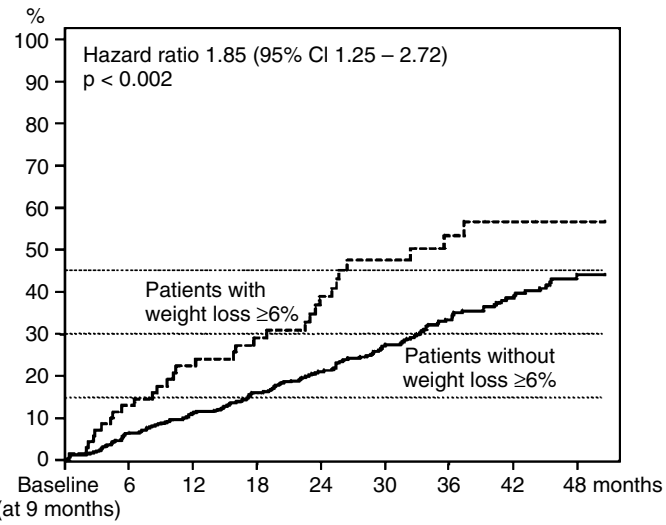

Figure 1 Cumulative survival in CHF-patients enrolled in the V-HeFT-II study with or without ≥6% weight loss (Adapted from Anker *et al.*, 2003. Copyright Elsevier)

this study, peak oxygen consumption, New York heart association (NYHA) class, exercise time, % ideal weight, left ventricular ejection fraction (LVEF), cachectic state, and age significantly predicted mortality. In a multivariate model of survival, the cachectic state was predictive of mortality independently of age, NYHA class, LVEF, peak VO_2, and sodium levels. Overall, the prognosis of cachectic patients was dire, with 50% of patients dying within 18 months. Subsequently, we found in the SOLVD population that stable CHF patients developed ≥6% weight loss in 17.2% at 12 months and 40.5% at 36 months. In the V-HeFT-II population, weight loss ≥6% at 9 months was associated with 85% increased subsequent mortality (see Figure 1).

BODY COMPOSITION ALTERATIONS

Patients with CHF typically have evidence of muscle atrophy (Lipkin *et al.*, 1988; Drexler *et al.*, 1992), and it has been reported to be present in up to 68% of CHF patients (Mancini *et al.*, 1992). CHF patients suffer from muscle weakness, a decline in exercise capacity and an increased fatigability. In the largest study reported to date (including 101 CHF patients), we found muscle weakness and fatigue to occur mainly in NYHA class 3 and 4 patients (Harrington *et al.*, 1997), or in cachectic subjects (Anker *et al.*, 1997d). In AIDS and cancer patients, the loss of lean tissue has been found to predict prognosis (Kotler *et al.*, 1989). A similar relationship between tissue wasting and survival has not been reported in CHF patients so far. However, it has been demonstrated that CHF patients suffer from a significant loss of lean tissue, a reduction in fat tissue mass and a decreased bone mass (i.e. osteoporosis) (Harrington *et al.*, 1997). In addition, an impaired muscle quality (Anker *et al.*, 1997d) and a reduced peripheral blood supply (Volterrani *et al.*, 1994) has been found in CHF patients. These factors together contribute to the impaired functional capacity of CHF patients.

MECHANISMS OF CACHEXIA IN CHF

A simple reduction in food intake is often considered to be the main cause of cardiac cachexia, but this is not the case. Symptoms of heart failure (such as fatigue and dyspnea), side effects of heart failure medication (e.g. digoxin, Angiotensin-converting enzyme (ACE) inhibitors) or gastrointestinal malabsorbtion (intestinal edema or protein losing gastroenteropathy) are thought to be responsible for anorexia and malnutrition in CHF. Simple starvation, however, fails to explain the loss of lean tissue and osteoporosis as well as the normal albumin and liver enzyme plasma levels found in cachectic patients (Anker *et al.*, 1997a). These findings indicate the presence of a general wasting process (i.e. cachexia of chronic disease). Elderly CHF patients are generally less active and muscle deconditioning could theoretically account for the muscle atrophy observed in CHF patients. Histological studies, however, demonstrate that muscle atrophy in CHF is different from the muscle atrophy found in patients with muscle deconditioning due to prolonged inactivity (Vescovo *et al.*, 1996; Simioni *et al.*, 1995). It has been suggested that an increased total energy expenditure may contribute to cardiac cachexia (Poehlmann *et al.*, 1994). However, in subsequent studies, no evidence of increased resting metabolic rate in cachectic CHF patients could be found (Toth *et al.*, 1997).

IMMUNE ABNORMALITIES

It is becoming increasingly clear that CHF represents a state of immune-inflammatory activation. Levine and colleagues demonstrated in 1990 that tumor necrosis factor-alpha (TNF) is increased in patients with cardiac cachexia (Levine *et al.*, 1990). This finding could subsequently be confirmed by other groups (McMurray *et al.*, 1991; Dutka *et al.*, 1993). We showed that TNF plasma levels are mainly increased in cachectic CHF patients, and represent the strongest predictor of the degree of previous weight loss (Anker *et al.*, 1997a). TNF together with interleukin-1 (IL-1), IL-6, interferon-γ and transforming growth factor-β are important to the development of catabolism. These cytokines are produced mainly by monocytes/macrophages (Nathan, 1987; Hsi and Remick, 1995), and also by endothelial cells and the myocardium (Torre–Amione *et al.*, 1995, 1996a). The stimulus for increased TNF production in CHF remains unknown. The failing heart itself may account for an increase in circulating TNF (Torre–Amione *et al.*, 1996b). Alternatively, hypoxia could result in elevated TNF levels (Hasper *et al.*, 1998). It has also been hypothesized that

endotoxin translocation due to bowel wall edema could cause immune activation, leading to increased TNF-α production (Anker *et al.*, 1997b). In support of this hypothesis, raised concentrations of endotoxin and cytokines were reported in patients with chronic heart failure during acute edematous exacerbation with endotoxin concentrations normalizing after intensified diuretic treatment (Niebauer *et al.*, 1999).

Cytokines, such as TNF contribute to protein catabolism leading to skeletal muscle wasting. TNF also induces apoptosis (Kitajima *et al.*, 1994; Krown *et al.*, 1996), which may contribute to muscle atrophy and catabolism. Chronic treatment of rats with recombinant TNF results in a significant decrease in muscle protein content and is associated with a decrease in mRNA levels for myofibrillar proteins (Fong *et al.*, 1989). There is additional evidence that TNF significantly enhances muscle protein breakdown through accelerated ubiquitin-proteasome proteolysis (Tisdale, 2000). It has been demonstrated in animal experiments, that implantation of TNF producing cells in the brain cause profound anorexia (Tracey *et al.*, 1990). TNF also exerts detrimental effects on endothelial cells contributing to endothelial dysfunction in CHF (Tracey and Cerami, 1994). The association between elevated TNF levels and impaired peripheral blood supply in CHF patients supports the idea of detrimental effects of increased TNF levels (Anker *et al.*, 1998).

NEUROENDOCRINE ABNORMALITIES

Chronic heart failure is characterized by neurohormonal activation with raised catecholamine levels (Francis, 1985), overactivity of the renin-angiotensin-aldosterone system (Davis *et al.*, 1979) and increased secretion of natriuretic factors (Omland *et al.*, 1996) (see Figure 2). Activation of these systems is considered a contributing factor to disease progression and impaired prognosis. Several studies have found neurohormonal activation to be strongly related to mortality (Cohn *et al.*, 1984; Gottlieb *et al.*, 1989). In patients with CHF brain natriuretic peptide (BNP) levels are associated with increased mortality, need for cardiac transplantation and sudden cardiac death. Additionally, patients with increased concentrations of BNP despite aggressive treatment have been reported to be at especially high risk for adverse outcomes (De Lemos *et al.*, 2003). We found that cachectic CHF patients show markedly increased norepinephrine and epinephrine levels, while non-cachectic CHF patients demonstrate near-normal levels (Anker *et al.*, 1997a). In contrast, peak oxygen consumption, left ventricular ejection fraction and NYHA class were not significantly different between cachectic and non-cachectic patients.

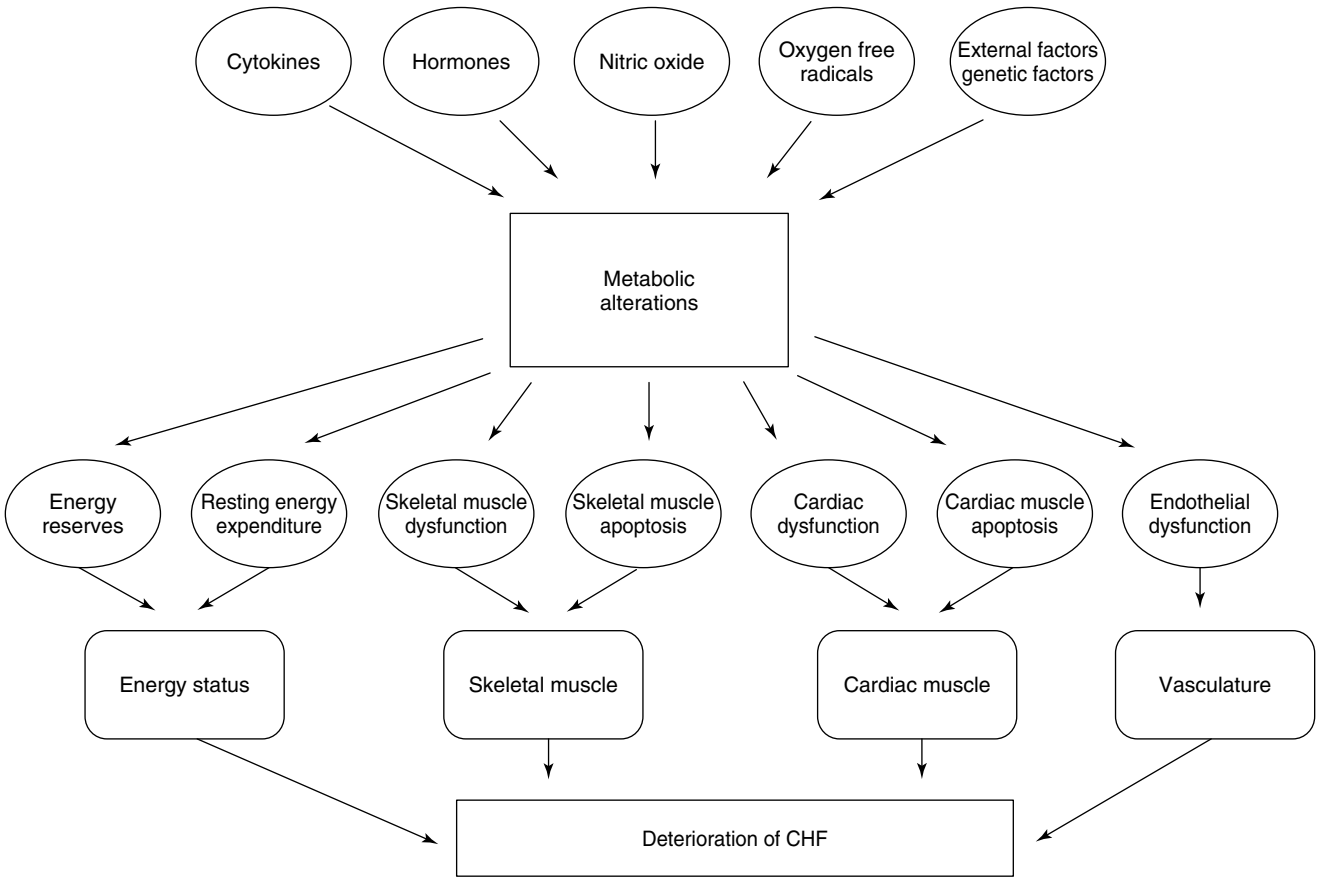

Figure 2 Figure illustrating the complex interactions between neurohormonal activation, immune activation, oxygen free radical release and endothelium derived mediators in CHF

Other factors considered to contribute to catabolic/anabolic imbalance are cortisol and androgens. Increased levels of cortisol and reduced dehydroepiandrosterone (DHEA) levels were reported in CHF patients and could lead to muscle catabolism (Anker *et al.*, 1997a). Additionally, the cortisol/DHEA ratio has been found to predict survival in CHF patients (unpublished report). Loss of adipose tissue is a common feature in cachectic patients. A recent study has shown that natriuretic peptides are powerful lipolytic agents in human adipose tissue both *in vivo* and *in vitro* (Segenes *et al.*, 2000). Studies have also confirmed that human adipose tissue expresses mRNA for natriuretic peptide receptors (Segenes *et al.*, 2000). This pathway in the control of human adipocyte lipolysis could represent a new link between cardiac failure and lipolysis.

CLINICAL IMPLICATIONS

Cardiac cachexia represents a multifactorial neuroendocrine, immune-inflammatory and metabolic disease where a complex imbalance of different body systems causes the development of body wasting. As there are no controlled studies for the various therapeutic strategies or for nutritional support in patients with cardiac cachexia, therapy remains a challenge.

Nutritional Support

Theoretically, it seems clear that nutritional intake has to be increased in order to regain energy reserve and to preserve lean tissue. However, except for perioperative nutritional support there are no controlled studies for the outcome of various management strategies in cardiac cachexia. In stable CHF patients with no signs of severe malnutrition, clinical status of heart failure is not improved by increased nutritional intake alone (Broqvist *et al.*, 1994). Also, postoperative parenteral hyperalimentation alone failed to improve survival in one study (Abel *et al.*, 1976), whereas in a separate study in which patients with cardiac cachexia received preoperative nutritional support (5–8 weeks duration, intravenously up to $1200\,\mathrm{kcal\,day^{-1}}$) an improvement in the mortality rate in the treatment group (17 vs 57%, $p < 0.05$) could be demonstrated (Otaki, 1994). The provision of 40 to $50\,\mathrm{kcal\,m^{-2}}$ of body per hour including 1.5 to $2\,\mathrm{g\,kg^{-1}\,hour^{-1}}$ protein, and sodium ($2\,\mathrm{g\,day^{-1}}$) as well as fluid restriction ($1000–1500\,\mathrm{ml\,day^{-1}}$) using high-density continuous feeding has been proposed for CHF patients (Abel *et al.*, 1976). In the future, we may also consider using appetite stimulants like megestrol acetate or dronabinol. So far, no studies have been performed with such drugs in cardiac cachexia. In the management of the cachectic CHF patient, the consultation of a dietitian is advisable.

Exercise

Skeletal muscle atrophy as well as impaired peripheral blood supply can be reversed by exercise training and results in an increased exercise capacity (Coats *et al.*, 1990, 1992). From our clinical experience, moderate exercise training is safe and can be recommended to cachectic CHF patients in NYHA classes I to III. We have demonstrated that peripheral blood supply rather than muscle size and strength correlates best with the degree of exercise limitation in cachectic CHF patients, while muscle strength and age represent the best predictors of exercise capacity in non-cachectic patients (Anker *et al.*, 1997d). Whether the use of physiotherapeutic procedures to increase peripheral blood supply before the start of any exercise training improves exercise capacity needs to be assessed.

Drugs

Neurohormonal and immune-inflammatory activation play an important role in the pathophysiology of CHF and cardiac cachexia. Modulation of the "neurohormonal milieu" using ACE-inhibitors and β-blockers resulted in improved survival of CHF patients (Torre–Amione, 1999). ACE-inhibitor therapy has been shown to reduce plasma concentrations of natriuretic peptides (Sigurdsson *et al.*, 1994), TNF (Liu and Zhao, 1999) and IL-6 (Gullestad *et al.*, 1999) and could confer benefits for cachectic CHF patients. We have recently demonstrated that ACE-inhibitor treatment (using enalapril) reduces the risk of weight loss in CHF patients by 19% (Anker *et al.*, 2003). A recent small study with 27 patients suggested that beta-blocker treatment may also be beneficial in preventing cachexia in CHF (Hryniewicz *et al.*, 2003). We have prospectively tested in the COPERNICUS study (Packer *et al.*, 2001), which assessed the effect of carvedilol versus placebo on mortality and morbidity of patients with CHF, whether carvedilol prevents cachexia development. We have found that carvedilol (uptitrated up to 25 mg bd) reduces weight-loss development by 33%, $p = 0.002$ (Anker *et al.*, unpublished observation).

Fish oil (n-3 polyunsaturated fatty acids) has been shown to have antiinflammatory effects both in healthy volunteers (Endres *et al.*, 1989) and patients with rheumatic disease (Kremer *et al.*, 1987). The effect of fish oil treatment on weight loss in cardiac cachexia has not been studied so far.

Recombinant human growth hormone (rhGH) may well represent a therapeutic option for patients with cardiac cachexia. However, it has been demonstrated that low doses of rhGH (2 IU per day given daily) did not confer clinical benefits after 3 months of treatment compared to placebo (Osterziel *et al.*, 1998). In contrast, two case reports (Cuneo *et al.*, 1989; O'Driscoll *et al.*, 1997) showed that high-dose GH treatment (70 to 98 IU per week) over short periods of time (1 week to 3 months) is safe and leads to an increase of muscle mass and strength and improves exercise capacity. It has been suggested that acquired GH resistance may account for the lack of benefit of GH treatment (Cicoira *et al.*, 2003).

Measuring plasma concentrations of GH-binding protein may be useful to assess presence of GH resistance and to guide GH therapy in cardiac cachexia (Anker *et al.*, 2001).

Theoretically, the use of anabolic steroids may be an option, but their side effects on renal function and the potential to induce prostate hyperplasia has limited their use so far.

The value of anticytokine therapies in the management of CHF is still a matter of debate (Anker and Coats, 2002). A pilot study, using etanercept (a TNF receptor fusion protein) including 18 patients with moderate heart failure and elevated TNF-α levels showed promising results (increased quality of life, 6-minute walk distance and left ventricular ejection fraction) (Deswal *et al.*, 1999). Subsequently, 2 large-scale clinical trials (RENAISSANCE, RECOVER) were initiated in CHF. In these studies, etanercept did not show a significant clinical benefit compared with placebo (Mann *et al.*, 2004; Chung *et al.*, 2003; Anker, 2000). Another trial (ATTACH) using a TNF antibody was stopped prematurely because initial analyses indicated an increased mortality in patients on active therapy (Anker and Coats, 2002). The role of anti-TNF therapy in CHF patients is uncertain and still a matter of debate. Possibly, TNF antagonist is only beneficial in patients with highly elevated TNF levels (such as NYHA class IV or with cardiac cachexia).

Chronic heart failure is prevalent, detectable, and, nowadays, effectively treatable. Owing to improved therapy of acute ischemic events and increasing proportion of elderly people in the population, the prevalence of CHF is likely to increase further. Cardiac cachexia contributes considerably to morbidity and mortality in heart failure, and it, too, is easily detectable.

There is a need to develop effective treatment options for cachexia, not only in CHF but also in other chronic diseases. There is currently no specific treatment available for patients with cachexia. Further research may lead to a better understanding of the pathophysiologic basis of cachexia and the development of new treatments in the future.

KEY POINTS

- Cachexia is a frequent complication of chronic heart failure and other chronic diseases.
- The prognosis of patients with cardiac cachexia is dire with upto 50% of patients dying within 18 months.
- Generalized loss of fat tissue, skeletal muscle, and bone tissue distinguish cardiac cachexia from starvation.
- Cardiac cachexia represents a multifactorial neuroendocrine, immune-inflammatory and metabolic disease where an imbalance of different body systems is responsible for the development of wasting.
- There are no controlled studies for the various therapeutic strategies or for nutritional support in patients with cardiac cachexia so far, therefore therapy remains a challenge.

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Cardiac Rehabilitation in Older People

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CARDIAC DISEASES AND REHABILITATION SERVICES

Epidemiological Data

In the year 2001, cardiovascular diseases were still the first among the leading causes of death in men and women of all ages in the United States, with coronary heart disease (CHD) alone accounting for 54% of all cardiovascular deaths. The prevalence of cardiovascular diseases – including CHD, stroke, and hypertension – increases with aging, becoming greater than 70% at age 75 years and older. A surveillance study that has been carried out by the National Heart, Blood and Lung Institute between 1987 and 2000 has reported that the incidence of first heart attack is also increasing exponentially with increasing age (American Heart Association, 2004).

Thanks to remarkable advances in the management of acute coronary syndromes, chronic heart failure (CHF), and cardiovascular risk factors as well (Unal *et al.*, 2004), the specific mortality for heart disease has been continuously declining during the last two decades, especially among men. Furthermore, preventive medicine has shifted the age at which patients develop CHF but has not reduced, and rather may have increased, the global epidemiological burden. As a consequence, a growing number of cardiac patients presently can survive longer, but with substantial functional limitations that are secondary to several manifestations of CHD such as CHF, whose incidence has been steadily increasing, particularly in older populations, suggesting that in these last years we have been facing a real "heart failure epidemic" (Cleland *et al.*, 2001). Indeed, the National Health and Nutrition Examination Survey (NHANES) epidemiologic study has reported that the prevalence of CHF is less than 5% among individuals aged 65 years or younger, but doubles among those older than 75 years (He *et al.*, 2001), and data from the World Health Organization (WHO) suggest that these figures differ little around the world, at least in more affluent countries (Cleland *et al.*, 2001).

As we will discuss in this chapter, integrated cardiac rehabilitation programs are highly effective in accelerating the functional recovery after acute cardiac events and in improving exercise tolerance, adherence with secondary prevention measures, quality of life, and also long-term prognosis of cardiac patients. These results, together with epidemiological data on the aging-dependent increase in the prevalence of CHD, would recommend a particular need for cardiac rehabilitation programs specifically targeting older individuals with the most disabling consequences of CHD, such as postmyocardial infarction angina or CHF.

Utilization of Cardiac Rehabilitation Services: An International Perspective

In spite of the high incidence and prevalence of heart disease and of the negative impact of CHD and CHF on overall functional abilities (Pinsky *et al.*, 1990), and although cardiac rehabilitation is strongly recommended as a standard component of secondary prevention programs after a coronary event (Giannuzzi *et al.*, 2003a), utilization of cardiac rehabilitation is still relatively low.

The level of cardiac rehabilitation service coverage across European Union States could be estimated from a survey of 454 phase II (medium-term recovery after hospital release) and 383 phase III (long-term maintenance) centers in 13 states of the European Union. Fewer than 50% of eligible patients do participate in cardiac rehabilitation programs in most countries, with services in particularly short supply in countries with the greatest burden of cardiovascular diseases (Vanhees *et al.*, 2002). According to another survey of the European Society of Cardiology, only 67% of patients are prescribed cardiac rehabilitation soon after coronary artery bypass grafting surgery, while this proportion drops to 49, 35, and 17% among those with recent myocardial infarction, percutaneous transluminal coronary angioplasty, or chronic myocardial ischemia, respectively. Furthermore, utilization of cardiac rehabilitation service is largely variable

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cross-nationally, with an average participation after any type of coronary event ranging from 4% in Spain to 71% in Slovenia (EUROASPIRE II Study Group, 2001). More importantly, it is to be pointed out that the data refers only to patients younger than 70 years, who were selected to get the information on cardiac rehabilitation service coverage in that survey. Given the almost systematic exclusion of older patients that has also been reported by the most recent meta-analyses of cardiac rehabilitation in patients with CHD (Taylor, 2004) or CHF (Smart and Marwick, 2004), underprescription is expectedly even more marked in the older subset of the clinical population of cardiac patients.

The situation is similar in the United States, where only about 20% of appropriate candidates of any age (Ades, 2001) and about 10–15% of those older than 70 years are estimated to participate in cardiac rehabilitation programs, despite this treatment being recognized and recommended as a fundamental component of secondary prevention programs in subjects older than 75 years (Williams *et al.*, 2002).

CARDIAC REHABILITATION: DEFINITION AND AIMS

Cardiac rehabilitation is defined as the "*sum of activities and interventions required to ensure the best possible physical, mental, and social conditions so that patients with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume their proper place in society and lead an active life*" (World Health Organization, 1993).

In this perspective, cardiac rehabilitation and secondary prevention are aimed at (1) preventing the disability that may result from heart disease, particularly in older persons and in those with occupations implying physical exertion, and (2) preventing subsequent cardiovascular events (Giannuzzi *et al.*, 2003a). These goals can be best achieved through programs combining use of evidence-based prescription of drug therapy with exercise training and education, counseling, behavioral strategies, and psychosocial interventions to help patients optimally control their coronary risk factors (Ades, 2001; Balady *et al.*, 2000; Haskell *et al.*, 1994; Taylor, 2004; Thompson *et al.*, 2003a). Therefore, cardiac rehabilitation is an integrated process of care, whose aims are well beyond the simple functional assessment and exercise prescription (Table 1), and which is currently indicated not only for cardiac patients already disabled or at increased risk of disability but also for those with a diagnosis of CHD, intermittent claudication, or with coronary risk factors. Guidelines (Wenger *et al.*, 1995; World Health Organization, 1993) or position papers (Balady *et al.*, 2000; Giannuzzi *et al.*, 2001; Piña *et al.*, 2003; Wood *et al.*, 1998), and evidences from randomized controlled trials (Belardinelli *et al.*, 1999; Hambrecht *et al.*, 2000a), suggest that cardiac rehabilitation is also indicated for patients with CHF.

The progressively shortened hospital stay reduces deconditioning, but also the time available to check physical activity and promote the lifestyle changes that are necessary to reduce the cardiovascular risk, reinforcing the need for rehabilitation programs that function as comprehensive, secondary prevention services and are based in the hospital, in the community, or at home (Balady *et al.*, 2000; Fletcher *et al.*, 2001; Wenger *et al.*, 1995; Wood *et al.*, 1998).

Table 1 Aims and role of cardiac rehabilitation as integrated secondary prevention tool

- Clinical support to optimize pharmacological and nonpharmacological therapy
- Risk stratification, to define the probability of new events and deterioration of cardiac function, overall functional capacity, and quality of life
- Assessment of physical exercise capacity, with exercise prescription in short-term training and long-term maintenance programs
- Assessment of cardiovascular risk factors, and implementation of counseling and education programs to promote a healthy lifestyle
- Assessment of psychosocial and occupational profile, to design interventions aimed at promoting an active lifestyle
- Clinical and instrumental follow-up, to improve the efficacy of secondary prevention programs

Because of the improved clinical management of cardiac diseases leading to increased survival rates, and to increasing evidence on the beneficial effects of rehabilitation in a wide spectrum of cardiac conditions, the delivery of cardiac rehabilitation has markedly changed over the past 30 years. In the 1960s, patients recovering from uncomplicated myocardial infarction accounted for almost the totality of referrals for cardiac rehabilitation. Complicated postinfarction patients, or patients recovering from myocardial revascularization, also have been enrolled in rehabilitative programs in later years. Patients once considered at too high a risk to participate in rehabilitation programs, such as those with myocardial ischemia, CHF, or harmful arrhythmias, are currently enrolled in programs of cardiac rehabilitation based on more gradual, protracted, and most often supervised exercise training (Ades, 2001; Balady *et al.*, 2000; Cobelli and Tavazzi, 1996; Giannuzzi *et al.*, 2001; Wenger *et al.*, 1995). Furthermore, as a result of the progressive aging of the population, rehabilitation should be provided now to increasing numbers of older patients, characterized by more complicated coronary illness, comorbidities (Ades, 2001; Balady *et al.*, 2000; Pasquali *et al.*, 2001), functional or cognitive impairment, emotional disorders, or social isolation, which are all factors that may reduce the enrollment rate in (Marchionni *et al.*, 2003), and the adherence to, standardized rehabilitation programs. Paradoxically, though some of these factors represent specific indications to rehabilitation (Pashkow, 1996), female gender, older age (Harlan *et al.*, 1995), a low formal education and, most importantly, deterioration of functional conditions (Fletcher *et al.*, 2001), are all negative predictors of enrollment in cardiac rehabilitation. Therefore, rehabilitation centers have to become familiar with the aims and skills of multidimensional geriatric assessment (Fretwell, 1988), in order to implement strongly individualized rehabilitation programs that may allow the enrollment and treatment of frail, older individuals.

Studies have proved that cardiac rehabilitation is at least equally effective in younger and older cardiac patients (Pasquali *et al.*, 2001), even as old as 86 years (Marchionni *et al.*, 2003), to improve their exercise tolerance and quality of life. However, no one study yet has demonstrated the efficacy of cardiac rehabilitation on outcomes that are most typically desirable in geriatric medicine, such as reverting or limiting the progression of functional dependence in the frail segment of the older population.

Secondary Prevention Strategies in Integrated Cardiac Rehabilitation Programs

Guidelines indicate that secondary prevention should be based on nonpharmacologic and pharmacologic interventions that can reduce the risk of new events and disease progression, and should be aimed at improving both the prognosis and the quality of life (De Backer *et al.*, 2003). Nonpharmacologic interventions consist of education, counseling, and psychosocial interventions targeted at smoking cessation, improving dietary habits, controlling body weight, and increasing physical activity and long-term adherence with prescriptions.

Educational Principles

A meta-analysis of 37 trials (Dusseldorp *et al.*, 1999) found that cardiac rehabilitation programs including psychological and/or educational interventions resulted in a significant reduction in incident cardiovascular events at 1–10 years, with studies with the greatest response to intervention showing the greatest impact. The desirable characteristics of the educational and counseling approach have been outlined after a meta-analysis demonstrating that the most important determinant of effectiveness is the quality of intervention (Mullen *et al.*, 1997), defined as behaviorally orientated interventions adhering to the five principles of adult learning:

- relevance (tailored to patients' knowledge, beliefs, circumstances)
- individualization (tailored to personal needs)
- feedback (informed regarding progress with learning or change)
- reinforcement (rewarded for progress)
- facilitation (provided with means to take action and/or reduce barriers).

Behavioral techniques such as self-monitoring and personal communication, including written or audiovisual techniques, may further improve the outcome, whereas information provision alone was found to be less effective (Mullen *et al.*, 1997).

Psychosocial Interventions

Some anxiety and depression are found in at least 20–25% of patients with various forms of heart disease (Frasure-Smith *et al.*, 1993; Gonzalez *et al.*, 1996) but, particularly when they persist, should not be accepted as an appropriate reaction to heart disease. Emotional disorders reduce exercise capacity (Marchionni *et al.*, 2000), quality of life, adherence with secondary prevention measures, and substantially increase the risk of new events after myocardial infarction (Frasure-Smith *et al.*, 1995) or in CHF (Jiang *et al.*, 2001). Depressive disorders are probably more common among older patients, who frequently suffer from isolation and financial constraints which, indeed, are negative prognostic factors after myocardial infarction (Ruberman *et al.*, 1984). However, the long-term consequences of emotional disorders among older cardiac patients in rehabilitation programs have been poorly addressed, and patients above age 75 years are at higher risk of underrecognition and undertreatment of depressive disorders (Pouget *et al.*, 2000).

Randomized trials proved that early psychological interventions improve the mood of middle-aged cardiac patients (Johnston *et al.*, 1999; Lewin *et al.*, 1992; Mayou *et al.*, 2002; Thompson and Meddis 1990), but information on efficacy at older ages is not available. However, particularly for most severe or disabling cases of persistent depression, psychological support therapies should be used in conjunction with antidepressants. Selective serotonine reuptake inhibitors, such as sertraline, which was proven more effectively than placebo on depression following a coronary event in the absence of any side effect (Glassman *et al.*, 2002), should probably be the preferred agents.

Smoking Cessation

A recent Cochrane review has confirmed the beneficial effects of smoking cessation, which reduces the risk of fatal and nonfatal new events up to 40% (Critchley and Capewell, 2004), similarly to what is seen with pharmacologic correction of other cardiovascular risk factors. Smoking induces chronic dependence that makes relapses highly probable. Systematic encouragement to smoking cessation is based on the "5A-strategy" of Asking, Assessing, Advising, Assisting, Arranging. In this process, it is necessary to identify smokers, to evaluate the degree of their dependence and their willingness to quit, to support those who are trying to quit with behavioral counseling, prescription of nicotine substitutes, and participation in educational meetings, with regular follow-up visits.

Healthy Eating and Diet

Dietary prescriptions, adapted to local habits and individualized as much as possible, should be aimed at control of body weight and provision of all elements of proven efficacy in secondary prevention (Sdringola *et al.*, 2003). Dietary habits should be assessed objectively, with use of reproducible questionnaires, and checking individual knowledge of nutrients and of possible substitutes. Education, rather than prescription, should be provided, limiting dietary restrictions to patients with defined metabolic abnormalities. Education

and counseling should be provided by professional dietitians, who perform better than physicians in obtaining a long-term reduction in plasma cholesterol levels (Thompson *et al.*, 2003b).

Increasing Physical Activity

Promoting a long-term increase in usual physical activity is a fundamental objective of integrated cardiac rehabilitation programs finalized at secondary prevention. Indeed, regular physical exercise improves the lipid profile and delays the progression of coronary atherosclerosis in middle-aged, CHD male patients (Niebauer *et al.*, 1997), and reduces cardiovascular mortality in the general population (Manson *et al.*, 2002). In the Harvard Alumni Health Study (Lee *et al.*, 2003), the relative (i.e. perceived) intensity of physical activity was a strong predictor of lower CHD rates, with a clear dose–effect relationship and an effect that was similar, if not superior, among subjects older compared to those younger than 70 years. Interestingly, the absolute intensity of physical activity did not perform as well as the relative one in distinguishing CHD risk groups, suggesting that physical activity recommendations need to be tailored to the individual. Standard recommendations of regular performance of activities at an intensity of at least 3 METs (metabolic equivalents, 1 MET corresponding to 3.5 ml of oxygen consumption for kilogram of body weight, see also the following text) may therefore be inappropriate, especially for older persons (Lee *et al.*, 2003).

Long-term Adherence and Follow-up

Once the process of short-term recovery is complete, the emphasis of cardiac rehabilitation shifts to long-term maintenance of physical activity, lifestyle changes, and prophylactic drug therapy, in the perspective of "comprehensive cardiac care" as the final goal, following evidence-based recommendations that are summarized in Table 2. In this context, it is important to remind that the beneficial effects of lipid-lowering therapy with statins extend to older patients (Lewis, 2004; Mungall and Gaw, 2004), and that results of a recent trial (Heart Protection Study Collaborative Group, 2002) extend the indications for statin therapy to all patients with CHD, irrespective of their serum cholesterol.

A systematic review of 12 randomized trials of secondary prevention programs in CHD found that structured disease management programs improve risk factor profiles and secondary preventive treatment, while reducing hospital readmissions and enhancing the quality of life (McAlister *et al.*, 2001). The programs included in the review differed considerably; all were multifaceted, with about a half including medical and lifestyle treatments, and the rest being predominantly lifestyle and psychosocial. Most were hospital based, but two conducted in the UK primary care suggest that a structured approach benefits health-related quality of life and uptake of secondary prevention. Indeed, long-term adherence with recommendations and prescriptions made during rehabilitation is difficult to maintain, being usually reduced to 50–60% at one year, and to 20–30% at three years. Therefore, to enhance long-term maintenance of the goals attained during cardiac rehabilitation, it is highly recommended that structured care and follow-up are provided in primary care (Dalal *et al.*, 2004), and studies suggest that low-cost physical training programs carried out in the community are safe and help patients maintain the physical work performance levels they had attained during hospital-based rehabilitation (Perk *et al.*, 1989).

Table 2 Evidence-based recommendations for lifestyle modification and drug therapy for secondary prevention of coronary heart disease

Drug therapy	– Aspirin (75 mg day^{-1}) or clopidogrel (75 mg day^{-1}) – Statin (if total cholesterol $\geq$ 5 mmol l^{-1})[a] – Beta-blocker – ACE inhibitor
Hypertension	– BP lowering (if BP $\geq$ 140/90 mmHg)
Diabetes	– Optimize glycemic and blood pressure control
Smoking	– Brief supportive advice, reinforced regularly – Nicotine replacement therapy
Diet	– Increase fruit and vegetables (at least 5 portions per day) – Increase omega-3 fatty acid (oily fish or rapeseed oil) – Replace saturated with unsaturated fat (e.g. olive oil) – Weight loss if obese (body mass index (BMI) $>$ 30 kg m^{-2})
Exercise	– Regular moderate intensity exercise (3–5 times per week)

[a]Data from the Heart Protection Study (Heart Protection Study Collaborative Group, 2002) extend the indications to all patients with coronary disease, irrespective of their serum cholesterol.

THE STRUCTURE OF CARDIAC REHABILITATION PROGRAMS

Cardiac rehabilitation programs consist usually of three phases, each representing a different step in the progression of individual patient care: inpatient care, the early postdischarge and exercise training period, and long-term follow-up. Common to each phase, and irrespective of which model of cardiac rehabilitation is chosen, is the need for individually tailored interventions.

Phase I occurs during in-hospital stay, when a "step change" (any acute coronary event, cardiac surgery, or first diagnosis of heart failure) has occurred in patient's cardiac condition. Medical evaluation and treatment, reassurance and information aimed at reducing emotional distress (Johnston *et al.*, 1999), risk factor assessment, mobilization, and discharge planning are the key elements during this phase.

Phase II includes the early postdischarge period – when baseline assessment and initial counseling on self-management of heart conditions usually take place (Lewin *et al.*, 1992), and subsequent structured exercise programs, which are carried out either in a hospital setting, in outpatient clinics, or, at least for selected patients, at home (Marchionni *et al.*, 2003). Guidelines (Wenger *et al.*, 1995) suggest that,

for the greatest secondary prevention success, training must be associated with educational and psychological support and advice on risk factors, such as smoking cessation and weight management, vocational rehabilitation to assist return to work or retirement, and referral to a psychologist, cardiologist, or exercise physiologist. It has been demonstrated that phase II programs of integrated, multicomponent cardiac rehabilitation can be undertaken safely and successfully also in the community (Bethell and Mullee, 1990).

Phase III involves the long-term maintenance of physical activity and lifestyle changes. Available evidence suggests that both must be sustained for benefits to continue (Cupples and McKnight, 1999; Schnohr *et al.*, 2000). Membership of a local cardiac support group, which involves exercise in a community center, such as a gym or leisure center, and structured care and follow-up in primary care (Dalal *et al.*, 2004), may help maintain physical activity and behavioral change.

Baseline Assessment

Baseline evaluation is a process of crucial importance that has to be completed prior to enrollment in a cardiac rehabilitation program. In this process, several clinical, functional and, particularly in older persons, emotional, cognitive, and social elements must be taken into account, as they are used to assign the patient to the program most appropriate for her/his clinical and functional conditions, to pursue reliable and clinically valuable outcomes, to reduce the probability of program-related complications, and to promote individual adherence with the program (Balady *et al.*, 2000). Exercise training programs for older persons also need to take into account commonly associated comorbidities that can alter the modalities and intensities of the exercise that is required to produce a training effect. These include, but are not limited to, CHF, arthritis and osteoporosis, chronic lung disease, diabetes, and peripheral or cerebrovascular disease.

Risk Stratification

Risk stratification and assessment of exercise capacity (Fleg *et al.*, 2000) are the two fundamental steps of baseline evaluation. These two steps are closely linked, as information gathered with assessment of exercise capacity is used not only for an appropriate exercise prescription to each individual patient but also as one of the criteria for assigning each patient to one risk category. Risk stratification, on the other hand, will serve to optimize pharmacological therapy and possibly to indicate the need for invasive procedures (e.g. coronary angiography and myocardial revascularization; implantation of pacemakers or intracardiac defibrillators), but also as a further information to be taken into account for exercise prescription.

In essence, risk stratification relies upon evaluation of clinical stability, left ventricular function, presence of residual myocardial ischemia or of sustained ventricular arrhythmias, and exercise tolerance. Following the criteria that are outlined in Table 3, patients are classified as at low, intermediate, or high risk.

Assessment of Exercise Capacity

Baseline exercise capacity can be evaluated by several methods, among which those used most commonly are the

Table 3 Criteria for baseline risk stratification of candidates to a cardiac rehabilitation program

	Class of risk		
Criteria	Low	Intermediate[a]	High[a]
Clinical course	Uncomplicated in-hospital course	Uncomplicated in-hospital course	– severe complications (e.g. cardiac arrest; shock; cardiac/respiratory failure) during in-hospital course OR – persisting clinical instability (e.g. cardiac failure; renal failure)
LVEF (%)	≥ 50	31–49	≤ 30
Myocardial ischemia	No	Yes – at intermediate (≥ 100 W) workload OR – with ST-segment depression < 2 mm OR – limited asynergies or perfusion defects at stress echocardiography or scintigraphy	Yes – at low (< 100 W) workload OR – with ST-segment depression > 2 mm OR – extensive asynergies or perfusion defects at stress echocardiography or scintigraphy
Ventricular arrhythmias	No	No	Yes Sustained ventricular arrhythmias
Exercise capacity	≥ 6 METs	< 6 METs	< 6 METs

LVEF: left ventricular ejection fraction; METs: metabolic equivalents of the task.
[a]Presence of any condition listed (with the exception of exercise capacity level) causes patient assignment to that risk class.

ergometric stress test, the cardiopulmonary exercise test, and the 6-minute walk test. Each of them is indicated in different conditions and provides different information.

The *ergometric stress test* is one of the most important diagnostic and prognostic instruments in cardiac patients, with the objectives of determining: (1) the exercise capacity, which is used for defining baseline functional capacity, training prescription, and evaluation of training results, and (2) the coronary reserve and the inotropic reserve. The cycle ergometer and the treadmill are the most diffused equipment for exercise stress testing, using protocols that may differ for the type of workload (constant vs increasing), the modality of delivering the workload (continuous vs at intervals), the rate of increase in workload (high vs low), the type and level of end point (predetermined vs symptom-limited, submaximal vs maximal). The specificity of the test is reduced with increasing age and its sensitivity, which should theoretically increase for the increased prevalence of CHD, may also be reduced. Indeed, it has been reported that a maximal, or symptom-limited, exercise stress testing is possible in only about 50% of individuals older than 75 years, as a consequence of aging-associated reduction in exercise capacity, detraining, and increased prevalence of comorbidities which may limit exercise capacity (Jeger *et al.*, 2004). Furthermore, the current use of a predetermined (220-age), maximal theoretical heart rate to assess the maximal intensity of physical exercise, does not represent a robust reference method, particularly in older patients with intrinsic functional limitations. The type of equipment and the protocol should be chosen on an individual basis, in order to adapt to the expected, individual exercise tolerance, which can be estimated from nomograms (Myers *et al.*, 1994) or standard references derived from population studies (Fletcher *et al.*, 2001). The test duration should not exceed 10–12 minutes (Buchfuhrer *et al.*, 1983), and smaller increases in workload (e.g. 10 W/step) are recommended for patients with expectedly reduced functional capacity. The indications and contraindications, and the diagnostic criteria for exercise stress testing, are detailed in guidelines of the American College of Cardiology/American Heart Association.

The *cardiopulmonary exercise test* is an ergometric test with simultaneous measurement of oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory quotient (VCO_2/VO_2), and pulmonary ventilation. This requires a relatively expensive equipment, which needs frequent calibration. Most commonly, the workload is increased by 10 W every 1–2 minutes. The large variability in the measurement of VO_2 – which is influenced by age, gender, level of fitness, severity of disease, and comorbidity – is the main limitation to standardize this test. Nonetheless, VO_2 max is the best available objective measure of aerobic capacity, though cardiac patients only rarely can exercise up to an intensity corresponding to their VO_2 max. Therefore, the VO_2 at peak exercise indexed by body weight (VO_2 peak, milliliters per minute per kilogram) is a more frequently used measure of exercise tolerance. During exercise, the respiratory quotient increases progressively until it becomes > 1, which corresponds to the anaerobic threshold (AT), a useful indicator of the workload that an individual can tolerate without overproducing lactic acid. Unfortunately, this cannot always be identified, particularly in patients with markedly reduced exercise tolerance (VO_2 peak $< 10\,ml\,min^{-1}\,kg^{-1}$). This test is particularly indicated to measure exercise tolerance and to define the prognosis of patients with CHF (Opasich *et al.*, 1998), and VO_2 peak or AT are also used to make the decision on patient inclusion in the waiting list for heart transplant.

With the *6-minute walk test* (Guyatt *et al.*, 1985), exercise tolerance is assessed by measuring the distance a patient can walk at her/his fastest possible pace over 6 minutes. A stopwatch, a notepad, and a measuring tape are the only materials required. The test has been standardized for application in a linear, enclosed, quiet, and seldom traveled corridor, at least 20 m in length, which must be marked throughout its length, to accurately determine the walked distance. Two chairs positioned at the two extremities of the corridor further delimit the path and permit the patient sit if she/he becomes so symptomatic during the test as to need some rest (Guyatt *et al.*, 1985). For safety purposes, the test is best carried out under continuous, telemetric control of heart rate and rhythm and of peripheral oxygen saturation, and in association with use of scales aimed at quantifying the perception of fatigue, and emergency equipment must be on hand. The main strengths of this test are represented by the fact that it is easy to carry out, does not require any special equipment and is based on a "natural" activity of common daily life. For these characteristics, the test has been extensively used to evaluate exercise tolerance especially in CHF and in older postinfarction or postsurgery patients (Harada *et al.*, 1999; Peeters and Mets, 1996), particularly when they are disabled to such an extent that they cannot perform reliably in a conventional ergometric stress test. The main limitation, on the other hand, is the scarce reproducibility, which is essentially due to variable motivation and self-assessment of fatigue, and which is improved with use of standardized encouragement by the test monitor (Guyatt *et al.*, 1985).

The Physical Exercise Training Program

The physical exercise training is the core component of cardiac rehabilitation programs, essentially aimed at improving exercise tolerance and, through this goal, at reducing disability, improving quality of life and control of cardiovascular risk factors, thereby reducing long-term morbidity and mortality.

Efficacy and safety are the most important characteristics to be considered in prescribing the physical exercise training in a cardiac rehabilitation program. Physical training is effective when it produces measurable benefits at the cardiocirculatory and skeletal muscles level, and is safe when it is not associated with either short- or long-term harmful effects.

Baseline assessment data is used to design individually adapted, effective, and safe training programs. To this

purpose, all factors that may limit the capability of exercising (e.g. presence and severity of angina or of concurrent diseases, such as disabling osteoarthritis), and the response to baseline, symptom-limited exercise stress test to be used to calculate the individual training workload, are the elements to be taken into fundamental account. The energy expenditure during physical exercise is influenced by the type of exercise (e.g. isotonic vs isometric), the amount of skeletal muscles involved, aerobic capacity, and also by the intensity, duration, frequency, and modality of exercise sessions.

Intensity of Exercise Training Sessions

Setting the intensity of exercise is a process of crucial importance, based on individual data and ideally leading to prescribe training at an intensity that is adequate for each patient. The intensity of exercise can be measured directly – as the amount of mechanical work produced (kilograms per minute; watt per minute; joules per minute), or indirectly – from measures of energy expenditure (such as kilocalories, or METs), or from exercise-related changes in physiologic variables (such as heart rate or VO_2). The method based on changes in heart rate is the simplest one, most commonly used in the clinical practice. Following this approach, a training exercise program is prescribed at an intensity (i.e. load) producing an increase in heart rate – defined as the "target" heart rate – to 70–85% of the maximal heart rate the patient has attained during a symptom-limited, baseline exercise stress test. The beneficial effects of training are maximized, exercise-related complications and lactic acid production in the peripheral organs are minimized, and the onset of fatigue is delayed, by maintaining the heart rate within its target range. Alternatively, training is prescribed at an intensity that will produce an increase in VO_2 to 60–80% of the VO_2 peak the patient has attained at baseline. These alternative approaches have been adopted in almost all the randomized trials reviewed by the 1995 Clinical Practice Guidelines on cardiac rehabilitation (Wenger *et al.*, 1995).

To further reduce the risk of complications, it is recommended that the intensity of exercise be increased gradually, allowing for a few minutes of warm-up before reaching the training workload. Beyond a generic recommendation of starting a training program at lower intensities with gradual increments during the next weeks, no conclusive data is available on how to adapt the training intensity to individual patient's clinical and functional profile. For practical purposes, however, it can be suggested that patients with CHD but without inducible myocardial ischemia or left ventricular systolic dysfunction start their training at an intensity corresponding to 70–85% of maximal heart rate, those with inducible ischemia exercise at an intensity almost corresponding to the ischemic threshold, whereas those with systolic left ventricular dysfunction or overt CHF should exercise at lower intensities, that is at 70–80% and 60–70% of maximal heart rate, respectively.

Beyond aerobic exercise, strength exercise is also increasingly being recognized as a useful component of the training program for selected patients (Daub *et al.* 1996; Fragnoli-Munn *et al.*, 1998; Pollock *et al.*, 2000; Stewart *et al.*, 1998), and muscular strength and endurance improve with strength training of moderate intensity in low-risk patients (DeGroot *et al.*, 1998), even at older ages (Fragnoli-Munn *et al.*, 1998). Information on safety and usefulness of strength training in high-risk patients is still limited, though it has been suggested (American College of Sports Medicine, 1990; Briant *et al.*, 1998) that low-intensity weight training can be safely and effectively introduced in the circuit training program for patients with CHD – even in the presence of inducible ischemia or left ventricular systolic dysfunction, or for patients with CHF (Maiorana *et al.*, 2000; Selig *et al.*, 2004).

Duration of Exercise Training Sessions

An individually prescribed duration of exercise sessions may range from 5 to 60 minutes, being indirectly proportional to the intensity of exercise. The duration of each session is usually shorter in the initial phase of training, to be increased gradually thereafter. An excessively prolonged duration may be associated with increased risk of lactacidosis and orthopedic complications. However, a reasonably prolonged exercise is necessary to activate the energy metabolism pathways: it is acknowledged that, for an intensity at about 80% of maximal heart rate, the optimal duration is in between 20 and 30 minutes. A practical method for determining the most appropriate duration of sessions is to use the product of workload by duration of exercise to calculate the energy expenditure, which should be of about 250–300 kcal/session, or of 1000–1500 kcal/week.

Frequency of Exercise Training Sessions

In the initial phase of an exercise program, when exercise intensity is gradually increased, daily sessions, at least five days a week, are to be preferred, also to check most accurately the cardiovascular response to exercise. This is particularly important because, during the initial phase of training, exercise-related changes in heart rate and arterial pressure may be remarkably different from those observed during the baseline stress test. Following the initial phase, three sessions per week are usually adequate to maintain the training effect. It is to be reminded that, if the training program is interrupted, exercise capacity usually is reduced by 50% within 4–5 weeks.

Modality of Exercise Training Sessions

A training program can be set up following the continuous, the interval, and the circuit training modality. The continuous training, which is particularly effective to increase cardiovascular and muscular endurance capacities, is carried out at moderate intensities, with a prolonged duration and without periods of recovery. In the interval training, periods of exercise at higher intensity are alternated with periods of recovery

or of exercise at lower intensity. The circuit training program is based on a series of different exercises (with or without equipments) carried out in a sequence. The circuit training is a program of moderate intensity, which improves not only the endurance capacity and muscular strength but also neuromuscular coordination and agility. Despite these multiple positive effects, this training modality is still uncommonly used in cardiac rehabilitation. Various equipment (e.g. cycle ergometer or treadmill) and various types of calisthenics have been used in training programs mostly aimed at enhancing aerobic capacity.

Each training session consists of different phases. A 5–10 minute warm-up phase, at intensities lower than the training intensity, is useful to increase muscular temperature and for joints mobilization, in order to reduce the risk orthopedic complications. By gradually increasing the workload to the heart, the risk of myocardial ischemia secondary to a brisk increase in myocardial oxygen demand is also reduced. The warm-up phase can include either stretching and flexibility, or aerobic exercises.

The training is the main phase of the program, aimed at improving the delivery of oxygen to the working muscles through both enhanced oxygen transportation capacity and extraction, and at maximizing caloric expenditure. Continuous and rhythmic exercises involving large muscle groups, such as walking, stepping on a staircase, exercising on the cycle ergometer, are the most effective modality of aerobic training. Calisthenics, particularly those involving large muscle masses, as well as strength training and recreational activities, can also be usefully included.

A 5–10 minute cool-down phase at a lower workload should follow the training phase, for a gradual recovery of heart rate and arterial pressure to their baseline level. A too brisk interruption of exercise can produce arterial hypotension and syncope, especially in older persons with blunted cardiovascular reflexes.

Progression and Duration of Training Programs

During the course of a training program, exercise intensity should be adapted to patient's improved exercise capacity. Changes in heart rate at submaximal exercise are the simplest method to be followed for this purpose. However, particularly in older patients and in those treated with beta-blocking agents, these may prove to be unreliable indicators of an improved aerobic capacity. Thus, use of the Borg's scale, which assesses the rate of perceived exertion (RPE) (Borg, 1982), is a commonly recommended, simple method to additionally confirm that exercise tolerance has improved from baseline. With a maximal possible value of 20 in the scale, patients should exercise at an RPE of 13–15. A reduction in RPE can be the consequence of enhanced cardiovascular and muscular fitness, but also of improved emotional profile and of increased confidence with the schemes of exercises and use of equipment. In any case, when the RPE at submaximal workloads is reduced, the intensity of exercise can be safely increased, in order to obtain a further training effect. Assessment of RPE is of particular importance in frail, older patients with CHF or comorbidity, or after prolonged bed rest for complicated cardiac surgery. In these subgroups, a standardized and reproducible assessment of perceived fatigue should guide the progression through strictly individualized rehabilitative programs, initially setting exercise intensity at an RPE of 9–11, which corresponds to about 60% of maximal heart rate, and slowly progressing to an RPE of 12–13 over the next weeks.

The duration of training programs is one of the most difficult characteristics to be exactly defined. Ideally, a training program should be prolonged enough to induce positive changes in functional conditions. Yet, this objective has to confront the organizational constraints of rehabilitation centers, which have to offer access to new patients following turnover programs. Furthermore, exact information on the relationship between program duration and attainable outcomes is still lacking, with the exception of documentation of variable increments in nonstandardized measures of exercise tolerance reported by training programs of variable duration. Three to 12 weeks are generally recommendable, with longer durations needed for patients at higher risk. At least 3 sessions/week at high workloads for 4 weeks are the minimal prescription to obtain a measurable and clinically valuable effect, while more sessions are necessary when – for safety reasons in front of markedly deteriorated functional profile or unstable clinical conditions – the workload has to be initially set at a low level. Following these general considerations, a program duration of at least 3 weeks is sufficient for most low-risk patients after uncomplicated infarction or cardiac surgery, whereas for patients at higher risk or with CHF, a duration respectively of 4–6 and 8–10 weeks is deemed to be more appropriate. Program duration should be prolonged also for older patients, who are usually trained at lower initial intensities. It is to be reminded that the duration of the training program is also a function of many other clinical elements, such as the adaptive changes in heart rate and arterial pressure, the absence of symptoms, the RPE, the capacity of obtaining at least a 10–20% increase in exercise tolerance from baseline, the stability of emotional profile, and adherence with the structure of overall preventive program.

As already mentioned, long-term, community-based physical exercise maintenance programs are effective in preserving the otherwise declining improvement in exercise tolerance attained with participation in hospital-based rehabilitation programs (Perk *et al.*, 1989).

Safety of Training Programs

Patients are admitted to a training program when in stable clinical conditions and in the absence of absolute contraindications to physical exercise (Table 4).

The safety of physical training in CHD patients has been for long a source of considerable controversies. Studies from the 1970–1980s reported an incidence of nonfatal events ranging from 1 event/34 000 hours of exercise-patient to 28 events/2 350 000 hours of exercise-patient, with an incidence of fatal events ranging from 1 event/116 000 to

Table 4 Contraindication to exercise training

Absolute	– Acute myocardial infarction – Unstable angina – Uncontrolled ventricular cardiac arrhythmias – Severe aortic stenosis – Unstable heart failure – Pulmonary embolism or infarction – Myocarditis or pericarditis – Aortic dissection
Relative	– Uncontrolled arterial hypertension (systolic/diastolic arterial pressure (SAP/DAP) > 180/110 mmHg) – Tachy- or bradyarrhythmias – High-degree atrioventricular block – Electrolyte abnormalities – Hypertrophic cardiomyopathy – Mental or physical impairment leading to inability to exercise adequately

Adapted from (American Association of Cardiovascular & Pulmonary Rehabilitation – AACVPR, 2004)

1 event/2 350 000 hours of exercise-patient. Lower overall rates, and absence of any fatality, have been reported by two reviews (Franklin *et al.*, 1998; Vongvanich *et al.*, 1996) that were based on more recent studies. Whether continuous ECG monitoring may reduce the risk of complications is still unknown. Usually, high-risk patients are constantly monitored during the whole training program, whereas low-risk patients are monitored only during the first few sessions. However, studies have suggested that the overall incidence of complications is low and similar across risk categories, and that the few complications are represented mostly by "minor" events such as angina, ST-segment depression, or nonsustained cardiac arrhythmias (Keteyian *et al.*, 1995). For the purpose of safety, multiple parameters must be taken under control during exercise training, in particular, the linearity of the increase in heart rate and arterial blood pressure, ECG morphology, and the RPE. Surveillance and monitoring must be especially close during the initial phase of the program, when physical detraining, or difficulties in learning how to carry out exercises, may contribute to abnormal increases in heart rate or arterial pressure. Adapting exercise prescriptions to a limited functional capacity – particularly in older, disabled, and comorbid individuals – further contributes to the feasibility and safety of exercise programs. A skilled staff that includes several different professionals such as physical therapists, nurses and technicians, and on-site devices and drugs that are necessary for immediate treatment of emergencies are the final elements that warrant program safety.

Exercise Training Programs in Special Cardiac Conditions

Cardiac Surgery

Exercise training after cardiac surgery can start when clinical conditions have become stable, and is usually preceded by short programs of respiratory physical therapy to recover respiratory dynamics, and of low-intensity exercise to improve mobility and flexibility. Extensive neurologic and cognitive evaluation is particularly recommended in older persons, in whom cerebral complications of prolonged anesthesia and extracorporeal circulation are more likely to occur (Roach *et al.*, 1996). In these patients, early rehabilitation program is aimed mainly at improving mobility and independence in activities of daily living. In the absence of specific contraindications that may occur after surgery (e.g. anemia with Hb $< 10\,g\,dl^{-1}$; pleural or pericardial effusion; delayed or complicated healing of surgical wounds), a 6-minute walk test is prescribed as soon as the patient is able to walk independently (on average, 10 days after surgery). A baseline, symptom-limited ergometric stress testing is carried out 3–4 weeks after surgery, when the sternum usually has stabilized and thoracic pain has relieved. As previously described, data acquired during the stress test is used to select the appropriate intensity for exercise training, which low-risk patients can usually be taught how to self-manage at home without risk. As for other categories of cardiac patients, assessment of cardiovascular risk factors, associated with education, counseling, and behavioral strategies to help achieve the best optimal control of coronary risk factors, are essential components of medium- and long-term rehabilitation programs (Engblom *et al.*, 1996).

Chronic Heart Failure

Patients with CHF must have been in a stable clinical condition with optimal drug therapy for at least one month before their exercise capacity is tested for the purpose of potential enrollment in a physical training program. Particularly in the presence of chronic atrial fibrillation, the cardiopulmonary exercise test is the preferred method for baseline assessment (Giannuzzi *et al.*, 2001), as it can evaluate aerobic capacity and, hence, exercise capacity also when heart rate response to exercise is inappropriate or difficult to determine precisely. Endurance training at the cycle ergometer, with intensity set at 50% of maximal workload attained at baseline cardiopulmonary exercise test, 15-minute sessions of interval training (exercise for 30 seconds, followed by 60 seconds of recovery), is the most commonly adopted training modality for CHF patients, since it would induce the best possible training effect without excessively increasing the sense of fatigue or producing undesirable metabolic effects (Meyer *et al.*, 1997). Alternative protocols include arm exercises, walking on treadmill, flexibility, and respiratory exercises. More recently, studies have demonstrated some positive effect from association of endurance training with strength training exercises (Hulsmann *et al.*, 2004). Since functional assessment of, and exercise prescription to CHF patients requires particularly high skills, these patients should participate only in programs that are run by well-experienced rehabilitation centers. At least in the initial phase, the training program should be carefully supervised. Studies have demonstrated the feasibility, safety and efficacy of home-based, low-intensity training programs for CHF patients (Corvera-Tindel *et al.*, 2004; Oka *et al.*, 2000) but, again, no specific data is yet available for older patients.

THE PHYSIOLOGIC EFFECTS OF AEROBIC TRAINING

Effects of Aerobic Training in Middle-aged and Older Adults with Coronary Heart Disease

The beneficial physiologic effects of physical training, that is, improved exercise tolerance associated with less fatigue, less angina, and increased sense of well-being, derive from both peripheral (vascular or skeletal muscle) and central (myocardial) adaptations.

Peripheral adaptations are mainly the consequence of improved skeletal muscle efficiency, leading to improved ability to extract oxygen from entering blood supply and to increased arterioveneous difference during physical exercise. This reduces the need for increasing cardiac output and, hence, the work the heart has to do to bring an adequate amount of oxygen to the tissues at submaximal exercise (Detry *et al.*, 1971). Therefore, the perceived fatigue and the tachycardic response at submaximal workloads are also reduced, workloads higher than at baseline can be tolerated, and VO_2 max and physical work capacity are substantially increased. In general, the lower the initial VO_2 max or physical work capacity, the greater the improvement after training (Marchionni *et al.*, 2003).

Central adaptations include increases in cardiac dimensions, stroke volume, cardiac output, and indexes of left ventricular function (Ehsani *et al.*, 1986; Hagberg *et al.*, 1983), which have been reported after training programs of variable duration in middle-aged patients with CHD. The mechanisms of physiologic adaptations to exercise training in older patients may be somewhat different from those seen in middle-aged patients. Probably because of the aging-associated increase in myocardial and vascular stiffness, adaptability to central remodeling is reduced, and exercise-induced adaptations in older coronary patients appear to be almost exclusively localized at the periphery. After three months of aerobic training, peak exercise cardiac output, peripheral vascular conductance and hyperemic calf blood flow are unchanged in older, low-risk patients with CHD, despite the fact that their exercise tolerance, VO_2 max, and arteriovenous oxygen difference have increased (Ades *et al.*, 1996). Histological analysis of skeletal muscle biopsies shows a marked increase in capillary density, and in oxidative enzyme capacity that fully accounts for improved adaptation to exercise (Ades *et al.*, 1996).

Effects of Aerobic Training in Patients with Chronic Heart Failure

Reduced exercise tolerance with increased breathlessness and muscle fatigue are the symptomatic hallmarks in CHF patients, who limit their activity to avoid these symptoms. This may result in further detraining, possibly leading to a vicious circle of progressively reduced exercise tolerance.

The origin of these symptoms is multifactorial, involving central cardiac factors (i.e. left ventricular systolic and diastolic dysfunction with increased pulmonary capillary pressure); central pulmonary factors (impaired ventilatory mechanics and increased physiologic dead space, altered ventilation/perfusion ratio, hypoxia of ventilatory muscles); and peripheral circulatory and muscular factors (impaired vasodilatation during physical exercise, metabolic and structural alterations of skeletal muscles). Peripheral pathophysiological changes appear to be the most important determinants of exercise capacity in CHF, as systemic and pulmonary hemodynamics correlate poorly with exercise capacity or exertional breathlessness and, while central hemodynamics improve rapidly with drug therapy, improvement in exercise capacity may be delayed for weeks or months.

Skeletal muscle hypoperfusion has been observed in CHF both at rest and during exercise (Sullivan *et al.*, 1989b). This is directly related to CHF severity, and is the consequence – together with sympathetic overactivity and parasympathetic withdrawal – of increased activity of endothelial angiotensin converting enzyme (ACE) and reduced endothelial production of nitric oxide, and is responsible for early occurrence of lactacidosis which, in turn, produces muscular exhaustion and increases the ventilatory needs (Piepoli *et al.*, 1996). It also has been demonstrated that unmyelinated and small myelinated afferents in muscle that are sensitive to metabolic changes related to work ("ergoreceptors"), are responsible for the early circulatory response to exercise, including activation of the sympathetic vasoconstrictor drive, and that this reflex is exaggerated in CHF, probably because of sensitization by muscular acidosis during exercise (Piepoli *et al.*, 1996). Limited physical activity, anorexia, and increased circulating substances with known catabolic effect, contribute all to induce a certain degree of muscular atrophy, which correlates with the reduction in strength and exercise tolerance. However, functional data suggests that muscular atrophy cannot fully account for the reduced exercise tolerance. When strength is measured for unit of muscular area, it correlates poorly with VO_2 max and exercise tolerance. This is consistent with qualitative alterations of muscular fibers, represented by a reduction in slow reacting, type I fibers – responsible for muscular endurance, with prevalent oxidative metabolism, with a relative increase in fast reacting type II fibers, whose metabolic pathways rely mainly on glycolysis.

Randomized trials have demonstrated that physical training determines a sustained improvement in functional class, maximal ventilation, exercise capacity (Hambrecht *et al.*, 2000a), and quality of life (Belardinelli *et al.*, 1999) in CHF patients, particularly when enrolled in long-term maintenance programs. Though some improvement in left ventricular ejection fraction at rest and in maximal stroke volume during exercise has occasionally been described (Hambrecht *et al.*, 2000a), changes in central hemodynamics after training are generally modest (Coats *et al.*, 1992; Sullivan *et al.*, 1989a). Thus, also in the case of CHF the major adaptations to training appear to be peripheral. Many of the peripheral vascular and muscular dysfunctions that concur to reduce exercise tolerance in CHF are fully reverted, or at least

partially corrected, by training. In particular, the endothelial production of nitric oxide in response to exercise is remarkably enhanced (Hambrecht *et al.*, 1995), and the exaggerated ergoreflex activity is attenuated (Piepoli *et al.*, 1996), with both effects contributing to reduce the inappropriately increased peripheral vascular resistance. Exercise training also reduces the concentration of circulating norepinephrine and atrial natriuretic peptide (Shemesh *et al.*, 1995). Analysis of percutaneous muscular biopsies, coupled with measurement of VO_2 max during symptom-limited cardiopulmonary exercise test, suggests that structural and functional changes in skeletal muscles are a further determinant of improvement in exercise tolerance observed with training in CHF. Indeed, ultrastructural morphometry demonstrated a training-associated increase in skeletal muscle cells mitochondria, suggesting that the improved functional capacity is linked to an increased oxidative capacity of skeletal muscles (Hambrecht *et al.*, 1995) and a concomitant reshift to type I fibers (Hambrecht *et al.*, 1997).

EVIDENCE-BASED RESULTS OF CARDIAC REHABILITATION IN DIFFERENT CARDIAC CONDITIONS

Coronary Heart Disease

Most randomized trials of cardiac rehabilitation in CHD have included mixed populations of patients with recent myocardial infarction, myocardial revascularization, or angina, and are based on exercise only or exercise in addition to psychological and educational interventions, which is usually termed *comprehensive cardiac rehabilitation*.

The most recent meta-analysis included 48 trials and 8940 patients (Taylor, 2004). Compared with usual care, cardiac rehabilitation was associated with a significant, 20 and 26% reduction in all-cause and cardiac mortality, respectively, and with larger reductions in plasma lipids, systolic blood pressure, and rates of persistent smoking. Rates of nonfatal myocardial infarction and revascularization, and changes in high- and low-density lipoprotein cholesterol levels, diastolic pressure, or health-related quality of life, were similar with cardiac rehabilitation or usual care. The effect of cardiac rehabilitation on total mortality was independent of CHD diagnosis, dose of exercise intervention, length of follow-up, trial quality, and trial publication date. In contrast with previous reports of greater benefit with comprehensive rehabilitation than with exercise-only programs (Oldridge *et al.*, 1988), the benefits were independent of type of rehabilitation program. Authors (Taylor, 2004) suggested that this may be due to the fact that follow-up in most studies was too short to observe indirect effects, which may need a longer time to occur. However, there are two alternative explanations. One is that exercise-only cardiac rehabilitation is likely to include psychological and educational support, even though not offered in a structured fashion. The other is that most of the exercise-only trials were conducted in the prethrombolytic era, whereas most of the comprehensive trials were more recent. This means that the benefits in the comprehensive rehabilitation trials are likely to be additional to the already great benefit of thrombolysis, prophylactic medication, and/or revascularization. Only one trial included in the meta-analysis has deliberately enrolled significant numbers of patients older than 75 years. In particular, this was the first randomized, controlled trial demonstrating the feasibility, safety and efficacy on exercise tolerance, and health-related quality of life of rehabilitation in postmyocardial infarction patients as old as 86 years of age (Marchionni *et al.*, 2003). The uniqueness of this trial is confirmed by the fact that the ages of patients enrolled in other trials ranged from 48 to 71 years and, accordingly, recommendations for further trials including subsets of older patients were made in Taylor's review (Taylor, 2004).

The precise mechanism(s) by which physical exercise training reduces mortality in CHD patients is still to be completely elucidated (Thompson *et al.*, 2003a). Exercise training exerts direct beneficial effects on myocardial oxygen demand, development of coronary collateral vessels and coronary endothelial function, cardiocirculatory autonomic tone, coagulation and clotting factors, inflammatory markers (Hambrecht *et al.*, 2000b). However, reduction in mortality may also be mediated via the indirect effects of exercise through improvements in the risk factors for atherosclerotic disease.

Cardiac Surgery

Though almost two-third of patients enrolled in cardiac rehabilitation programs in Europe are recovering from cardiac surgery, only few studies specifically have addressed the efficacy of cardiac rehabilitation after surgery. Furthermore, most meta-analysis have not examined the results of post-surgery cardiac rehabilitation separately from those in other clinical subsets. In the Cochrane Library Reviews (Jolliffe *et al.*, 2001), for example, randomized trials of cardiac rehabilitation after coronary artery bypass grafting have been pooled with trials of rehabilitation after myocardial infarction or coronary angioplasty. These aggregated analyses have demonstrated that cardiac rehabilitation is associated with a significant reduction in long-term mortality. Of the many randomized trials included in the Scottish Intercollegiate Guidelines (Scottish Intercollegiate Guidelines Network, 2002), only two had selectively enrolled patients with recent coronary artery bypass surgery, and none of them had been designed to assess the effects of rehabilitation on mortality or morbidity, but rather to test its efficacy on lipid profile and self-perceived health (Engblom *et al.*, 1997; Wosornu *et al.*, 1996).

Information on efficacy of postsurgery rehabilitation in older patients is even more limited, despite the demonstration that older age, together with female gender and comorbidity, are independent risk factors for cognitive, neurological and functional complications (Roach *et al.*, 1996), prolonged

hospital stay (Stewart *et al.*, 2003), worse long-term prognosis (Alexander *et al.*, 2000), and early hospital readmission (Hannan *et al.*, 2003) after cardiac surgery, which are all elements that would recommend a greater participation of older surgical patients in rehabilitation programs. Nonetheless, a recent review (Pasquali *et al.*, 2003) demonstrated that beyond age, disability, lower formal education, cardiac dysfunction, and poor quality of life, are all predictors of nonparticipation in rehabilitation after coronary artery bypass operations, though patients with these conditions would benefit the most from integrated, multicomponent cardiac rehabilitation programs.

Chronic Heart Failure

After the success with newer pharmacologic agents such as ACE inhibitors, beta-blockers, and antialdosteronic agents, a further "therapeutic revolution" recently has occurred in the management of CHF (Coats, 1999), consisting of a profound change in recommendations about physical activity. From the previous orientation in favor of a restriction in physical activity, newest guidelines recommend therapeutic exercise programs for the current management of CHF (Piña *et al.*, 2003). This came after the demonstration that supervised exercise training improves the functional capacity and quality of life of CHF patients (Belardinelli *et al.*, 1999), without any risk of unfavorable clinical events or deteriorating cardiac function, but rather with an anti-remodeling effect (Giannuzzi *et al.*, 2003b).

A recent review has pooled the results of 81 studies of exercise training in CHF (Smart and Marwick, 2004), which differed largely for the intensity (from 40 to 90% of VO_2 max), the frequency (from 1 to 7/week) and duration (from 15 to 120 minutes) of exercise training sessions, and for the overall program duration (from 2 to 104 weeks). Despite these differences, and the different characteristics of patients enrolled, a relatively homogeneous and significant improvement in exercise tolerance was reported by all studies. Pooled analysis also has demonstrated the absence of relevant, exercise-related adverse events, and significant, positive effects of training on combined end points (all-cause mortality plus new events). A meta-analysis (Piepoli *et al.*, 2004) including 9 randomized trials with 809 patients (395 exercise training vs 406 controls) has determined the effect of exercise training programs of at least 8 weeks with follow-up data for at least 3 months on survival in patients with CHF due to left ventricular systolic dysfunction. Exercise training significantly reduced all-cause mortality and the combined end point of hospital readmission by 35 and 28%, respectively, with no statistically significant subgroup treatment-specific effect. Age comparison was limited to patients younger and older than 60 years, since the vast majority of those enrolled in randomized trials were younger than 65 years. Moreover, most patients enrolled in randomized trials were highly selected individuals with little or no comorbidity, quite unlike older cardiac patients seen in everyday clinical practice (Lien *et al.*, 2002; McMurray, 2000), and the surrogate end points that frequently have been adopted in those trials (e.g. changes in VO_2 max) do not provide evidence that such therapy affects outcomes that are especially valuable in older persons, such as overall functional capacity or quality of life. For all these reasons, the applicability of evidence-based results to older CHF patients is still substantially limited.

ECONOMIC EVALUATION OF CARDIAC REHABILITATION

A major challenge for all health care systems is to identify the most efficient use of limited resources available for health care. Economic evaluation provides a balance sheet of the benefits, harms, and costs for making choices between alternative health care services and may help decision-makers to make rational choices about effective and efficient health care.

Only few studies have reported economic data of cardiac rehabilitation, and only rarely with inclusion of older patients. A randomized, controlled trial comparing outpatient, hospital-based, home-based cardiac rehabilitation and standard care, with substantial numbers of patients older than 75 reported some cost saving with cardiac rehabilitation during a 1-year follow-up, since rehabilitated patients required less medical visits and hospital readmissions than controls. Cost saving was independent of age and particularly remarkable with home-based rehabilitation, suggesting that this may be the most cost/effective modality of delivering cardiac rehabilitation services to low-risk older patients (Marchionni *et al.*, 2003). Quite similar results had been obtained in a previous controlled trial, which, in postmyocardial infarction patients younger than 65 years, reported a further reduction in costs due to a more frequent return to work of rehabilitated patients. However, also this report was simply a cost analysis and, therefore, the authors' conclusion that cardiac rehabilitation is highly cost/effective is inappropriate (Levin *et al.*, 1991), since a complete collection of costs and outcomes data on two or more alternatives is required for accurately determining cost/effectiveness (Oldridge, 1998).

A full economic evaluation of cardiac rehabilitation has been carried out in a single randomized trial of postmyocardial infarction patients (Oldridge *et al.*, 1993). Overall costs and health-related quality of life, measured with the time trade-off preference score were obtained and, together with survival data derived from published meta-analysis, cost-utility, and cost-effectiveness of cardiac rehabilitation were estimated. The best estimate of the incremental net direct 1-year costs for patients randomized to rehabilitation was US (1991) $480/patient. During the follow-up, rehabilitation patients required significantly fewer visits and gained 0.052 quality-adjusted life-year more than did the group randomized to usual care. The cost/utility ratio was $9200/quality-adjusted life-year gained with cardiac rehabilitation during the year of follow-up, providing evidence that

postmyocardial infarction cardiac rehabilitation is economically justifiable (Oldridge *et al.*, 1993).

The effectiveness of cardiac rehabilitation has also been assessed using the alternative approach of defining the number needed to treat (NNT) to attain an additional favorable outcome or to prevent an additional adverse outcome. With this method, which provides information about the impact of a certain treatment on clinically relevant outcomes, the closer NNT is to 1.0 – meaning that every patient who is treated achieves a benefit – the more effective the treatment is (Oldridge *et al.*, 2002). In this analysis, mortality data were taken into account as a primary outcome measure of effectiveness, by calculating the absolute risk reduction associated with cardiac rehabilitation compared to usual care and, from that, estimating the NNT. Using the data from three meta-analyses published between years 1988–1989 (O'Connor *et al.*, 1989; Oldridge *et al.*, 1988) and year 2001 (Jolliffe *et al.*, 2001), the respective estimated NNT for mortality were 32, 46, and 72 (95%CI 19–1403), suggesting a limited effect of cardiac rehabilitation, which has been attenuating over the last decades. This attenuation probably reflects the evolution of current cardiology practice, including coronary reperfusion with thrombolysis or primary coronary interventions, which could determine *per se* a substantial improvement in long-term outcomes (Oldridge *et al.*, 2002). The data from two randomized trials of cardiac rehabilitation carried out in Italy (Marchionni *et al.*, 2003) and in Canada (Oldridge *et al.*, 1991), were used to estimate NNT for exercise tolerance and health-related quality of life. Exercise tolerance increased significantly more with cardiac rehabilitation than with usual care in only one trial (Marchionni *et al.*, 2003), giving an estimated NNT of 5 (95%CI 3–13), which suggests a high efficacy and a clear superiority of cardiac rehabilitation over usual care in improving this outcome. Quality of life improved significantly more with cardiac rehabilitation in both trials, with estimated NNT of 12 (95%CI 5–26) and of 6 (95%CI 3–21) for the Italian and the Canadian trial, respectively. Therefore, the NNT-based analysis suggested a high efficacy of cardiac rehabilitation on both these relevant outcomes, with a more consistent efficacy on quality of life (Oldridge *et al.*, 2002).

KEY POINTS

- Cardiac rehabilitation is an integral component of secondary prevention, and is indicated for patients with a wide variety of cardiac conditions, ranging from coronary artery disease to CHF.
- Best results are obtained with integrated, multicomponent cardiac rehabilitation programs, which include exercise training together with counseling and psychosocial measures that may help patients maintain sustained changes toward a more healthy lifestyle. Studies suggest also that long-term maintenance programs carried out in the community after the in-hospital phase may achieve better long-term results.
- Robust evidence from randomized controlled trials and meta-analyses supports the efficacy of cardiac rehabilitation on clinically relevant outcomes such as reduced long-term morbidity and mortality, enhanced functional profile and improved control of cardiovascular risk factors. A limited number of economic analyses suggest that cardiac rehabilitation is also cost-effective.
- However, the vast majority of this evidence derives from trials with only small numbers of patients older than 70–75 years of age.
- Future research programs should therefore be aimed at specifically investigating the efficacy and effectiveness of cardiac rehabilitation in older, frail cardiac patients.

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PART III

Medicine in Old Age

Section 5

Respiratory Diseases

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Epidemiology of Respiratory Infection

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COMMUNITY-ACQUIRED PNEUMONIA

Most studies of community-acquired pneumonia in the elderly have primarily focused only on hospitalized cases (Granton and Grossman, 1993). Marston *et al.* (1997) evaluated all adults hospitalized for community-acquired pneumonia in 1991 who resided in two counties of the state of Ohio in the United States. The incidence of community-acquired pneumonia requiring hospitalization was 266.8 per 100 000 with an overall case fatality rate of 8.8%. The incidence was higher in males (29.1 vs 244.8; $P < 0.001$) and increased with age (91.6 in those <45 years old to 1012.2 in those ≥65 years old). Case fatality was significantly higher in those ≥65 years of age (12.5%) compared to those <65 years (4.6%; $P < 0.001$). Kaplan *et al.* (2002) performed a retrospective analysis of all Medicare recipients, aged 65 and older, hospitalized for community-acquired pneumonia in nonfederal hospitals in the United States in 1997. The overall incidence of pneumonia was 18.3 per 1000 population but increased from 8.4 per 1000 in those aged 65–69 years to 48.5 per 1000 in those aged 90 years and older and the incidence was higher in males (19.4 vs 15.6 per 1000; $P < 0.001$). Overall, hospital mortality was 10.6% but mortality doubled with age from 7.8% in those 65–69 years to 15.4% in those 90 years and older. Fernandez-Sabe *et al.* (2003) studied 1474 adult patients hospitalized with community-acquired pneumonia in one hospital in Spain between 1995 and 2001. These authors found that the "very elderly" (aged 80 and older) developed significantly more complications during hospitalization and had a significantly higher overall mortality than those <age 80.

There have been a small number of population-based studies that have provided age-specific incidence data for community-acquired pneumonia (Joikinen *et al.*, 1993; Jackson *et al.*, 2004). Among 47 000 citizens of four municipalities in a province in eastern Finland, the overall incidence of community-acquired pneumonia was 11.6 episodes per 1000 persons per year (Joikinen *et al.*, 1993). Among those aged 60 and older, the incidence was 19.9 per 1000 while it was 34.2 per 1000 for those aged 75 and older; the incidence was threefold higher in elderly males than in females (33/1000 vs 11.8/1000). Overall, 42% of all people with community-acquired pneumonia were hospitalized but the hospitalization rate was 67% in those aged 60 and older. The crude case fatality rate was 4% but it increased with age: 6% for those aged 60–74 years and 17% for those 75 years and older.

A more recent study (Jackson *et al.*, 2004) has provided the first extensive evaluation of the rates of community-acquired pneumonia in the elderly managed in the community and in the hospital. These investigators evaluated 46 237 seniors (aged 65 years and older) who were members of a health maintenance organization in one state in the United States between 1998 and 2001. Rates of community-acquired pneumonia increased with age, ranging from 18.2 episodes per 1000 person-years for those aged 65–69 to 59.9 per 1000 for those 90 years and older with the overall rate being 28.4 per 1000 person-years. In all age categories, males had a higher rate of pneumonia. In this population, 59% of all episodes of community-acquired pneumonia were treated on an outpatient basis. Independent risk factors for community-acquired pneumonia included older age, male sex, obstructive lung disease, asthma, diabetes, heart failure, and smoking. Among persons hospitalized for treatment 12.5% died within 30 days of admission, whereas only 0.4% of persons treated as outpatients died within 30 days of initial diagnosis. The importance of older age in the prognosis and in predicting the outcome of patients hospitalized with community-acquired pneumonia has been identified in several studies (Gilbert and Fine, 1994; Fine *et al.*, 1997).

NURSING HOME–ACQUIRED PNEUMONIA

In the nursing home setting, the reported incidence of pneumonia has ranged from 0.5–3.3 episodes per 1000 resident days (Mylotte, 2002). In a retrospective study, the incidence of pneumonia among a group of veterans in one

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nursing home in New York State was 1.46 episodes per 1000 resident care days (McDonald *et al.*, 1992). In a retrospective study of pneumonia occurring in 31 nursing homes in metropolitan St Paul, Minnesota, USA, the incidence was 0.5 episodes per 1000 resident care days (Degelau *et al.*, 1995). In a prospective study of lower respiratory tract infection in five nursing homes in Toronto, Ontario, Canada from 1993 to 1996, the incidence of pneumonia was 0.7 episodes per 1000 resident care days (Loeb *et al.*, 1999). In a random sample of nursing homes in three cities in Sweden between March 2000 and June 2001, the yearly incidence of pneumonia among 262 prospectively monitored residents was 13.7% (Sund-Levander *et al.*, 2003).

Several studies have evaluated risk factors for the development of nursing home–acquired pneumonia. In a prospective case-control study (Marrie *et al.*, 1986), those with nursing home–acquired pneumonia admitted to a hospital significantly more often had underlying dementia and cardiovascular disease than those admitted for community-acquired pneumonia (matched by age, sex, and time of admission); mortality is also significantly higher in the nursing home group (Marrie *et al.*, 1989). In a prospective case-control study three factors predicted nursing home–acquired pneumonia: difficulty with oropharyngeal secretions, deteriorating health, and occurrence of an unusual event (development of confusion, agitation, a fall, or wandering) (Harkness *et al.*, 1990). In a population-based study of nursing home–acquired infections, risk factors for lower respiratory tract infections (pneumonia and bronchitis combined) were the presence of a tracheostomy or feeding tubes, bedridden status, and underlying lung disease (Magaziner *et al.*, 1991). In a veteran population, risk factors for nursing home–acquired pneumonia were tube feedings, underlying neurologic disease, and bedridden status (McDonald *et al.*, 1992). In a Swedish study, the presence of chronic lung disease diagnosis, poor functional status, and male gender were significant predictors of pneumonia (Sund-Levander *et al.*, 2003). In summary, it is the debilitated nursing home resident, particularly the resident who is continually bedridden because of underlying disease, who is at a greater risk of developing nursing home–acquired pneumonia.

Several studies have evaluated risk factors for mortality among those with nursing home–acquired pneumonia. In a case-control study among residents with lower respiratory infection (pneumonia or bronchitis), the level of dependence as measured by activities of daily living (ADL) strongly influenced outcome (Mehr *et al.*, 1992). In a retrospective cohort study in one nursing home, independent risk factors for death among those hospitalized for the treatment of pneumonia were observed aspiration or a history of aspiration and severe dementia, whereas among those treated in the nursing home they were dependent functional status and use of parenteral antibiotics (Fried *et al.*, 1995). Prepneumonia functional status has also been identified as a predictor of mortality in those with nursing home pneumonia in other studies (Muder *et al.*, 1996; Fried *et al.*, 1997; Mehr *et al.*, 1998) but not all (Naughton *et al.*, 2000). Models to predict mortality among nursing home residents with lower respiratory tract infection (Mehr *et al.*, 2001) or with pneumonia (Naughton *et al.*, 2000) have been developed, but have yet to be independently validated.

HOSPITAL-ACQUIRED (NOSOCOMIAL) PNEUMONIA

Pneumonia is the third most common type of hospital-acquired infection overall, accounting for 17.3% of all infections in recent data available in the United States (NNIS, 1995). However, 80% or more of episodes of hospital-acquired pneumonia occur in the intensive care setting (Vincent *et al.*, 1995).

The burden of nosocomial infections falls heavily on the elderly. Evaluation of nosocomial infections in the elderly in the United States from 1986 to 1990 by the Centers for Disease Control indicated that 54% of all nosocomial infections occurred in those $\geq$65 years old; in the elderly, 44% of the infections were in the urinary tract and 18% were pneumonias (Emori *et al.*, 1991). Other studies of age-specific risk for nosocomial infection have also shown that rates of infection, in general, and nosocomial pneumonia, in particular, are significantly higher among the elderly than younger patients (Gross *et al.*, 1983; Hanson *et al.*, 1992; Klavs *et al.*, 2003). When the risk of nosocomial infection/pneumonia is adjusted for the duration of hospital stay, the likelihood of a first nosocomial infection after 1 week of stay is much greater in the elderly than in younger patients (Saviteer *et al.*, 1988).

Despite the association between age and the development of nosocomial pneumonia, age alone is not the only reason for the increased risk; age may be a surrogate for serious underlying disease or debility which, in turn, predisposes to pneumonia. In addition, life-saving interventions, such as intubation and mechanical ventilation, also increase the risk of nosocomial pneumonia. Celis *et al.* (1988) identified age greater than 70, intubation, depressed consciousness, underlying chronic lung disease, aspiration, and recent chest or abdominal surgery as independent predictors of nosocomial pneumonia while age >60 years and five other variables predisposed to a poor prognosis. However, in a more recent study (Salemi *et al.*, 1993) age was not a predictor of nosocomial pneumonia. Among mechanically ventilated patients (Torres *et al.*, 1990), age was also not found to be a predictor for nosocomial pneumonia; factors such as prior intubation, history of gastric content aspiration, ventilation longer than 3 days, underlying lung disease, and the use of positive end-expiratory pressure were predictors, emphasizing the role of interventions and underlying disease in this subset of patients. Age was one of several independent variables included in a model for predicting postoperative pneumonia in those undergoing noncardiac surgery (Arozullah *et al.*, 2001).

Several studies have identified risk factors for the development of nosocomial pneumonia specifically in elderly populations. Harkness *et al.* (1990) found only two factors

independently predicted nosocomial pneumonia in the hospitalized elderly: difficulty with oropharyngeal secretions and the presence of a nasogastric tube or gastric tube. In another study, albumin $<3.0\,g\,dl^{-1}$, neuromuscular disease, and intubation were independent predictors of nosocomial pneumonia in elderly patients (Hanson *et al.*, 1992).

In summary, the risk of nosocomial pneumonia is increased among the elderly. Although age *per se* has been found to be a predictor for the development of nosocomial pneumonia, the presence of debilitating underlying diseases, surgery, and device use are equally important predictors. The tendency for elderly patients to develop nosocomial pneumonia later in their hospital course coupled with the identification of risk factors for nosocomial pneumonia offers the opportunity to develop interventions to prevent this complication.

TUBERCULOSIS (*see* Chapter 61, Respiratory Disease in the Elderly)

Despite the impact of human immunodeficiency virus infection on the epidemiology of tuberculosis, the elderly continue to be a major reservoir for tuberculous infection and disease, especially in institutionalized settings (Rajagopalan, 2001). Since information about the epidemiology of tuberculosis in the elderly is most readily available from studies done in the United States, this section will focus on these studies. However, the global impact of tuberculosis is immense; tuberculosis is the leading cause of death among single infectious agents, and it is estimated that 7% of all deaths and 26% of all preventable deaths in the world are due to tuberculosis (Snider and La Montagne, 1994). The World Health Organization estimates that 19–43% of the world's population is infected with *Mycobacterium tuberculosis*, there are 8 million new cases each year, and >2 million people die from tuberculosis yearly (World Health Organization, 1999).

In a population-based survey of tuberculosis among institutionalized people in 29 states in the United States in 1984–85, the incidence of tuberculosis among nursing home residents aged 65 and older was 39.2 per 100 000 population per year compared to 21.5 per 100 000 for community-dwelling people aged 65 and older, 30.6 per 100 000 for correctional facility residents aged 15 and older, and 7.9 per 100 000 for community-dwelling people aged 15–64 (Hutton *et al.*, 1993). In high endemic areas of the United States, rates of tuberculosis are even more dramatic in the elderly. In Arkansas in 1981, the overall case rate of tuberculosis was 8 per 100 000 but the rates in those 70 years and older (both community and institutionalized elderly) ranged from 55 to 110 per 100 000 (Stead and Lofgren, 1983). These studies emphasize the importance of the elderly, especially those in nursing homes, as a reservoir for tuberculosis in the United States. Transmission of tuberculosis in nursing homes has been well documented and has led to a better understanding of the epidemiology of tuberculosis among the elderly. These findings can be summarized as follows (Stead and To, 1987). First, most sporadic cases of tuberculosis develop among tuberculin reactors indicating that these cases represent reactivation of dormant infection; these cases most often are the "index" cases of tuberculosis in nursing homes. Second, secondary cases of tuberculosis usually occur among untreated tuberculin skin test converters; these cases often present as primary tuberculosis in previously uninfected residents or in those who have outlived a prior tuberculous infection and are at risk for exogenous reinfection. Third, the proportion of residents with positive tuberculin skin tests increases as the duration of stay in the nursing home increases; this phenomenon is due to several factors: rapid demise of some tuberculin negative residents, improvement in nutrition in survivors, and unidentified spread of tuberculosis. Fourth, the risk of tuberculosis is much higher among nursing home residents with tuberculin skin test conversion after admission (converters) than those with a positive tuberculin test on admission (reactors).

NONINFLUENZA VIRAL RESPIRATORY INFECTION

Respiratory infection in this section refers to illnesses manifested primarily by one or more of the following symptoms: cough, nasal congestion, rhinorrhea, sore throat, hoarseness, fever, or wheezing with or without other constitutional symptoms. Specific infections include: the common cold, pharyngitis, sinusitis, bronchitis, otitis media, and influenza.

The longitudinal studies of Monto and Sullivan (1993) in one community in the United States found that the mean annual number of respiratory illnesses (approximately 1.2) among those 60 and older was similar to that observed among those 20–59 years of age. Viruses were the most commonly identified cause of respiratory infection in all age-groups, but viral isolation rates declined significantly as age increased. Among those 40 and older, the most common viruses isolated (isolation rate per 1000 person-years of observation) were rhinoviruses (9.7), influenza A (6.8), parainfluenza viruses (2.3), respiratory syncytial viruses (2.3), and adenoviruses (1.1). Ruben *et al.* (1995), in a population-based study evaluating the development of infections among community-dwelling elderly found that the overall rate of respiratory infection (including pneumonia) was 3 episodes per 100 person months of observation with similar overall rates in males (2.9) and females (3.1). Specific rates of respiratory illnesses (per 100 person months) were: common cold (1.3), bronchitis (0.9), otitis (0.2), and pharyngitis (0.1). Falsey *et al.* (1995) evaluated the incidence and etiology of acute respiratory infections in frail elderly requiring help with ADL who attended a senior day-care program. During a 15-month study period, the overall rate of acute respiratory infection was 10.8 episodes per 100 person-months of observation, more than 3 times the rate of community-dwelling elderly described by Ruben *et al.* (1995). Viruses were the most commonly identified etiologic agents, including respiratory

syncytial viruses, influenza A virus, and coronaviruses. The authors postulated that the higher rate of respiratory infection may be due to a more susceptible population and an increased exposure to infectious agents in the day-care setting compared to the community setting. In a prospective study of viral respiratory infections occurring in one nursing home over a 3-month period, a viral etiology was identified in 62 (42%) of 149 illnesses; 40 episodes were documented to be due to respiratory syncytial virus infection and 14 due to rhinovirus (Falsey *et al.*, 1992). In a 4-year retrospective study comparing rates of infection on an Alzheimer's special care unit with rates on traditional nursing home units in the same facility, rates of upper respiratory infection were significantly higher in 3 of 4 years on the Alzheimer's unit (Perls and Herget, 1995).

Nicholson *et al.* (1997) assessed the role of rhinovirus infection in a population of ambulatory elderly (60 years and older). Viral infection was documented in 43% of almost 500 episodes of respiratory infection and rhinovirus caused about half of these infections. The median overall duration of illness was 16 days, and if lower respiratory symptoms were present (cough, wheezing), the median duration was longer (16 days) than if they were absent (12 days). ADL were restricted in 20% with rhinovirus infection, but hospitalization was infrequent. In a separate analysis (Nicholson *et al.*, 1996), these investigators found that lower respiratory symptoms related to rhinovirus infection in the elderly were significantly associated with current smoking, presence of chronic lung disease diagnosis, or the presence of other underlying medical illness. Falsey *et al.* (1997) also documented that rhinovirus infection was common among elderly people attending senior day care and that it was moderately debilitating. Ellis *et al.* (2003) studied residents of 381 nursing homes in Tennessee between 1995 and 1999 and found that respiratory syncytial virus infection increased hospitalization rates, antibiotic use, and deaths, each winter during the study. Agents such as rhinovirus and coronavirus that commonly cause colds in young adults or healthy elderly and are usually benign may result in hospitalization of frail elderly people with underlying cardiac or lung disease (Falsey *et al.*, 2002). Human metapneumovirus is a newly discovered respiratory pathogen that occurs in all age-groups; infection may be severe in the frail elderly and may result in a significant number of hospitalizations (Falsey *et al.*, 2003).

The epidemiology of noninfluenza viral respiratory infections in the elderly can be summarized as follows. First, acute respiratory infections of a viral etiology are common in the elderly. The frail elderly appear to be particularly vulnerable to more severe infections and hospitalization. Second, certain environments may facilitate transmission of viruses among the elderly, for example, day care or closed units for the care of people with dementia. Third, influenza-like illness in the nursing home setting has a complex etiology and can often be due to respiratory syncytial virus or coronavirus infection rather than influenza. Fourth, the clinical presentations and severity of illness vary depending on the virus, for example, respiratory syncytial virus can produce life-threatening infections, whereas rhinovirus infections tend to be less severe. Fifth, outbreaks due to various respiratory viruses, including respiratory syncytial virus and rhinovirus, have been documented in the nursing home setting; handwashing appears to be the most important measure for preventing transmission of most of these viruses.

KEY POINTS

- The incidence of community-acquired pneumonia and associated case fatality is highest in the elderly.
- Debilitated, bedridden people are at greatest risk for developing pneumonia in the nursing home setting.
- Rates of hospital-acquired pneumonia are higher in the elderly compared to younger people.
- Incidence of tuberculosis is highest in the elderly in developed countries, especially in the institutionalized setting.
- Common respiratory viral infections may produce severe illness in the frail elderly.

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The Effect of Aging on the Respiratory Skeletal Muscles

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INTRODUCTION

The respiratory muscles include the diaphragm, intercostals, neck, back, and abdominal muscles (Edwards and Faulkner, 1995). The diaphragm and abdominal muscles provide the major contribution to thoracic volume changes. The other muscles become more important when demand for ventilation increases such as in exercise or through illness. A better understanding of the effects of aging on the respiratory muscles is important as many conditions affecting respiratory performance (such as chronic obstructive lung disease and congestive heart failure secondary to ischemic heart disease) are common in old age. Like all skeletal muscles, the respiratory muscles change their structure, biochemical properties, and contractile function in response to alterations in the pattern of use, nutritional state, and during normal growth and development. It has been appreciated for many years that skeletal muscles in the limbs undergo deleterious changes during aging. Our understanding of the effects of the aging process on the respiratory muscles is less complete. It has been suggested that, since the respiratory skeletal muscles remain active *continuously* throughout life, they may be spared the changes produced by aging. A number of studies suggest, however, that the structure and function of human respiratory muscles are, in fact, adversely affected by advanced age.

The study of the effects of aging on the respiratory muscles is complicated by the fact that aging also changes the physical properties of the lung and chest wall, as well as ventilatory control (Bischetto *et al.*, 1984; Estenne, 1985; Enright *et al.*, 1994). These aging-related changes can be expected to alter the load placed on the respiratory muscles and their pattern of activity. End expiratory lung volume and lung compliance increase with aging, while chest wall compliance and ventilatory responses to hypercapnia and hypoxia are decreased. These confounding effects may either modify the effects of aging on the respiratory muscles, or at least complicate interpretation of studies designed specifically to evaluate the direct effects of aging on the respiratory muscles. Many studies concerning the effects of aging on these inspiratory muscles have used measurements that are readily performed but have numerous drawbacks. Finally, biopsy of the human respiratory muscles *in vivo* is difficult. Information from studies of the effects of aging on human limb skeletal muscle and on respiratory muscles in animal models can help to overcome these limitations.

STRUCTURAL ORGANIZATION OF SKELETAL MUSCLE

Skeletal muscles are composed of a mix of several muscle fiber types organized into motor units by the shared motor neuron that innervates them. The muscle fibers comprising a motor unit have identical contractile and biochemical properties. The classification schema of muscle fibers is based on their intrinsic contractile properties (i.e. the rapidity with which they develop tension and undergo fatigue) and their histochemical appearance. Motor units made up of *fast twitch fibers* generate and dissipate tension rapidly but fatigue quickly with repeated contraction. Fast twitch units have been subclassified as fast fatiguable (F_f), fast intermediate (F_{int}), and fast-fatigue resistant (F_{resist}), based on their relative tendency to fatigue. Motor units made up of *slow twitch fibers* generate and dissipate tension more slowly but are more resistant to fatigue than fast twitch units.

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Muscle twitch characteristics correlate with myosin ATPase activity. Fibers have been typed histochemically based on the pH lability of the myosin ATPase activity. In alkaline pH, fast twitch fibers have high ATPase activity and stain intensely (type II) while slow twitch fibers stain weakly (type I) due to markedly reduced myosin ATPase activity. Fast twitch muscle fibers have been subclassified on the basis of the susceptibility of their myosin ATPase activity to acid pH (i.e. types IIa *fast-fatigue resistant* and IIb *fast-fatiguable* categories) (Brooke and Kaiser, 1970).

The fiber composition (i.e. type I, IIa, and IIb fibers) of skeletal muscles is largely determined by the pattern of activity and functional role in the body. Not surprisingly, therefore, the fiber composition of the respiratory muscles varies considerably across muscles. This variability in fiber composition may possibly affect the relative susceptibility to the effects of aging of various respiratory skeletal muscles.

The costal and crural diaphragm as principal muscles of inspiration are active during resting breathing throughout life. The costal diaphragm consists of approximately 50% type I fibers; 25% type IIa fibers; and 25% type IIb fibers in adult subjects with normal respiratory function. The crural component of the diaphragm has the same distribution of fiber types as the costal diaphragm (Sanchez *et al.*, 1982). The average cross-sectional area of diaphragmatic muscle fibers is approximately 2200 km^2 and, hence, smaller than those fibers in limb skeletal muscle in untrained subjects (Mizuno and Secher, 1989).

Other muscles active during resting inspiration include the parasternal (or intercartilaginous) intercostal muscles, the scalenes, the external intercostal muscles of the posterior superior thorax, and some of the abdominal muscles (i.e. transversus abdominus) when breathing in the upright position (Edwards and Faulkner, 1995). The percentage of type I fibers in the inspiratory intercostal muscles (62%) and the scalenes (59%) exceeds that of the diaphragm as well as peripheral skeletal muscles from untrained athletes (Mizuno, 1991). Like the diaphragm, however, these muscles have a near-equal distribution of type IIa and type IIb fibers. The sternomastoid, pectoralis major, pectoralis minor, and trapezii are usually considered *accessory muscles*, which are recruited during more intense respiratory efforts, such as during exercise. These muscles are also active when the strength (i.e. pressure-generating capacity) of the primary inspiratory muscles is decreased by decreases in contractility of the diaphragm (e.g. bilateral diaphragm paralysis). The composition of the sternomastoid muscle has been described by Mizuno (1991) and comprises 35% type I fibers and 65% type II fibers while the composition of the other accessory inspiratory muscles is still unknown.

Although quiet expiration in humans is generally considered to be a passive process, the lateral internal interosseous intercostal muscles of the lower rib cage are electrically active during expiration. These expiratory intercostals have the same proportion of type I fibers as the inspiratory intercostals (Mizuno, 1991). However, the percentage of type IIa fibers is considerably greater (35 vs 22%, respectively) and the percentage of type II fibers is far smaller than that of the inspiratory intercostal muscles (1 vs 19%, respectively) (Mizuno, 1991). The considerable differences in the percentage of type II fibers between the inspiratory and expiratory intercostals may very well represent an adaptation by the expiratory intercostals to the performance of nonventilatory activities such as coughing, sneezing, and even stabilizing the spine during lifting and reaching.

The mean cross-sectional area of the expiratory intercostal muscle fibers is considerably larger (4300 km^2) than that of the inspiratory intercostal muscles (2900 km^2) and the diaphragm[20]. Since muscle fiber cross-sectional area depends in part on the forces the fibers must generate, the larger size of the expiratory intercostal fibers suggests that the load against which these muscles must contract exceeds that of the inspiratory muscles. Mizuno (1991) found that the distribution of fiber types of the four abdominal muscles (rectus abdominus, external oblique, internal oblique, and transversus abdominus) closely resembles the distribution of fiber types of the diaphragm (54% type I; 20% type IIa; 23% type IIb).

EFFECTS OF AGING ON LIMB SKELETAL MUSCLES IN HUMANS

Advancing age is associated with loss of muscle mass and muscle strength termed *sarcopenia* (Doherty, 2003). Sacropenia has a multifactorial basis and reduced protein and calorie intake, smoking, physical inactivity, sex steroid changes, reductions in growth hormone, and possible increased effects of cytokines adversely affect the balance between anabolic and catabolic stimuli on muscle (Szule *et al.*, 2004; Baumgartner *et al.*, 1998). Between the ages of 20 and 80 years, contractile strength is decreased by between 20 and 40% in proximal and distal muscles (Doherty, 2003). Men may lose more muscle strength than women but as women live longer, sarcopenia in women is likely to have a greater public health impact. In the New Mexico Elder study, women and men with greater degrees of sarcopenia were less able to carry out functional tasks and were more likely to report use of walking aids and falls (Baumgartner *et al.*, 1998).

Loss of muscle mass appears to be due to direct loss of muscle fibers (possibly affecting type II preferentially) and in the very old, secondary atrophy due to a chronic neuropathic process. It appears that fiber atrophy and age-related changes in motor unit number and size preferentially affect the largest and fastest conducting motor units (i.e. F_f and F_{int}). The finding of "enclosed fibers" (one fiber surrounded by fibers of the same type) in elderly subjects has been interpreted as evidence for denervation of fast twitch fibers and reinnervation by axons from slow motor units (Grimby *et al.*, 1982). Decreases in the proportion of type II fibers in elderly subjects correlates with decreases in isometric and dynamic strength in limb muscle (Larsson *et al.*, 1979). These findings are not universal, however, and some studies suggest that the composition of aging muscle does not change appreciably (Aniansson *et al.*, 1980).

There is some evidence that in contrast to the effects of aging on muscle strength, capillary density, activity level of mitochondrial enzymes, and the ability to synthesize ATP appear to be well preserved in the aging muscle (Grimby *et al.*, 1982; Stahlberg and Fawcept, 1982). Thus, aerobic metabolism seems to be relatively well maintained in the aging limb muscle. While maximum oxygen uptake does decrease with advanced aging, the maximal oxygen uptake per unit (i.e. per kilogram) of muscle mass does not appear to change with aging (Grimby and Saltin, 1983).

It is important to understand that the effects of aging on muscle structure and function are not uniform across muscles. In general, muscles made up of primarily fast fibers appear to be affected to a greater extent than muscles made up primarily of slow fibers (Larsson *et al.*, 1979). Differences in susceptibility to the effects of aging are not well explained, but may be related to different intrinsic and extrinsic factors such as physical activity, hormone status (Baumgartner *et al.*, 1998; Szule *et al.*, 2004). Lower extremity muscles show greater changes than those in the upper extremity (Grimby *et al.*, 1982).

These skeletal muscle changes of aging are not inevitable since it is now well established that community-living elderly with or without a history of falls benefit from resistive muscle exercises, particularly when this is combined with other interventions to reduce falls. Once or twice weekly exercises targeting major muscle groups in the upper and lower body over months are likely to lead to increased muscle mass and improved physical functioning in adults of all ages. Furthermore, resistive muscle exercises can be associated with fat loss and increased insulin sensitivity (Kirwan *et al.*, 1993).

THE EFFECT OF AGING ON RESPIRATORY MUSCLE STRUCTURE IN HUMANS

Autopsy studies provide some information on the effects of aging on fiber size in human respiratory muscles. One study showed no differences in the mean cross-sectional fiber area between diaphragmatic fibers from men aged 24–47 (Mizuno, 1991). The mean cross-sectional area of both the inspiratory and expiratory intercostal muscles also appears to remain fairly constant throughout the fifth decade. Thereafter, the mean cross-sectional area of expiratory intercostal muscle fibers decreased by 20%, while the inspiratory intercostal muscles decreased by less than 7% (Mizuno, 1991). Since the expiratory intercostal muscles perform a number of nonventilatory tasks, as described above, atrophy of these muscle fibers may be related to reduction in those other activities during advanced age. Again, data from subjects older than 65 years are lacking.

Computerized tomography (CT) scans have been used in an attempt to characterize the structure of the human diaphragm *in vivo*. This technique has also been used to evaluate the effects of aging on the diaphragm. Caskey *et al.* (1989) measured the thickness of the crural diaphragm seen on the chest and abdominal CT scans of 120 patients aged 20–90 years (10 from each decade). The study found no significant relationship between diaphragm thickness and aging (right hemidiaphragm thickness 0.57 ± 0.1 cm in men aged 20–29 years and 0.54 ± 0.15 cm in men aged 70–79 years). Aging was related to greater width in the esophageal hiatus over 6 decades ($r = 0.61$, $p < 0.001$) and none of the patients in their 20s or 30s had any diaphragmatic defects. The possibility that the increased frequency of defects in the diaphragms of aged individuals may have been related to a higher prevalence of emphysema in the older individuals was not specifically evaluated and cannot be excluded.

EFFECTS OF AGING ON RESPIRATORY MUSCLE STRENGTH IN MAN

Given the diverse nature of the insertions of the respiratory muscles in man, and the need to be noninvasive, direct measurement of the force output of the human respiratory muscles in life is not practical. Most frequently, respiratory muscle force output (or strength) has been assessed indirectly from measurements of maximum static inspiratory and expiratory pressures made at the mouth with the airway occluded. With this technique, changes in airway pressure reflect the quasi-isometric force of contraction of the respiratory muscles acting in aggregate. However, there are significant limitations to the use of measurements made in this fashion. Measurements of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) depend on subject motivation and coordination, reflect the mechanical action of the entire inspiratory and expiratory musculature, are a function of lung volume, and reflect the elastic properties of the lungs and chest wall (Rochester, 1988).

As early as 1966, Rinquist (1966) performed extensive studies of the effects of aging on the MIP and MEP in normal human adults. The effects of aging on the strength of the respiratory muscles were compared to changes in the strength of the limb muscles and trunk flexors (Rinquist, 1966). His studies included 200 men and women in the age range 18–83 years. He reported that MIP decreased linearly and MEP decreased in a curvilinear fashion with advancing age by approximately 15% between the ages of 20 and 65 years. Although the intrasubject measurements were highly reproducible, intersubject variability was considerable even in subjects of the same age (coefficient of variation approximately 20% for the MEP and 25% for the MIP). Maximal static respiratory pressures and the isometric strength of the nonrespiratory muscles were significantly related, suggesting that aging-related changes in respiratory muscle strength correlated in magnitude with changes in the strength of the peripheral skeletal muscles.

Several years later, Black and Hyatt (1969) measured the MIP and MEP in 120 men and women of age range 20–86 years (10 subjects in each decade). Subjects in the study were free of lung disease, although cigarette smokers

were included in the study. They reported that maximal static respiratory pressures decreased with advancing age in both men and women by approximately 15–20% between the ages of 20 and 70 years. However, unlike Rinquist's previous study, changes did not appear to reach statistical significance until age 55. In female subjects older than 55 years, both MIP and MEP were significant and inversely related to age. In male subjects older than 55 years, only MEP was significantly related to age.

Measurements of respiratory muscle strength made during the multicenter Cardiovascular Health Study were recently reported (Enright *et al.*, 1994). The MIP was measured in more than 4400 subjects and the MEP was measured in nearly 800 subjects who were at least 65 years of age. A healthy subgroup was selected by eliminating cigarette smokers, subjects felt to be in only "fair–good health", and subjects with an forced expiratory volume in one second (FEV_1) that was less than 65% predicted. Between the ages of 65 and 85 years, the cross-sectional decreases of MIP with age were 0.8–2.7 cm H_2O/year. Similar to other studies, age-related decline was more prominent in men than in women.

The strength (force-generating capacity) of the diaphragm has been evaluated by making measurements of the maximum pressure that can be generated across the diaphragm (transdiaphragmatic pressure or P_{dimax}). Transdiaphragmatic pressure (P_{di}) is calculated as the difference between the gastric (P_{ga}) and esophageal (P_{es}) pressures ($P_{di} = P_{ga} - P_{es}$) generated during a respiratory effort or during phrenic nerve stimulation. This static parameter closely reflects the tension developed by the diaphragm. Unlike MIP and MEP, the measurements of P_{di} are not affected by lung or chest wall elastic recoil pressures. Tolep and colleagues compared the P_{dimax} in 10 healthy elderly subjects (aged 65–74) and nine young subjects (aged 18–32). P_{dimax} was measured during a combined maximal inspiratory–expulsive maneuver, made with the glottis open. This maneuver has been considered the one that results in maximal activation of the diaphragm. Similar to another study measuring pressures during sniffing and cervical magnetic stimulation, aging is associated with associated with a reduction in diaphragm strength.

While the lung and chest wall elastic recoil pressures do not affect measurements of P_{dimax}, other factors do need to be considered. Changes in lung volume have been shown to affect the pressure-generating capacity of the diaphragm. For example, increases in lung volume above FRC will diminish the P_{di}. Systemic factors, such as nutritional status, have also been shown to affect diaphragmatic strength (Arora and Rochester, 1982a,b). However, the lower P_{dimax} values in the elderly subjects in the previously mentioned study (P_{dimax} reduced by approximately 20%) were not related to changes in lung volume or to differences in the nutritional status of the elderly compared to the younger subjects.

To date, all studies examining the effects of aging on respiratory muscle strength have involved separate groups of young and old subjects. Longitudinal studies involving serial measurements in the same individual over many years have not been performed. This is a significant shortcoming in our knowledge base. Despite the limitation of cross-sectional studies, the bulk of the available evidence does strongly suggest that advanced age reduces the capacity of the respiratory muscles to generate pressures.

Respiratory muscle strength in older people in the community can be increased through resistive exercises. In a Chilean study, 98 out of 149 subjects 70 years and over who entered a randomized controlled trail of nutritional supplementation with or without resistive exercises were reviewed at 18 months, and there was some evidence that these interventions contributed to maintaining functionality and increasing inspiratory muscle strength. In elite sports, inspiratory muscle training is widely practiced and considered to influence exercise tolerance and decrease breathlessness. The role of respiratory muscle training in healthy elderly is underresearched and the results of the Chilean study needs to be explored further.

RESPIRATORY MUSCLE ENDURANCE IN MAN

Like all skeletal muscles, the respiratory skeletal muscles may become *fatigued* when generating sufficiently intense contractions for a long enough period of time. Fatigue can be defined as an impaired force-generating and/or shortening capacity of actively contractile muscle, which may be reversed with rest. Fatigue of all of the inspiratory muscles, including the diaphragm, will develop when the ratio of the average pressure developed during a breath divided by the maximum pressure that can be generated (P_{Iavg}/P_{Imax} or P_{diavg}/P_{dimax}) exceeds 50–60% (Russous and MacLin, 1977). Reductions in global inspiratory muscle strength may therefore make older subjects more prone to develop inspiratory muscle fatigue than younger adults, when the work of breathing is increased as in pneumonia or pulmonary edema. In some studies, respiratory muscle endurance is defined by the length of time subjects can sustain high levels of ventilation or breathing against an external load. In others, endurance is quantified by measuring the maximal pressure (or load) that can be generated (or tolerated) for a preset period of time.

No studies have directly compared the endurance of the respiratory muscles in young and elderly subjects. However, studies of endurance in both young and elderly groups are available in one study by Morrison and colleagues (1989), the endurance of normal elderly subjects (i.e. $P_{pk}/\text{MIP} = 79 \pm 19\%$) was similar to the endurance measured in another study by Martyn and colleagues (1987) of young subjects aged 21–44 years ($P_{pk}/\text{MIP} = 77 \pm 6\%$). Unfortunately, the breathing pattern (or duty cycle: T_I/T_{tot}), which is an important determinant of inspiratory muscle endurance, was not constrained during these endurance trials. This is a potentially important omission since subjects can sustain a higher P_I/P_{max} ratio at a given level of ventilation by decreasing the duration of inspiration (i.e. shortening the T_I/T_{tot} ratio). Despite these limitations, the findings of these studies on the respiratory muscles of elderly individuals are

consistent with the findings of studies of the endurance of peripheral skeletal muscles in elderly individuals. That is, it appears that the inherent endurance of the inspiratory muscles is similar in both young and elderly individuals, when differences in muscle strength are taken into account.

The compliance and the resistance of the respiratory system determine the pressure needed to be developed for inspiration, or the numerator in the P_I/P_{max} relationship. The denominator of this relationship reflects inspiratory muscle strength. During eupneic breathing, as well as exercise, elderly subjects are likely to have higher P_I/P_{max} ratios than young adults because of increases in the numerator (increased inspiratory impedance) and decreases in the denominator (decreased inspiratory muscle strength). Accordingly, the "force reserve" of the diaphragm and other inspiratory muscles is likely to be reduced in the elderly, compared to the young adult.

Respiratory muscle oxygen consumption for a given change in ventilation is increased in the healthy elderly. In one study, the oxygen uptake from healthy male volunteers, ranging in age from 23 to 77 years, was measured (Takishima *et al.*, 1990). Oxygen consumption was measured from the volume change of a spirometer filled with 100% O_2. The increase in overall oxygen uptake (V_{O2}) with increasing levels of ventilation (V_E) was taken to represent the oxygen consumption of the respiratory muscles. Oxygen consumption at a V_E equal to 0 was taken to represent the V_{O2} of the nonrespiratory muscles. The V_{O2}/V_E was increased in the elderly subjects compared to the younger subjects, with a linear relationship between this ratio and age ($r = 0.77$; $p < 0.001$). The V_{O2}/V_E relationship was also found to be related to height and the level of airflow obstruction (FEV_1). On the other hand, nonrespiratory muscle oxygen uptake was reduced with increasing age ($r = -0.79$; $p < 0.001$). The increase in the oxygen uptake of the respiratory muscles with increasing ventilation in the elderly subjects was attributed to decreases in chest wall compliance and increases in airway resistance seen in elderly individuals. Unfortunately, maximum respiratory pressures were not measured, so that the potential relationship between changes in respiratory oxygen uptake and strength was not studied. Taken together, these several studies suggest that respiratory muscle strength is decreased in the elderly and muscle energy utilization is greater. The elderly subject therefore appears to be predisposed to develop fatigue of the inspiratory muscles in the setting of lung, cardiovascular, or neuromuscular diseases, which result in deranged lung mechanics or result in further impairment in inspiratory muscle strength.

CLINICAL IMPLICATIONS

Table 1 outlines the diseases associated with respiratory muscle weakness that a geriatrician may see in older people. For many of these diseases, respiratory muscle weakness occurs with other pathophysiological abnormalities affecting respiratory function. The geriatrician needs to be aware that respiratory muscle weakness and the underlying cause, for example, motor neurone disease (MND), may be easily overlooked as "another chest infection" in an elderly patient. In patients suspected as having respiratory muscle weakness, review by a respiratory physician is essential. Initial testing will include spirometry, and if supine vital capacity is low, maximal inspiratory and expiratory mouth pressures will be undertaken. If these pressures are low, then respiratory muscle weakness is likely to be present. The strength of the diaphragm can be measured using the maximum transdiaphragmatic pressures at different lung volumes and with sniffing. Transdiaphragmatic pressures require balloons to be inserted in the stomach and the esophagus, and this and other tests of respiratory muscle function may be unreliable and difficult to perform in sick elderly people or anyone with moderate or severe cognitive impairment.

Table 1 Diseases and respiratory muscle weakness in elderly patients

Chronic obstructive pulmonary disease
Motor neurone disease
Parkinson's disease
Heart failure
Mechanical ventilation
Stroke and spinal cord injury
Multiple sclerosis
Myasthenia gravis and myasthenic syndromes
Guillain-Barré syndrome
Undernutrition

COPD

COPD (chronic obstructive pulmonary disease) is one of the most common chronic diseases in older people. The changes that occur in respiratory muscles in COPD are complex. The disease itself is characterized by increased resistance to airflow, air trapping, and hyperinflation of the lungs. Patients primarily complain of dyspnea, and this is as a result of a decrease in the capacity of the respiratory muscles to meet an increased mechanical load. This imbalance is due to an increase in the energy demands of inspiration and hyperinflation. Because of air trapping, the inspiratory muscles have to offset a threshold load, which is not the case in healthy subjects. This is known as *auto* or *intrinsic* positive end-expiratory pressure (PEEP). Hyperinflation puts the inspiratory muscles, especially the diaphragm, at a mechanical disadvantage. Hyperinflation impairs the capacity of the respiratory muscles to generate negative intrathoracic pressure through several mechanisms: worsening of the length–tension relationship, decrease in the zone of apposition, decrease in the curvature of the diaphragm, change in the mechanical arrangement of costal and crural components of the diaphragm, and increase in the elastic recoil of the thoracic cage (Laghi and Tobin, 2003). Thus, COPD not only makes it harder to breathe but also impairs the capacity of the respiratory muscles to handle the added load (Rochester, 1991). Observational studies have

demonstrated a reduction in muscle strength and bulk in patients with COPD (Gosselink and Decramer, 1998; Bernard *et al.*, 1998; Clark *et al.*, 1996).

Histochemical analysis has shown altered fiber type profiles compared with healthy controls, with COPD patients showing a reduction of type I ("slow twitch") fibers and a lower fiber to capillary ratio (Whittom *et al.*, 1998).

These changes often occur in patients who have weight loss and muscle wasting: 20% of stable outpatients with COPD (Engelen *et al.*, 1994) and 70% of patients requiring mechanical ventilation (Laaban *et al.*, 1993). The effects of malnutrition on respiratory muscles are discussed later in this section.

The management of patients with stable COPD involves both pharmacological and nonpharmacological approaches and is discussed in detail, in **Chapter 61, Respiratory Disease in the Elderly**.

Motor Neurone Disease

In MND, progressive motor weakness and bulbar dysfunction may lead to premature death, usually from respiratory failure. Although it is a relatively rare disease, the mean age of onset is around 60 years, which should increase the awareness of geriatricians toward it. The course is relentless: over 50% of patients will die within three years and 90% within five years of the first symptom. Development of respiratory or bulbar symptoms early on in the disease, as well as advancing age are adverse prognostic indicators (Ringel *et al.*, 1993; Haverkamp *et al.*, 1995; Stambler *et al.*, 1998).

MND can present in a number of ways ranging from weakness and wasting of the limbs to bulbar symptoms. Very occasionally, respiratory failure is the first presentation of MND. This can be due to weakness of the respiratory muscles themselves, or indirectly due to aspiration from bulbar weakness or defects in central control. Other respiratory symptoms seen in MND include orthopnea, dyspnea, and symptoms due to hypercapnia.

In order to measure respiratory muscle strength, forced vital capacity (FVC) can be used and is a useful predictor of the development of respiratory failure in MND (Lyall *et al.*, 2001; Hopkins *et al.*, 1996; Melo *et al.*, 1999; Brooks, 1996; Schiffman and Belsh, 1993). Other markers of respiratory failure include maximal inspiratory and expiratory mouth pressures and maximum sniff nasal pressure (Lyall *et al.*, 2001). Inspiratory and expiratory mouth pressures are often reduced at presentation (Serisier *et al.*, 1982; Kreitzer *et al.*, 1978).

Noninvasive positive pressure ventilation has an increasingly recognized role in the management of MND (Aboussouan *et al.*, 1997; Cazzolli and Oppenheimer, 1996; Hillberg and Johnson, 1997; Pinto *et al.*, 1995; Kleopa *et al.*, 1999; Carrey *et al.*, 1990). It can alleviate the symptoms of respiratory failure and also increase life expectancy. It helps to reduce the work of breathing, improves gas exchange, and enhances sleep quality. Some patients may proceed to tracheostomy. However, not all patients with MND are appropriate for mechanical ventilation. Careful discussion with patients and their carers as well as input from a respiratory physician are essential. When making the decision, the fact that mechanical ventilation may lead to unwanted prolongation, should always be considered.

As mentioned above, respiratory failure is the usual cause of death in patients with MND. Thus, treatment of dyspnea in the terminal stages of the disease is also of importance. Morphine is useful for this as well as for anxiety and pain. Laryngospasm may also occur and benzodiazepines may be helpful in this instance.

Parkinson's Disease

The spectrum of respiratory abnormality with parkinsonism has broadened to include not just impairment of ventilatory muscle function but also upper airway obstruction, abnormal control of ventilation, and pulmonary sequelae attributed to the drugs used to treat the disorder (Brown, 1994).

There are a number of changes in pulmonary function, which occur in Parkinson's disease. There is a reduction in both maximal static inspiratory and expiratory pressures as well as inspiratory and expiratory flows (Boggard *et al.*, 1989). Aspiration pneumonia is the leading cause of death in Parkinson's disease. It has been shown that in the early stages of Parkinson's disease, the motor component only of cough is impaired, but in advanced stages, both motor and sensory components of cough are impaired (Tzelepis *et al.*, 1988).

Such patients are unable to generate a rapid rise in peak expiratory flow, which may be important for a maximally important cough (Polkey *et al.*, 1999). These abnormalities are correctable in part by the administration of apomorphine (De Bruin *et al.*, 1993), suggesting that, as with the peripheral muscles, the problem is coordination and control of the different muscle groups.

There is also evidence that there is an increased incidence of lack of control of the upper airway muscles in patients with Parkinson's disorder. Flow volume loops have shown a "sawtooth" alteration of both inspiratory and expiratory limbs, thought to result from rapid change in laryngeal and supraglottic diameter (Vincken *et al.*, 1984). Obstructive sleep apneas are more common in Parkinsonian patients, although a range of other abnormalities may result in fragmented sleep architecture (Askensay, 1993). In the related condition of multisystem atrophy, upper airway obstruction may occur (Isozaki *et al.*, 1996) and has been suggested as a possible cause of sudden death. Full polysomnography may be indicated in symptomatic patients and, rarely, tracheostomy.

The drugs used in the treatment of Parkinson's disease may themselves lead to respiratory dysfunction. Case reports (Granerus *et al.*, 1974; Kim, 1968) have shown the development of respiratory symptoms (mainly dyspnea) following the administration of L-Dopa. In addition, a fall in FVC, FEV1, and respiratory pressures has been demonstrated following L-Dopa, consistent with a pattern of neuromuscular impairment. Ergot derivatives used in the treatment of

Parkinson's disease have been implicated in the development of pleural disease and pulmonary infiltrates, in particular, bromocriptine (Zupnick *et al.*, 1990).

Heart Failure

The prevalence of heart failure in the elderly is likely to rise given the new therapies for hypertension and myocardial infarction, resulting in these patients living longer, only to develop heart failure later on in life (Rosamund *et al.*, 1998).

Diagnosis is particularly challenging in the elderly population. Breathlessness, usually a common presenting complaint in heart failure, may be misleading in the older patient due to the potential number of additional reasons for it. Moreover, these patients may lead a more sedentary lifestyle and may not complain of exertional dyspnea. Similarly, edema may be mistaken for venous insufficiency or hypoalbuminemia.

Given that the diagnosis on clinical grounds alone is difficult, an electrocardiogram (ECG) and echocardiogram are essential. Treatment is aimed at preventing heart failure together with improving mortality and morbidity. Medical comorbidities, drug interactions, and noncompliance often make this difficult.

Mechanisms causing exertional fatigue and dyspnea include abnormalities of limb muscle fibers, such as atrophy, an increase in easily fatigable type IIb fibers, a decrease in oxidative enzymes, and a decrease in size and number of mitochondria (Drexler *et al.*, 1992). It has been shown that respiratory muscles are weak in heart failure (Hammond *et al.*, 1990; Nishimura *et al.*, 1994; Mancini *et al.*, 1992; McParland *et al.*, 1992) and reduced inspiratory muscle strength may be a risk factor for ischemic heart disease (Van der Palen *et al.*, 2004). This weakness reflects a more generalized myopathic process and may be related to reduced cardiac output. Decreased respiratory muscle strength and endurance contribute to dyspnea (Mancini *et al.*, 1992) and decreased exercise capacity (Mancini *et al.*, 1995) in these patients.

Mechanical Ventilation

Mechanical ventilation is used to replace or aid the work usually carried out be respiratory muscles. As the elderly population increases, the need for mechanical ventilation, whether it is from primary lung disease or following major surgery, will also increase. As healthcare resources are limited, the appropriateness for mechanical ventilation needs to be evaluated carefully. Data from the Study to Understand to Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT) investigators (Giugliano *et al.*, 1998; Hamel *et al.*, 1996) have shown that age (especially 70–75 years) greatly affects the intensity of care given to patients and that both physician and patient preferences for cardiopulmonary resuscitation influence consumption of hospital resources (Hakim *et al.*, 1996).

Age has been considered an important prognostic indicator of inpatient hospital outcome (Sage *et al.*, 1987; Knaus *et al.*, 1986). However, the role of age on outcomes from mechanical ventilation is more controversial. Many of the studies are limited by retrospective design, and of those prospectively designed, there is diversity in their conclusions (Nunn *et al.*, 1979; Witek *et al.*, 1985; Steiner *et al.*, 1997; Zilberberg and Epstein, 1998; Ely *et al.*, 1999). The contrasting findings are likely to be secondary to differences in the patient sample, comorbidities, and variations in patient selection. Thus, selection for mechanical ventilation in the elderly should be taken with great care. Ideally, the decision should be made by the patient, family, and medical staff jointly, basing these on the patient's goals, prognosis, and doctor's judgment.

Mechanical ventilation itself may have a profound effect on the respiratory muscles. In animal models, it has been shown to cause diaphragmatic atrophy after just 48 hours (Le Bourdelles *et al.*, 1994). Aging itself has been shown not to exacerbate the relative mechanical ventilation-induced impairment in diaphragmatic isometric tension, however, the additive effect of aging and mechanical ventilation have dramatic effects on diaphragmatic force reserve (Criswell *et al.*, 2003). Some animal experiments have shown that diaphragm atrophy does not occur if paralytic agents are used to achieve partial or intermittent paralysis.

Respiratory muscle weakness is one of the major determinants of the success of weaning from mechanical ventilation. Failure to wean has been attributed to an imbalance between the load faced by the respiratory muscles and their neuromuscular competence (Alia and Esteban, 2000). Impairment in skeletal muscle strength in the intensive care unit is multifactorial, including electrolyte disturbance (in particular, hypophosphotemia), malnutrition, myopathy, hyperinflation, drugs, and sepsis. All these are particularly relevant in the elderly. In COPD, the shape of the diaphragm is altered, with flattening from hyperinflation. The inspiratory muscles are forced to operate at an unfavorable position in their length-tension curve and the costal and crural fibers of the diaphragm are arranged in series, rather than in parallel. This will result in a mechanical disadvantage that will impair function. Despite this, studies have shown that neither FEV1 nor functional performance status in patients mechanically ventilated with COPD, predict long-term outcome (Breen *et al.*, 2002).

Noninvasive mechanical ventilation (NIV) is now an established treatment for exacerbations of COPD (Brochard *et al.*, 1995; Plant *et al.*, 2000). It has been shown to reduce mortality and the need for invasive ventilation. This is important in the elderly as often age and comorbidities make this population "unfit" for admission to intensive care. Most of the improvement in outcome can be attributed to avoiding the complications of invasive intubation such as nosocomial pneumonia. It is important that, at the time of initiation of NIV, a decision is made as to whether progression to invasive mechanical ventilation is appropriate.

Stroke and Spinal Cord Injury

Disturbances in respiratory function and complications affecting the respiratory system are common after stroke and are one of the major contributors to mortality and morbidity. Stroke may disrupt breathing by causing a disturbance of central rhythm generation, interrupting the descending respiratory pathways leading to a reduced respiratory drive, or causing bulbar weakness leading to aspiration (Howard *et al.*, 2001).

Different patterns of breathing occur after stoke. Cheyne-Stokes respiration is characterized by smooth waxing and waning of breath volume, separated by periods of apnea. It does not indicate a specific anatomical site, but may occur in up to 50% of patients after a unilateral stroke (Nachtmann *et al.*, 1995). Hyperventilation is common after stroke, but is more likely to be due to intrinsic pulmonary involvement (Mazzara *et al.*, 1974; North and Jennett, 1974; Leigh and Shaw, 1976). Apneustic breathing (apnea during sustained inspiration) is infrequently associated with stroke, due to bilateral infarcts in the pons. Ataxic breathing is characterized by a totally irregular respiratory cycle and may reflect damage to the medulla. "Ondine's curse" results from a lesion in the lateral medulla and leads to loss of autonomic respiration, but preservation of voluntary control. Thus, the patient may present with mild cyanosis when awake, but major depression of respiratory function when asleep; in this situation, nocturnal ventilatory support may be indicated. Ischemic lesions in the basal pons or medullary pyramids may result in the "Locked-in" syndrome leading to a loss of voluntary control. This may result in a highly regular breathing pattern but a complete inability to initiate any spontaneous respiratory movements (Bogousslavsky *et al.*, 1990). Hiccups may occur after a lateral medullary stroke due to incoordination of glottic closure and diaphragmatic contraction.

Transtentorial herniation due to raised intracranial pressure or trauma leads to immediate changes in the respiratory pattern. As herniation progresses, the respiratory pattern changes from normal breathing to Cheyne-Stokes respiration, followed by hyperventilation, and eventually irregular breathing that immediately precedes death.

High cervical cord lesions lead to loss of both voluntary and involuntary control of the respiratory muscles. Infarction of the cord at this level is usually due to occlusion of the anterior spinal artery. The patient may initially present with neck pain followed by a rapidly involving tetraplegia and respiratory insufficiency culminating in death. To prevent this, ventilatory support is required. Cervical myelopathy may also be associated with respiratory muscle weakness.

Hemispheric ischemic strokes can lead to reduced diaphragmatic excursion on the contralateral side, with associated reduction in chest wall movement. This infers that the diaphragm has bilateral cortical representation, which has been confirmed by transcranial magnetic stimulation (Oppenheimer and Hachinski, 1992).

Another identified complication after stroke is sleep disordered breathing, although it is currently unclear whether this is a consequence (mainly central events) or a cause (mainly obstructive events) of stroke (Harbison and Gibson, 2000). The incidence of upper airway obstruction in the first 24 hours has been shown to increase in patients with typical obstructive sleep apnoea (OSA) risk factors (body mass index (BMI) and neck circumference) when nursed in the supine position (Turkington *et al.*, 2002).

Hypoxia following stroke results in anaerobic metabolism and depletion of energy stores, thereby worsening brain injury (Bhalla *et al.*, 2001). Stroke patients are at risk of hypoxia due to the changes in patterns of respiration and upper airway obstruction as described above and also due to direct insults on the lung such as pulmonary embolism and aspiration pneumonia. By improving oxygen content, the risk of further neurological deterioration in stroke may be prevented.

Multiple Sclerosis

Multiple sclerosis (MS) commonly causes severe inspiratory and expiratory muscle weakness (Gosselink *et al.*, 2000), however, patients rarely complain of dyspnea (Minden *et al.*, 2004; Smeltzer *et al.*, 1992). This may be due to the limited capacity of patients to exert themselves; difficulty in communicating symptoms because of cognitive impairment is a factor later in the course. As paralysis ascends from the lower to upper body, the expiratory muscles are often weaker than the inspiratory muscles (Minden *et al.*, 2004; Gosselink *et al.*, 2000; Smeltzer *et al.*, 1992). Demyelination delays the transmission of neural impulses to the diaphragm even before demonstrable respiratory muscle dysfunction. Respiratory muscle weakness may also be due to deconditioning, steroid myopathy, and the release of tumor necrosis factor- α during exacerbations (Gosselink *et al.*, 1999).

Respiratory muscle weakness may result from involvement of the descending respiratory pathways, lower respiratory motor neurons (Howard *et al.*, 1992), and anterior roots. The phrenic motor neurons arise in the cervical cord and, therefore, more than half of patients developing respiratory failure (cervical cord involvement) become quadriplegic during a relapse. Respiratory failure may also be caused by conduction block (fever decreases conduction in partially demyelinated fibers), bulbar dysfunction (associated with aspiration), and abnormal control of breathing (apneustic breathing, Ondine's curse, and apnea) (Howard *et al.*, 1992).

Treatments for MS are aimed at symptoms and disease modification; however, few treatments are specific for the serious respiratory complications. Intravenous glucocorticoids, plasma exchange, and ß interferon have beneficial effects on the acute disorder, but their effects on respiratory muscle function are unclear.

Myasthenia Gravis and Myasthenic Syndromes

Respiratory muscle weakness is a feature of myasthenia gravis, and rarely may present with respiratory failure alone. Only a small proportion of patients will require mechanical ventilation (Hughes and Bihari, 1993) but up to 50% of treated patients can be found to have respiratory muscle weakness (Mier-Jedrzejowicz *et al.*, 1988). Edrophonium, a short-acting anticholinesterase, produces a rapid (within two minutes) and short-lived (less than five minutes) improvement in muscle strength and should be considered in patients complaining of dyspnea even if optimal therapy with respect to the peripheral muscles has been achieved as this may unmask under-treatment of respiratory muscles.

Thymectomy, immunosuppressive treatment, short-term immunotherapies, and anticholinesterase agents (Vincent *et al.*, 2001) improve respiratory muscle function when administered alone or in combination. There is also evidence that in patients with moderate-to-severe myasthenia gravis, training (with threshold load) increases respiratory muscle strength and endurance and decreased dyspnea (Weiner *et al.*, 1998). Myasthenic crises are life-threatening episodes of respiratory or bulbar paralysis with a high mortality rate (Thomas *et al.*, 1997; Berrouschot *et al.*, 1997). There is often a precipitant such as infection, medication, or surgery. Ventilatory failure typically develops within 3 days of a patient noticing worsening of bulbar, skeletal, or respiratory muscle weakness.

Lambert-Eaton myasthenic syndrome (LEMS) is a rare myasthenic syndrome presenting as variable weakness affecting predominantly the proximal limb muscles. Older patients with LEMS with a smoking history usually have underlying small cell carcinoma of the lung. Potentially reversible diaphragmatic weakness is a feature and may lead to ventilatory failure (Laroche *et al.*, 1989).

Guillain-Barré Syndrome

Respiratory failure requiring mechanical ventilation occurs in 14–44% of patients with Guillain-Barré syndrome (GBS) (Hughes and Bihari, 1993; The Guillain-Barré Syndrome Study Group, 1985). The disease may progress over a few hours to respiratory failure and about one-third of the patients may require either mechanical ventilation because of ventilatory failure or intubation for airway protection (patients with bulbar involvement) (Hahn, 1998; Gourie-Devi and Ganapathy, 1985). Respiratory failure is primarily due to diaphragmatic weakness, although weakness of intercostals, abdominal and accessory muscles of respiration, retained airway secretions, atelectasis, and supine posture are also contributory factors.

As respiratory failure is such a serious and common complication of GBS, all patients must have frequent vital capacity measurements. A fall in vital capacity precedes the requirement for mechanical ventilation, which on average occurs when the vital capacity falls below $15\,ml\,kg^{-1}$ body weight (Chevrolet and Delamont, 1991). In children, other reported predictors of the need for ventilatory support include cranial nerve involvement, the history of an infection in the 8 days before the onset of GBS, and a greatly increased cerebrospinal fluid protein (Rantala *et al.*, 1995). However, risk factors are unknown in the elderly. Other measures, which have been shown to be of use in predicting the development of respiratory failure, include prolonged phrenic nerve conduction times (Gourie-Devi and Ganapathy, 1985) and diaphragmatic electromyograms (Zifko *et al.*, 1996) (which, if normal, suggests that a patient will not develop respiratory failure).

Instituting plasma exchange or intravenous immune globulin within two weeks of symptoms has been shown to decrease disability in patients with severe disease (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997). In those patients requiring mechanical ventilation, plasma exchange has been shown to reduce its duration by 2 weeks (French Cooperative Group, 1987). Despite this, respiratory failure and age are risk factors for long term disability in GBS (Ng *et al.*, 1995; McKhann *et al.*, 1988).

Undernutrition

Undernutrition in the elderly is associated with an increased risk of mortality and morbidity. The reason why undernutrition occurs in the elderly is multifactorial. Firstly, the physiological effects of aging itself may have an effect on nutrition, that is, difficulties with swallowing due to diminished salivary secretions, reduced motility rates and gastric secretions, and loss of teeth. In addition, elderly may have lowered responsiveness to internal cues of hunger and thirst (Rolls, 1989).

Coexisting medical conditions such as stroke, rheumatoid arthritis, and underlying gastroenterological diseases have implications on the physical actions of eating. Drugs can cause nausea and have a direct effect on appetite. Commonly, social isolation will have an impact on nutrient intake (McCormack, 1997).

Respiratory muscle strength is related to nutritional status. There is a significant correlation between maximal inspiratory (MIP) or expiratory (MEP) pressures and lean body mass (Enright *et al.*, 1994). It has also been shown that respiratory muscle weakness in poor nutritional status is distributed evenly between inspiratory and expiratory muscles, and is directly proportional to the degree of weight loss (Arora and Rochester, 1982a, b). Undernutrition leads to wasting of the diaphragm and changes the composition of diaphragmatic fibers toward a slower phenotype (Polla *et al.*, 2004). This has a considerable effect on the contractile and fatigue properties of the diaphragm. In addition to having an effect on ventilatory muscle strength, malnutrition also has an effect on peripheral muscle strength, thus compounding a reduction in overall exercise tolerance.

Concurrently, high-wasted ventilation and the high-oxygen cost of ventilation may also cause weight loss, as seen in patients with COPD where there is excessive calorific

expenditure dictated by the high energy requirements of the respiratory muscles.

Undernutrition is common in hospitalized patients and, therefore, has clear clinical implications. In particular, the respiratory muscle weakness as a result of undernutrition may lead to the inability to generate an effective cough predisposing to respiratory infection. In addition, nutrition has a profound effect on the immune system, and it has been demonstrated that oropharyngeal aspiration and a low serum albumin are independent risk factors for community-acquired pneumonia in the elderly (Marik and Kaplan, 2003).

In summary, undernutrition has direct effects on respiratory muscle strength and is common in patients with chronic lung disease. It should be identified and treated early, especially in the elderly, to prevent progression of lung disease.

CONCLUSION

Respiratory muscle weakness that has clinical impact in old age is largely accounted for by the presence of neurological or cardiopulmonary disease. There is also evidence that in healthy older people, respiratory muscle strength is reduced but whether it independently contributes to respiratory illness or ability to remain physically active is unclear. Both inspiratory and expiratory muscle strength are reduced with aging. Preferential atrophy of type II muscle fibers, changes in myosin heavy chain content, and decreases in capillary density that have been observed in animal models may provide the explanations for the observed changes. There is, however, a relative paucity of data on the effects of aging on the respiratory muscle structure in humans.

In healthy elderly individuals, decreases in muscle strength do not appear to affect breathing at rest, when fatigue-resistant type I motor units are active, or contribute to aging-related reductions in total body exercise performance. In contrast to the effects of aging on muscle strength, it appears that respiratory muscle endurance is not affected by aging in humans. More information is also needed in this regard, especially since studies have suggested that diaphragm endurance is reduced in small animal species. Respiratory muscle energy utilization does appear to be increased in healthy elderly individuals secondary to changes in the mechanics of breathing. Since respiratory muscle endurance and strength are interrelated, the ability to increase the level of ventilation under certain conditions may be decreased in elderly individuals under certain circumstances, as described above.

Respiratory muscle weakness is a complication of a range of different neurological, cardiological, and pulmonary diseases. Rarely, respiratory failure may form the initial presentation of neurological diseases like MND. Geriatricians must be aware of how to investigate suspected respiratory muscle weakness and the need to look for an underlying cause. Access to a respiratory physician is important for patient care. Inspiratory muscle training in selected diseases in older people associated with respiratory muscle weakness can be beneficial. For healthy older people, research into the benefits of inspiratory muscle training needs to be explored in further studies.

KEY POINTS

- Respiratory muscle weakness that has clinical impact in old age is largely accounted for by the presence of neurological, cardiac, or pulmonary disease.
- Respiratory muscle strength is reduced with healthy aging but whether it independently contributes to respiratory illness or the ability to remain physically active is unclear.
- Geriatricians need to be aware of the range of neurological and cardiorespiratory diseases seen in old age associated with respiratory muscle weakness.
- The presentation of respiratory muscle weakness can be as breathlessness or a more life-threatening complication as in type II respiratory failure.
- Where respiratory muscle weakness is suspected, respiratory physicians and where appropriate, neurologists will need to be involved in patient care.

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Aspiration Pneumonia

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ASPIRATION PNEUMONIA AND ASPIRATION PNEUMONITIS

Pneumonia is a common cause of death among older people despite the availability of potent novel antimicrobials. Whereas the death rate of juvenile pneumonia has declined nearly to zero, that of old people has remained unchanged over the past 100 years. In other words, the traditional approach has proven a limited success; as Osler put it 100 years ago, "pneumonia is actually a friend to the old" (Osler, 1898). Both the increased incidence of pneumonia and high mortality among older people are a consequence of a number of age-related factors including coexisting illnesses, therapeutic interventions, and decreased host defense mechanisms. In these, aspiration is possibly the most important risk factor for pneumonia in the elderly (Yamaya *et al.*, 2001a).

Aspiration is defined as the inhalation of oropharyngeal or gastric contents into the larynx and lower respiratory tract. Several pulmonary syndromes may occur after aspiration, depending on the amount and nature of the aspirated material, the frequency of aspiration, and the host's response to the aspirated material (Marik, 2001). Aspiration pneumonia is an infectious process caused by the inhalation of oropharyngeal secretions that are colonized by pathogenic bacteria, whereas aspiration pneumonitis (Mendelson syndrome) is a chemical injury caused by the inhalation of sterile gastric contents (Marik, 2001). Although there is some overlap between these syndromes, they are distinct clinical entities. This chapter focuses on the pathophysiology and the management of aspiration pneumonia and aspiration pneumonitis.

MECHANISMS FOR DEVELOPMENT OF ASPIRATION PNEUMONIA OR ASPIRATION PNEUMONITIS

Aspiration Pneumonia

Pneumonia in the elderly is often caused by an inapparent swallowing disorder (Yamaya *et al.*, 2001a; Yamaya *et al.*, 2002; Ohrui *et al.*, 2003).

Such silent aspiration frequently occurs and is a more important cause of pneumonia than the acute aspiration of gastric content in older people (Berk *et al.*, 1983). Silent aspiration of oropharyngeal bacterial pathogens to the lower respiratory tract is an important risk factor for community-acquired pneumonia (Kikuchi *et al.*, 1994) as well as nosocomial pneumonia in the elderly (Johanson *et al.*, 1972). Normal hosts are less likely to develop pneumonia because they either aspirate smaller volumes or are able to clear bacteria rapidly (Toews *et al.*, 1990). However, an extremely small volume (0.01 ml) of saliva contains pathogenic numbers of bacteria (Toews *et al.*, 1990). Elderly patients with a predisposition to aspiration frequently aspirate oropharyngeal secretions, and the development of pneumonia occurs when normal pulmonary defense mechanisms are overwhelmed (Nakagawa *et al.*, 1997).

Adequate protective reflexes in the airway are important and the suppression or absence of these reflexes has been suggested as leading to pneumonia (Nakagawa *et al.*, 1997). For example, Nakajoh *et al.* (2000) reported that the incidence of pneumonia was higher in patients having both a latency of swallowing response longer than 5 seconds following stimulation and a cough threshold for inhalation of citric acid aerosol higher than a concentration of 1.35 (log mg ml^{-1}). Thus, the progressive loss of protective reflexes (i.e. swallowing and cough reflexes) with age is thought to be one of the mechanisms for aspiration pneumonia, which is often seen in older people (Pontoppidan and Beecher, 1960). In fact, impaired swallowing and cough reflexes have been shown in patients suffering from aspiration pneumonia (Sekizawa *et al.*, 1990; Nakazawa *et al.*, 1993). However, reevaluation of age-related changes in protective reflexes in individuals who lead active daily lives has shown that both reflexes do not decrease with the advance of age (Katsumata *et al.*, 1995; Kobayashi *et al.*, 1997b), indicating that involutional and degenerative changes associated with aging often result in marginally compensated protective reflexes (Sheth and Diner, 1988).

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Disorders of the central nervous system are more likely to develop in the elderly, and pneumonia has been estimated to occur in about one third of patients with stroke (Walker *et al.*, 1981; Kobayashi *et al.*, 1994). The most important factor contributing to the risk of pneumonia in patients with stroke is suggested to be dysphagia with aspiration (Horner *et al.*, 1988). Nakagawa *et al.* (1997) have shown that the risk of pneumonia was significantly higher in patients with basal ganglia infarcts than in patients with or without cerebral hemispheric strokes in other locations. They found that multiple episodes of pneumonia occurred only in patients with bilateral basal ganglia infarcts and that there was a higher mortality rate associated with pneumonia in these patients (Nakagawa *et al.*, 1997). Delayed triggering of the swallowing reflex occurs in patients with infarcts in the basal ganglia (Sheth and Diner, 1988). These results strongly suggest that disruption of basal ganglia functions is critically important in the development of aspiration pneumonia.

The pharyngeal, laryngeal, and tracheal epithelium, the sites most important for initiation of swallowing and cough reflexes, have an extensive plexus of nerves that contains substance P (Pernow, 1983; Baluk *et al.*, 1992). Capsaicin desensitization, which abolishes substance P from the airway and upper digestive tract, or a neurokinin (NK)-1 receptor antagonist markedly attenuated the cough response to tussive stimuli (Ujiie *et al.*, 1993; Sekizawa *et al.*, 1995; Ebihara *et al.*, 1996), and distilled water-induced swallowing reflex in guinea pigs (Jin *et al.*, 1994), suggesting an important role of substance P-containing nerves in the initiation of these protective reflexes. Thus, irritation of laryngeal and pharyngeal mucosa by stimuli may activate capsaicin-sensitive sensory nerves, releasing substance P, with the result that protective reflexes are initiated by stimulation of the glossopharyngeal and vagal sensory nerves (Sekizawa *et al.*, 1996).

Dopamine agonist treatments in the rat bring about a heightened striosomal expression of substance P and both dopamine D_1 and D_2 antagonists decrease substance P (Graybiel, 1990). Mice lacking the dopamine D_1 receptor (Xu *et al.*, 1994), and those treated with dopamine D_1 receptor antagonist (Jia *et al.*, 1998), showed abnormal motor activities and feeding and swallowing problems. An impairment of dopamine metabolism in the basal ganglia is observed in patients with infarcts in the basal ganglia (Itoh *et al.*, 1993; Itoh *et al.*, 1994). Taking these facts together, the mechanisms of silent aspiration may be speculated as shown in Figure 1. Patients with basal ganglion infarcts may suffer from reduced dopamine metabolism, which decreases substance P in the glossopharyngeal and vagal sensory nerves. Suppression of substance P concentration in these nerves impairs both swallowing and cough reflexes, which increases the frequency of silent aspiration. Because the act of swallowing and coughing is a fundamental defense mechanism against aspiration of oropharyngeal contents into the respiratory tract, impairment of both reflexes is one of the major reasons for the development of aspiration pneumonia (see Figure 1).

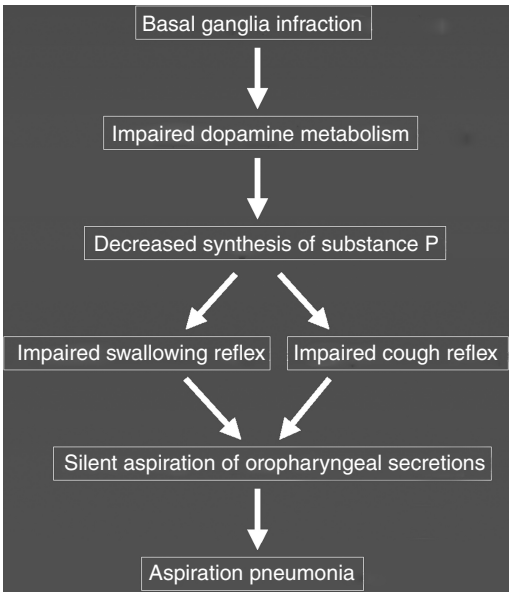

Figure 1 Possible mechanisms for development of aspiration pneumonia in patients with basal ganglia infarction

In patients with aspiration pneumonia, unlike those with aspiration pneumonitis, the episode of aspiration is generally not witnessed. The diagnosis is therefore inferred when a patient at risk for aspiration has radiographic evidence of an infiltrate in a characteristic bronchopulmonary segment. Elderly persons frequently receive poor oral care, resulting in oropharyngeal colonization by potential respiratory tract pathogens, including *Enterobacteriaceae, Pseudomonas aeruginosa*, and *Staphylococcus aureus*. These pathogens are aspirated and may cause pneumonia (Marik, 2001).

Aspiration Pneumonitis

Aspiration pneumonitis is defined as acute lung injury after the inhalation of regurgitated sterile gastric contents. This syndrome occurs in patients who have a marked disturbance of consciousness such as that resulting from a drug overdose, seizures, a massive cerebrovascular accident, or the use of anesthesia (Marik, 2001). The syndrome most commonly described as aspiration pneumonitis is Mendelson syndrome (Mendelson, 1946). Reflux of gastric fluids into the airway can damage the respiratory tract (Ohrui *et al.*, 1997). Marked damage to the tracheal mucosa can occur even when the volume of aspirated gastric fluid is too small to cause clinically significant aspiration pneumonia, and repeated long periods of aspiration of gastric fluid may even cause interstitial pulmonary fibrosis. Damage is always more severe when the pH of the gastric contents is low, but gastric fluids also contains substances other than acid which cause airway damage and delay healing of the airway epithelial damage (Marik, 2001; Ohrui *et al.*, 1997). Since airway epithelial damage by gastric content

probably arises from the additive effects of acidity (Ohrui *et al.*, 1997), treatment of gastroesophageal reflux using antiacids such as histamine-H2 receptor antagonists alone may not improve symptoms caused by aspiration of gastric fluids (Marik, 2001).

TREATMENTS FOR ASPIRATION PNEUMONIA AND ASPIRATION PNEUMONITIS

Aspiration Pneumonia

Antibiotic therapy is unequivocally indicated in patients with aspiration pneumonia. The choice of antibiotics should depend on the setting in which the aspiration occurs as well as the patient's general health. However, antibiotic agents with activity against gram-negative organisms, such as third-generation cephalosporins, fluoroquinolones, and piperacillin, are usually required (Marik, 2001). Kanda *et al.* (2004) evaluated an additive effect of angiotensin-converting enzyme inhibitor and amantadine to the conventional antibiotic therapy for pneumonia and found that the combinatorial usage of these drugs can shorten the duration of hospitalization and antibiotic usage, inhibit methicillin-resistant staphylococcus aureus (MRSA) infection, and lower the medical costs for treatment of pneumonia.

Aspiration Pneumonitis

Although it is common practice, the prophylactic use of antibiotics in patients in whom aspiration is suspected or witnessed is not recommended (Marik, 2001). However, empirical antibiotic therapy is appropriate for patients who aspirate gastric contents and who have small-bowel obstruction or other conditions associated with colonization of the gastric contents (Marik, 2001). Antibiotic therapy should be considered for patients with aspiration pneumonitis that fails to resolve within 48 hours after aspiration. Empirical therapy with broad-spectrum agents such as fluoroquinolone or piperacillin is recommended. Corticosteroids have been used for decades in the management of aspiration pneumonitis. However, there are limited data on the role of these agents (Marik, 2001; Bernard *et al.*, 1987).

STRATEGIES FOR THE PREVENTION OF ASPIRATION PNEUMONIA (FIGURE 2)

Pharmacologic Therapy

Capsaicin

Because substance P is a neurotransmitter of the swallowing reflex and substance P is depleted in patients with aspiration pneumonia (Nakagawa *et al.*, 1995), capsaicin, a pungent substance in red peppers that stimulates sensory nerves, may improve the swallowing reflex in these patients (Yamaya *et al.*, 2001a). Ebihara *et al.* (1993) measured the swallowing reflex with a bolus injection of 1 ml of solution into the pharynx through a nasal catheter and suggested that the addition of a low dose of capsaicin to liquid or food may stimulate the swallowing reflex and help to prevent aspiration pneumonia in the elderly.

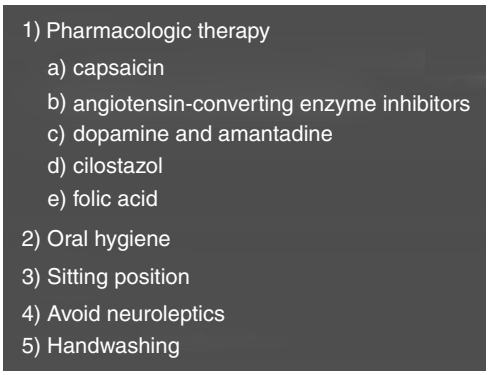

Figure 2 Preventive strategies for aspiration pneumonia

Angiotensin-converting Enzyme (ACE) Inhibitors

A well-known adverse effect of angiotensin-converting enzyme (ACE) inhibitor is a dry cough (Israili and Hall, 1992). Substance P is degraded by ACE (Skidgel and Erdos, 1987), and its action is potentiated by ACE inhibitors (Cascieri *et al.*, 1984; Shore *et al.*, 1988). Using ACE inhibitors, substance P might accumulate in the upper respiratory tract because of inhibited ACE activity and cause an increase in the sensitivity of the cough reflex (Yamaya *et al.*, 2001a; Ebihara *et al.*, 1996; Sekizawa *et al.*, 1996). In a similar way to the cough reflex, ACE inhibitors improve the swallowing reflex in older patients with aspiration pneumonia (Nakayama *et al.*, 1998). Sekizawa *et al.* (1998) compared the rate of pneumonia in stroke patients treated with ACE inhibitors with that in stroke patients treated with other antihypertensive drugs and found that the risk of pneumonia is reduced by about a third if ACE inhibitors are used for hypertension, compared with the use of other antihypertensive drugs. ACE inhibitors, therefore, may have beneficial effects on the prevention of pneumonia in these patients. Arai *et al.* (1998) reported that the rate of pneumonia was significantly lower in elderly hypertensive patients given ACE inhibitors than in those treated with calcium channel blockers. However, Teramoto and Ouchi, (1999) denied the advantage of ACE inhibitors over calcium channel blockers in preventing pneumonia in adult and elderly hypertensives. In elderly individuals, the severity of the underlying cerebrovascular disease greatly affects susceptibility to pneumonia. ACE inhibitors could be useful in the prevention of aspiration pneumonia in elderly patients with stroke but not in those with hypertension.

Dopamine and Amantadine

Delayed triggering of the swallowing reflex occurs in patients with basal ganglia infarctions (Yamaya *et al.*, 2001a; Nakazawa *et al.*, 1993), and an impairment of dopamine metabolism in the basal ganglia is observed in these patients (Itoh *et al.*, 1993; Itoh *et al.*, 1994). Kobayashi *et al.* (1996) investigated whether levodopa improves the swallowing reflex in patients with basal ganglia infarctions who had a history of aspiration pneumonia. The subjects were given an intravenous drip infusion of levodopa (50 mg in 20 ml saline) for 30 minutes. They found that the administration of levodopa improved the impaired swallowing reflex in these patients.

Since dopamine supplementation improves the swallowing reflex in patients with cerebral infarctions, Nakagawa *et al.* (1999) investigated whether amantadine, a drug that acts as a dopamine releaser from dopaminergic nerve terminals, lowers the incidence of pneumonia in patients with cerebral infarctions. Patients were randomly assigned amantadine 100 mg per day or no active treatment and were investigated for 3 years. During follow-up, a relative risk of developing pneumonia in patients on no active treatment compared with those on amantadine was 5.92. Their findings suggest that the risk of pneumonia is lowered by about 20% if amantadine is used in patients with previous stroke. Amantadine may, therefore, have beneficial effects on the prevention of pneumonia in these patients. Of course, other recognized effects of amantadine might also have impacted the incidence of pneumonia in these studies. For example, amantadine improves the conscious state in patients with brain injury (Zafonte *et al.*, 1998), and more alert stroke patients may be less likely to aspirate. In addition, dopaminergic receptors have been identified in the lower esophageal sphincter, and amantadine might reduce gastroesophageal reflux (Wakabayashi *et al.*, 1989), and thereby lower the risk of aspiration pneumonia. Finally, antiviral effects and prevention of influenza infection might also lower the incidence of pneumonia over a 3-year period (Zimmerman *et al.*, 1997). Thus, the mechanisms by which amantadine might positively affect the incidence of pneumonia remains to be proven (Sekizawa *et al.*, 1999).

Cilostazol

Disorders of the central nervous system including dementia and atherosclerotic cerebrovascular disease are more often associated with aspiration than other specific neuromuscular disorders (Yamaya *et al.*, 2001a; Feinberg *et al.*, 1990). The mechanisms by which brain injury affects the risk of aspiration are beginning to be delineated. For example, in healthy people, the frequency of swallowing during sleep is slightly less than when awake (Miller, 1982), but severe delay of the swallowing response in the night compared with that in the day was observed in patients with multiple lacunar infarctions (Pinto *et al.*, 1994). Cough reflex(Wang *et al.*, 1998) and spontaneous cough (Zheng *et al.*, 1997) are also suppressed during sleep in patients with evidence of cerebrovascular injury. Thus, patients with cerebrovascular disease are particularly susceptible to the development of aspiration pneumonia during sleep.

Other evidence from the importance of cerebrovascular disease comes from studies of patients with silent cerebral infarction, that is, patients with radiographic evidence of infarction without frank signs of neurological impairment. Silent cerebral infarction is quite common among the elderly. Silent cerebral infarction was observed in 23% of elderly people in the United States (Longstreth *et al.*, 1998), in 42% of older adults in one Japanese study (Hougaku *et al.*, 1992), and in 51% in another Japanese study (Imai *et al.*, 1996). Not only is silent stroke a risk factor for clinical stroke (Kobayashi *et al.*, 1997a) that obviously increases the risk of aspiration pneumonia, but Nakagawa *et al.* (2000) reported that patients with silent cerebral infarction were more likely to develop pneumonia (20%) than were controls (5%) without silent cerebral infarction over a two year period. In this study, deep silent infarcts were more closely associated with the incidence of pneumonia (29%) than superficial infarcts (7%)(Nakagawa *et al.*, 2000). Thus, silent cerebral infarction should be considered as a potential risk for the development of aspiration pneumonia. Taken together, it is reasonable to propose that treatment aimed at reducing the incidence and severity of cerebral vascular disease, for example, antihypertensive therapy, or anticoagulation and antiplatelet therapy in selected populations, may not only prevent future stroke but also reduce the incidence of aspiration pneumonia. In a comparison between a group receiving cilostazol, an antiplatelet agent, for three years and a cilostazol nonreceiving group, the incidence of cerebral infarction decreased to 50% in the cilostazol group (Yamaya *et al.*, 2001b). Furthermore, the incidence rate of pneumonia also reduced by approximately half (Yamaya *et al.*, 2001b).

Folic Acid

Folate plays a pivotal role in the synthesis of dopamine and its deficiency is common in older people, especially in institutionalized subjects. Folate deficiency may be an independent marker for increased risk of aspiration pneumonia in older people (Sato *et al.*, 2001). Folic acid supplementation may prevent the incidence of pneumonia by improving the swallowing function in these susceptible subjects (Sato *et al.*, 2001). Therefore, for older people, in order to prevent pneumonia nutrition has to be taken into consideration as well.

Oral Hygiene

The microbiologic etiology of aspiration pneumonia is usually traced to organisms that inhabit the oropharynx, and aspiration of pharyngeal contents has been suggested as the mechanism by which these bacteria reach the lower respiratory tract (Yamaya *et al.*, 2001a; Pierce and Sanford, 1974).

Johanson and Harris (1980) speculated that the pulmonary infections caused by bacteria following the introduction of pathogenic organisms by aspiration of oropharyngeal contents is one of the major reasons for pneumonia in the elderly. Since aspiration of bacteria in oropharyngeal secretions is an important risk factor for nosocomial pneumonia in the elderly (Johanson *et al.*, 1972), poor oral health may also contribute to the development of pneumonia. Yoneyama *et al.* (1999) assessed the rate of pneumonia in elderly people receiving oral care and in those who did not. During 2 years of follow-up, pneumonia was diagnosed in 19% of participants who did not receive oral care and 11% of those who received it. The relative risk of developing pneumonia on no active oral care compared with oral care was 1.67 (95% CI 1.01–2.75, $p < 0.05$). Thus, monitoring the attention given to the oral hygiene of dependent patients can probably lower the incidence of aspiration pneumonia.

Furthermore, in a previous study, Yoshino *et al.* (2001) stimulated the gum-ridge with a brush with no toothpaste immediately after a meal. No matter where in their mouth they stimulated, the swallowing reflex improved after the stimulation on the gum-ridge. This result tells us that stimulation in the mouth is transmitted to the brain, and certainly improves the swallowing reflex, which is one of the most important defensive reflexes against microorganisms with which the human body is equipped. Brushing in the mouth is not only good for the prevention of dental caries and gumboils but also very good for improving the reflexes. Stimulation of the mouth requires less time and effort than stimulation of the arms and legs. All we need is a little bit of stimulus.

Sitting Position

Gastroesophageal reflux is very common in general and more common in elderly subjects. It has been estimated that more than one third of older people have intermittent symptoms of gastroesophageal reflux. In addition, the supine position, possibly by increasing the likelihood of aspiration of gastric contents into the lung, may lead to pneumonia in patients on mechanical ventilators (Yamaya *et al.*, 2001a). Finally, nasogastric tubes promote aspiration of gastric contents by impairing swallowing, causing stagnation of oropharyngeal secretions and reducing the tone of the lower esophageal sphincter (Yamaya *et al.*, 2001a). The simple approach to all of these problems may involve elevating the head of the bed. Meguro *et al.* (1992) showed that elevating the bed after each meal for 2 hours may lower the febrile days presumptively caused by aspiration of gastric contents. Matsui *et al.* (2002) also emphasized the importance of patient sitting position for the prevention of respiratory tract infections.

Avoid Neuroleptics

The cough reflex can, of course, be suppressed by sedating drugs. Irwin *et al.* (1998) reported a consensus panel report of the American College of Chest Physicians, "Managing Cough as a Defense Mechanism and as a Symptom," and did not identify any age-related changes in cough reflex (Teramoto *et al.*, 1999). However, depression of cough reflex by anesthesia, sedative hypnotics, or analgesic narcotics should be considered to be a major risk for aspiration pneumonia in older patients, especially during sleep (Huxley *et al.*, 1978). Attention to minimizing the use of agents that suppress the cough reflex is crucial in caring for elderly patients.

When older people take benzodiazepines, their swallowing reflex will not go down significantly. However, when they take neuroleptics, which mostly act as a dopamine receptor antagonist, their swallowing reflex does go down clearly, which makes things even more troublesome and leads to pneumonia (Wada *et al.*, 2001).

Handwashing

Gram-negative bacilli and *Staphylococcus aureus* commonly colonize the hands of health-care providers (Maki, 1978). Although usually transient, hand colonization may persist, particularly in workers with dermatitis. Handwashing before and after contact with patients is an effective method for removing transient bacteria (Craven *et al.*, 1991), but this is often a neglected behavior by medical personnel. The use of gloves and gowns can significantly reduce nosocomial infection and pneumonia (Leclair *et al.*, 1987). Hospitals with effective surveillance and infection control programs have rates of pneumonia 20% lower than hospitals without such programs (Haley *et al.*, 1985). Adherence to infection control practices such as handwashing is fundamental for the prevention of nosocomial pneumonia. Unfortunately, such barrier methods will not be effective in preventing infection with organisms that are part of the critically ill patient's endogenous flora; thus, most gram-negative pneumonias cannot be avoided by isolation methods (American Thoracic Society, 1995). Improved handwashing practices and appropriate handling of mechanical feeding, suction, and respiratory devices should reduce the spread of infectious agents in institutional settings.

PREVENTION OF PNEUMONIA AMONG THE ELDERLY BY VACCINES

Influenza Vaccines

Influenza vaccination is effective in older adults not only in preventing primary influenza pneumonia but also secondary bacterial pneumonia (Muder, 1998). Although an increased risk of pneumonia mortality is found in patients with limitations in activities of daily living (Nichol *et al.*, 1998; Fukushima *et al.*, 1999a), even bedridden elderly patients can be effectively immunized against influenza (Fukushima *et al.*, 1999b), and the duration of febrile days

and all respiratory conditions associated with influenza can be reduced (Fukushima *et al.*, 1999c).

23-Valent Pneumococcal Vaccines

The efficacy of pneumococcal vaccine among high-risk patients has been the subject of some controversy. Some investigators estimate an approximately 60% to 95% prevention rate of pneumonia by 23-valent pneumococcal vaccine in immunocompetent elderly and other high-risk patients (Sims *et al.*, 1988). It is currently recommended in the United States that all adults 65 years or older and those at risk because of underlying illnesses receive both of these vaccines (U.S. Department of Health and Human Services, 1997). Chiba *et al.* (2004) demonstrated that pneumococcal vaccination significantly shortened the overall febrile days and significantly reduced the rate of hospitalization for pneumonia even in bedridden patients. Pneumococcal vaccination is of benefit and recommended for elderly disabled patients at high risk for pneumonia.

Bacillus Calmette–Guérin (BCG) Vaccines

The tuberculin skin test is an easy way to check the cell-mediated immunity in elderly people (Fukushima *et al.*, 1999a; Nakayama *et al.*, 2000). Almost all Japanese over 65 years old may have a positive tuberculin skin test. If a person shows negative, it means that his or her cell-mediated immunity is depressed. We undertook a trial to vaccinate bedridden elderly people with Bacillus Calmette-Guérin (BCG) vaccine. During follow-up, new pneumonia was diagnosed in 42% of the elderly disabled patients with negative tuberculin responses, in 15% of the tuberculin converted patients by BCG, and in 13% of the patients with positive tuberculin responses. BCG inoculation might reactivate the depressed T helper-1 mediated cellular immunity and prevent pneumonia in immobile elderly patients (Nakayama *et al.*, 2002).

CONCLUSION

Silent aspiration, which is frequently observed in patients with basal ganglia infarctions, might be an important risk factor for elderly pneumonia. Measurement of a swallowing latency is useful to identify a subject susceptible to pneumonia. The swallowing function might be partly regulated by dopaminergic neurons and substance P-containing sensory nerves. Disruption of the basal ganglia leads to an impairment of the swallowing function and may predispose stroke patients to pneumonia. ACE inhibitors and amantadine may have beneficial effects on the prevention of pneumonia. Similarly, oral care improves swallowing reflexes and lowers the risk of pneumonia. Vaccines are also effective even in disabled elderly patients in a bedridden condition. Since pneumonia in elderly frequently recurs and is often lethal, it is important to identify and protect high-risk patients.

KEY POINTS

- The main theme of this chapter is to discuss how aspiration pneumonia develops in older people and to suggest preventive strategies that may reduce the incidence of pneumonia among older adults.
- Silent aspiration of oropharyngeal bacterial pathogens to the lower respiratory tract is one of the most important risk factors for elderly pneumonia. Impairments in swallowing and cough reflexes among older adults, for example, related to cerebral basal ganglia infarctions, increase the risk of pneumonia.
- Since both swallowing and cough reflexes are mediated by endogenous substance P contained in the vagal and glossopharyngeal nerves, pharmacologic therapy using angiotensin-converting enzyme inhibitors, which decrease substance P catabolism, can both improve reflexes and result in the lowering of the risk of pneumonia.
- Since the production of substance P is regulated by dopaminergic neurons in the cerebral basal ganglia, treatment with dopamine analogs or potentiating drugs such as amantadine can reduce the incidence of pneumonia.
- Since mortality from infections correlates with cutaneous anergy, interventions that reverse these age-associated changes in the immune system are also effective.

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Respiratory Disease in the Elderly

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INTRODUCTION

Respiratory diseases produce enormous morbidity and potentially avoidable mortality in elderly people in the western world. The burden of many of these pathologies (asthma, chronic obstructive pulmonary disease and pulmonary tuberculosis) is increasing in this age-group. Nearly 10% of all hospital admissions among the elderly in England are attributable to respiratory conditions (Lung and Asthma Information Agency, 1995). General Practitioners (GPs) can expect 700 respiratory consultations each year from every 1000 elderly on their list (National Heart and Lung Institute, 1998).

The elderly themselves regard respiratory conditions as second only to musculoskeletal disorders (and four times as common as stroke) as a cause of severe disability (Hunt, 1976).

Despite this, elderly people with respiratory conditions have until recently fallen between two stools – one occupied by respiratory physicians with little expertise in the care of elderly people and the other occupied by geriatricians with little interest or expertise in respiratory disease. The consequences of this have been difficult to measure in terms of clinical outcomes, but are clear in terms of the paucity of the evidence base concerning respiratory disease and its management in elderly people when compared with the evidence base in other body systems and pathologies. This situation is thankfully changing, both in the United Kingdom and elsewhere, in part, in recognition of the increasing burden of the demographic time bomb on acute hospital care.

In common with other areas of geriatric medicine, "atypical" presentation of respiratory disease is common in old age (so common perhaps as to render the word "atypical" inappropriate) with both symptoms and physical signs displaying reduced predictive values in elderly people with acute respiratory problems. Partly because of this, and because of aging changes in the respiratory system, there are considerable age-related differences in the assessment and management of respiratory conditions.

The present chapter therefore aims to present major respiratory pathologies affecting the old in the context of aging changes in the respiratory system, etiology and epidemiology, clinical presentation and assessment, and management. It also aims to emphasize continuing areas of uncertainty. Within the confines of the present work, a comprehensive review of every area is not possible, and reference will therefore be made to both original research and recent, more extensive reviews.

PATTERNS OF SYMPTOMS AND SIGNS, AND "RESPIRATORY FUNCTION TESTS"

Signs

Though acute or chronic respiratory disease in the elderly may present nonspecifically both in terms of symptoms and physical signs, there remain certain classical features of the history and examination which can be grouped into "patterns", suggestive of a specific diagnosis or a more general diagnostic area. Historical patterns (symptoms) will be given in the appropriate disease subsections below. What follows is a brief summary of patterns of examination features that point toward specific diagnostic areas.

Airways Obstruction

The following refers to chronic obstruction although many will also apply to acute obstruction (e.g. acute asthma).

1. Use of accessory muscles.
2. High shoulders.
3. Increased anteroposterior diameter of chest.
4. Prolonged expiration.
5. Audible wheeze.
6. Inward movement of costal margin.

Principles and Practice of Geriatric Medicine, 4th Edition. Edited by M.S. John Pathy, Alan J. Sinclair and John E. Morley.
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7. Absent (or lowered) liver dullness.
8. Rhonchi and impaired air entry (in severe obstruction, air entry may be so poor that rhonchi are absent).

Diffuse Lung Fibrosis (e.g. Fibrosing Alveolitis)

1. Fine, late inspiratory, or pan-inspiratory crepitations ("Velcro" crepitations).
2. Clubbing (not found in all conditions producing diffuse lung fibrosis).
3. Cyanosis.

Collapse

1. Reduced movement of the affected side, tracheal deviation to the affected side, and displacement of the apex beat toward the affected side may all indicate reduced lung volume in the area of collapse.
2. Diminished breath sounds.

Consolidation

1. Signs of collapse often seen as collapse and consolidation often coexist.
2. Dullness to percussion.
3. Crepitations (not always).
4. Increased vocal resonance (aegophony).
5. Bronchial breathing.

Pneumothorax (Air in the Pleural Space)

1. Reduced or absent breath sounds.
2. Pleural click (left-sided pneumothoraces only).

When a pneumothorax occurs with tension, other signs may occur in addition. "Tension" indicates increasing accumulation of air in the pleural space with each inspiration due to a "flap" of pleura producing one-way valve effect.

3. Displacement of the apex and trachea *away* from the affected side.
4. Hyper-resonance to percussion.
5. Absent breath sounds.
6. Tachycardia.
7. Hypotension.
8. Respiratory distress.
9. Cyanosis.
10. Sweating.
11. Raised jugular venous pulse (JVP).

Pleural Effusion

1. Reduced chest movement over the effusion.
2. Displacement of the apex and trachea *away* from the effusion.
3. Profound dullness to percussion ("stony dullness").
4. Reduced breath sounds.
5. Reduced vocal resonance.
6. Reduced vocal fremitus.

Respiratory Function Tests

This section does not aim to explain in detail the derivation of respiratory function tests and their normal values. Instead, it merely provides a summary of the most commonly used nonradiological investigations in respiratory disease together with the typical patterns seen in different classes of respiratory pathology.

The most commonly used respiratory function tests are as follows:

1. FEV_1 – the forced expiratory volume in one second (liters). This is the volume of air expired during the first second of a forced expiratory maneuver from vital capacity.
2. FVC – forced vital capacity (liters). The total volume of air expired during forced expiration from vital capacity. This is usually identical to slow vital capacity (SVC – i.e. that capacity expired during a nonforced maneuver). However, in severe emphysema with loss of elastic support, FVC may fall disproportionately more than SVC.
3. PEFR (or PEF) – peak expiratory flow rate (liters per minute). A simple measure of maximum expiratory flow rate – less useful in chronic obstructive pulmonary disease (COPD) than in asthma.
4. TL_{CO} – transfer factor (millimols per minute). A measure of the ability of the lung to oxygenate hemoglobin. Usually measured as a single breath technique using carbon monoxide.
5. K_{CO} – transfer coefficient (millimols per minute per kPa per $litre_{BTPS}$, where BTPS = corrected to body temperature and ambient pressure saturated with water vapor). Essentially, the transfer factor corrected for lung volume.

In addition to the above, blood gases are frequently performed in the investigation of patients with respiratory problems. Their purpose is to assess acid–base balance and oxygenation. The most important measures are therefore partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2) and pH.

There are essentially two characteristic "patterns" of abnormal respiratory function: obstructive and restrictive.

Obstructive Pattern

This is most commonly found in asthma and COPD and is characterized by the following:

1. Reduced FEV_1 and PEF (in COPD, PEF may be misleadingly relatively high (see below) and thus in COPD,

monitoring of FEV_1 is more reliable than monitoring of PEF).
2. Reduced FVC though proportionally less so than FEV_1.
3. Reduced FEV_1/FVC ratio (normally approximately 70%, though there is some evidence that this normal value may be lower in the elderly).
4. pO_2 usually normal in asthma (apart from severe exacerbation) but may be low in moderate to severe COPD (either chronically or more commonly during acute exacerbation).
5. pCO_2 may be raised in chronic severe COPD or in acute exacerbations of COPD. pCO_2 is usually either normal or even low (due to hyperventilation) in acute exacerbations of asthma. A rise in pCO_2 (due to patient exhaustion) in acute asthma, or a fall in pH is a severe prognostic sign suggesting the need for assisted ventilation.
6. pH may be low during acute exacerbations of COPD and may indicate the need for noninvasive or even invasive ventilation (see below).

Restrictive Pattern (e.g. Interstitial Fibrotic Lung Disease)

1. Reduced FVC.
2. Similarly reduced FEV_1.
3. Normal or sometimes increased FEV_1/FVC ratio.
4. Reduced TL_{CO} and K_{CO}.
5. Reduced pO_2.
6. Normal or low pCO_2 (the latter due to hyperventilation).
7. Normal or high pH.

AGE-RELATED CHANGES IN THE RESPIRATORY SYSTEM

No other internal organ is so intimately exposed to external environmental influences as the lung. It is therefore difficult, even in the absence of disease, to differentiate with certainty between the physical and physiological changes of aging itself and those brought about by a lifetime sum of diverse environmental insults. This is complicated further by reliance on cross-sectional studies (comparing a group of elderly people to a separate group of young people) rather than prospective or longitudinal studies. This section will deal therefore with "age-related" changes rather than "aging" (prospective or longitudinal) changes. Environmental influences will however be mentioned when there is clear evidence of their relevance. These changes comprise physical (structural) changes and physiological (functional) changes, both in the lung and in ventilatory control and oxygen exchange and uptake.

Age-related Structural Changes

The most important age-related change in the large airways is a reduction in the number of glandular epithelial cells (and hence a reduced production of protective mucous leading to impaired defense against respiratory infection). Small airways display qualitative and quantitative change in the supportive elastin and collagen with coiling and rupture of fibers and consequent dilation of alveolar ducts and air spaces (so-called *senile emphysema*) (Verbeken *et al.*, 1992), and a sometimes clinically relevant increased tendency for small airways to collapse during expiration (see below). There is an approximately 20% reduction in alveolar surface area which leads to reduced respiratory reserve, although this is of little or no significance in the healthy elderly.

The major age-related change in respiratory muscles is a reduction in the proportion of type IIA (fatigue resistant) fibers with consequent impairment of strength and (more importantly) endurance (*see* **Chapter 59, The Effect of Aging on the Respiratory Skeletal Muscles**).

Ossification of costal cartilages (Teale *et al.*, 1989), loss of vertebral disc space (with increased anteroposterior diameter), and calcification of rib articulatory surfaces combined with muscle changes result in impaired mobility of the thoracic cage. These "normal" changes may be compounded by osteoporotic vertebral collapse and/or rib fracture.

Age-related Functional Changes

The most clinically important functional changes in the aging respiratory system are: (1) the increased tendency for small airways to collapse sooner (at higher lung volumes) during expiration (increased "closing volume"); (2) the reduction in respiratory muscle strength and endurance (as discussed above) and its consequences; (3) changes in the monitoring and control of breathing. None of these changes are easy to quantify clinically in contrast to reductions in lung volumes which are easily measurable.

Increased closing volume is the consequence of degeneration of the elastin and collagen in the support structure of the small airways. In the normal elderly, airway closure in the dependent zones takes place during tidal breathing (Anthoniesen *et al.*, 1970), with consequent impairment of ventilation of the dependent areas, ventilation provision mismatch and reduced resting arterial oxygen tension (Young *et al.*, 1987). It also is the probable cause of the poor reliability of bilateral basal crepitations as a physical sign in old age (Connolly *et al.*, 1992b).

Respiratory muscle strength and endurance fall with age, in large part the consequence of type IIA fiber atrophy. Such changes may be of limited functional significance in the healthy elderly person but result in impairment of reserve to combat respiratory challenges such as pulmonary edema, pulmonary embolism or pneumonia. Although there is a wide range of normality, maximum inspiratory mouth pressures (an indirect measure of respiratory muscle strength) fall. In men, this fall may be as

much as 35% between the age of 20 and 70 years (Dow and Carroll, 1996).

In common with changes in other bodily control mechanisms (impaired homeostasis), a variety of age-related changes result in relative inefficiency in the monitoring and control of ventilation. The much reported study of Kronenberg and Drage (1973) found that elderly subjects have impaired ventilatory responses to both hypoxia and hypercapnia at rest. This data has subsequently been challenged with evidence of a normal response to resting eucapnic hypoxia, but an impaired response to hypoxia during sustained hypercapnia (Smith *et al.*, 1995; Poulin *et al.*, 1993). In addition, in the elderly, there is *increased* ventilatory response to exercise-induced carbon dioxide production (Brischetto *et al.*, 1984). Conversely, episodes of apnea during sleep appear more common in even the healthy elderly (Haward *et al.*, 1992). The significance of this latter observation is unclear.

Elderly people are less able to perceive elastic or resistive loads on inspiration or expiration (Tack *et al.*, 1981, 1982) and have markedly reduced appreciation of acute bronchoconstriction (Connolly *et al.*, 1992a; Ekici *et al.*, 2001; Ottanlli *et al.*, 2001). Such age-related abnormalities may potentially have clinical implications (see below).

Maximal oxygen uptake declines with age at a rate of about 1% per year. This produces a decline in *maximal* exercise capacity (in contrast to exercise endurance which is affected to a lesser degree) and also a decline in reserve (again of importance during respiratory stresses such as pneumonia and pulmonary embolus). The fall in maximal uptake is largely the result of a fall in maximum tachycardic response and in cardiac output (Young *et al.*, 1987), together with a fall in alveolar capillary volume and the problems of ventilation perfusion mismatch as discussed above. Regular aerobic training reduces the age-related fall in oxygen uptake and improves functional reserve with the suggestion that this may enhance rate of recovery from acute illness (Bortz, 1982; Larson and Bruce, 1987). There is as yet no direct evidence that dietary antioxidant supplementation attenuates age-related decline in lung function, although there is considerable interest in this area at present.

In terms of more easily measurable lung volumes, most studies have unfortunately included only very few elderly subjects and have usually obtained "normal" values by extrapolation (probably invalid), whilst others have been exclusively cross sectional. Studies that have not fallen foul of either of these methodological flaws have shown a more rapid age-related fall in FEV_1 and FVC. The FEV_1/FVC ratio falls by approximately 0.2% per year (from a ratio of 70% at the beginning of the fifth decade of life) (Milne, 1978; Milne and Williamson, 1973; Tager *et al.*, 1988) Enright's group have produced lung function data for elderly which are rapidly becoming accepted as the norm (Dykstra *et al.*, 1999; Marion *et al.*, 2001).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Epidemiology

The newly formulated National Institute of Clinical Excellence (NICE) guidelines on COPD (The National Collaborating Centre for Chronic Conditions, 2004) define the condition as a disease characterized by airflow obstruction. The airflow obstruction "is usually progressive, not fully reversible and does not change markedly over several months". COPD is almost always the result of cigarette smoking, and a smoking history of less than 10 pack years (1 pack year = 20 cigarettes per day for one year) should alert the physician to the possibility of an alternative diagnosis such as chronic asthma. Epidemiological surveys reveal a high prevalence of COPD in the elderly, much of which is undetected clinically and untreated. The national estimates for the United Kingdom suggest a prevalence of at least 11% (The National Collaborating Centre for Chronic Conditions, 2004; Cox, 1987), and increases with increasing age. This is not surprising given that the cohort of people making up today's elderly have had the highest uptake of cigarette smoking (Lee *et al.*, 1990). Our own studies suggest that nearly 30% of Caucasian inner-city community dwellers over the age of 65 have airways obstruction (COPD + asthma), but that 63% of these receive no treatment (Renwick and Connolly, 1996a). British and European epidemiological studies from less industrialized areas with a lower smoking prevalence report COPD prevalence of between 7 and 16% (Horsley *et al.*, 1991; Dow *et al.*, 1992b; Isoaho *et al.*, 1994), although a British survey of the more dependent elderly reported a prevalence (COPD + asthma) of over 40% (Banerjee *et al.*, 1987). The prevalence is at least static and may even be increasing, particularly in women (Office for National Statistics, 2000a). There were nearly 28 000 deaths certified as being due to COPD in the United Kingdom in 1999 (Office for National Statistics, 2000b) and due to difficulty with collection of mortality statistics, the death rate may be even higher than this. About 12% of all adult emergency hospital admissions are due to COPD, and general practice consultation rates are twice as high as those for ischemic heart disease, rising precipitately with age (Anderson *et al.*, 1994; Office of Population Census and Surveys, 1995). The majority of respiratory disability in old age is the consequence of COPD.

Presentation

COPD is characterized by a variable phase (usually several years) of minimal symptoms, with the possible exception "smokers cough". This latter may result in a possible label of chronic bronchitis defined as the production of sputum each day for at least 3 months on 2 consecutive years (which the patient may not feel is abnormal). During this latent period, affected individuals will usually have no physical

signs and are unlikely to complain of breathlessness. This is particularly so in the elderly in whom COPD often presents late and is poorly diagnosed and under treated (Renwick and Connolly, 1996a; Roberts and Bateman, 1994). This is probably related to a combination of reduced mobility (less exertion–related dyspnea), reduced expectation on the part of the patient and physician, impaired subject of awareness of acute bronchoconstriction (Connolly *et al.*, 1992a; Ekici *et al.*, 2001; Ottanlli *et al.*, 2001), and the poor predictive value of "typical" respiratory symptoms in old age (Dow *et al.*, 1992b; Renwick and Connolly, 1999). Nonetheless, COPD in the elderly produces significant morbidity and impairment of quality of life (see below).

Initial presenting symptoms are usually exertional breathlessness particularly during episodes of "winter bronchitis" which is often associated with acute exacerbations of dyspnea. The essential abnormality in lung function in COPD is obstructive (reduced FEV_1 and FEV_1/FVC ratio) and it is only when FEV_1 falls below 60% of predicted (or even lower in the elderly) that breathlessness and wheeze on exertion become troublesome (Connolly *et al.*, 1992a; Ekici *et al.*, 2001; Ottanlli *et al.*, 2001). Other symptoms include fatigue (often neglected), cough, and sputum production (as for chronic bronchitis). As the condition progresses over the years (FEV_1 falling below 40% predicted) breathlessness and wheeze worsen and hyperinflation of the chest, cyanosis, and signs of right heart strain appear (due to pulmonary vasoconstriction from chronic hypoxia) – right ventricular heave, raised jugular venous pressure and peripheral edema. Secondary polycythemia affects some sufferers. It is usually only in this latter phase (FEV_1 below 40% predicted) that sufferers become known to hospital services, generally because of emergency admission with intermittent exacerbations (see below). Nocturnal hypoxia and hypoventilation may affect sleep pattern and quality (Meacham Jones *et al.*, 1995; Meacham Jones and Wedzicha, 1993, 1996). Prognosis is inversely related to age and to lung function (particularly to postbronchodilator lung function (The Intermittent Positive Pressure Breathing Trial Group, 1983)), as well as to level of respiratory disability (Yohannes *et al.*, 2002). In severe disease, weight loss is common and is a further adverse prognostic factor.

Management – The Chronic Condition

Formal lung function testing (FEV_1 and FVC) is essential for diagnosis. Reliance on peak flow measurements is inappropriate as these can be misleadingly high in COPD. Reversibility testing (either to bronchodilators or to a combination of bronchodilators and a course of oral corticosteroids) is no longer recommended as necessary for all patients but should be used to exclude other conditions most particularly asthma.

Smoking cessation is the cornerstone of management at all levels of severity. This is at least as successful in elderly patients (Vetter and Ford, 1990) and possibly even more so (Campbell *et al.*, 1996), with 1-year "quit-rates" of 10–15% without support. The British Thoracic Society (BTS) Guidelines on Smoking Cessation (British Thoracic Society, 1998) confirm both the effectiveness, and the cost-effectiveness (cost per life year gained) of smoking cessation, and the various strategies to support it. The cardiovascular and respiratory health benefits of smoking cessation persist well into old age and include improvement in quality of life and compression of morbidity. It is likely that both these factors are of even greater importance in the elderly, the latter both at an individual level and at a socioeconomic level (Burchfiel *et al.*, 1985; Shinton and Beevers, 1989; Shaper *et al.*, 1991; Kawachi *et al.*, 1993; Rosenberg *et al.*, 1990; Higgins *et al.*, 1993; Fries *et al.*, 1989; Hirdes and Maxwell, 1994). There is, in addition, some evidence that smoking may be a risk factor for cognitive impairment in old age (Huadong *et al.*, 2003). There is as yet no evidence of the benefits of cessation in this latter regard, although it is clear that the benefits of cessation upon rate of loss of lung function remain worthwhile up to the age of 80 (particularly for women) (Burchfiel *et al.*, 1985).

Despite this evidence, health-care professionals are less likely to give antismoking advice to the elderly than to younger patients (Maguire *et al.*, 2000; Kviz *et al.*, 1995; Buckland and Connolly, 2004). This is unfortunate, as advice from health professionals and the belief by the individual that their symptoms result from a smoking-related condition are particularly important predictors of cessation for elderly smokers (Wagner *et al.*, 1990; Clark *et al.*, 1997). Furthermore, elderly smokers are no less motivated to quit and indeed may be more likely to be preparing to quit (Clark *et al.*, 1997; Velicer *et al.*, 1995; Etter *et al.*, 1997; Turner *et al.*, 2001). Indeed, among the elderly, it is those smokers with the highest level of consumption (and thus the greatest likelihood of smoking-related disease) who have the best chance of successful quitting (Coambs *et al.*, 1992), despite the counterintuitive nature of this assertion.

The chances of successful quitting can be improved with nicotine replacement in old age from 10–15% to as much as 20% (Russel *et al.*, 1993; Campbell *et al.*, 1996). As yet bupropion is not proven in smoking cessation in old age (Lantz and Giambanco, 2001), however, it seems to be of even greater beneficial effect than nicotine replacement in younger smokers (Tashkin *et al.*, 2001; Dale *et al.*, 2001).

Drug Treatment

In the last 10 years, the evidence base for pharmacological treatment in COPD has improved and thus evidence in newer guidelines (The National Collaborating Centre for Chronic Conditions, 2004) is much less dependent upon mere consensus. Many of the controversies, particularly concerning the use of inhaled steroids, have been laid to rest (at least for the time being). New drugs (particularly long-acting inhaled β_2-agonists and long-acting antimuscarinics) have been developed and trials conducted and the evidence base for previously neglected treatments (mucolytics) has been reexamined.

In younger patients, inhaled bronchodilators (β_2-agonists and anticholinergics) are usually recommended on a "prn" basis (i.e. as required). It is questionable whether this is appropriate for the elderly as a reduced appreciation of bronchoconstriction may impair "demand" (Connolly *et al.*, 1992a; Ekici *et al.*, 2001; Ottanlli *et al.*, 2001). It is thus arguable that inhaled bronchodilators should be given regularly in the elderly. The NICE Guidelines (The National Collaborating Centre for Chronic Conditions, 2004) recommend that long-acting inhaled bronchodilators (both β_2-agonists and the long-acting anticholinergic tiotropium) should be used to control symptoms and improve exercise tolerance in patients who continue to experience breathlessness and reduced exercise capacity despite the use of short-acting bronchodilators. The evidence base of this recommendation comes from meta-analyses and randomized controlled trials. Many of these trials have, in addition, shown that long-acting bronchodilators, as well as improving symptoms, improve quality of life and reduce exacerbation rates. This has been particularly consistently shown with tiotropium.

Until recently, there had been controversy as to whether inhaled corticosteroids reduce disease progression in COPD. However, several large-scale trials and meta-analyses of these trials have shown no benefit (or only statistically minimal beneficial effect and certainly no clinically beneficial effect). However, these same trials have indicated that inhaled corticosteroids when given to patients with severe disease and/or with frequent exacerbations reduce exacerbation frequency, and thus the NICE Guidelines recommend that inhaled steroids should be added to long-acting bronchodilators in patients with an FEV_1 of less than or equal to 50% of predicted who have had two or more exacerbations requiring antibiotics or corticosteroid treatment in the previous 12 months. There is little or no place for oral corticosteroids in the chronic management of COPD. β-blockers including eye drops should be avoided as they may exacerbate bronchoconstriction (Diggory *et al.*, 1995).

Most elderly people *can* be taught to use simple metered dose inhalers (MDIs) successfully, the chief barriers to their use being impaired hand-grip strength (commonly due to arthritic conditions) and cognitive impairment (Allen and Prior, 1988; Armitage and Williams, 1988; Allen, 1997). However, in practice, MDI technique is variable in old age and worse than in younger patients (Allen and Prior, 1988; Armitage and Williams, 1988; Connolly, 1995). Large volume spacers are easier for the elderly to use and well liked by this age-group (Connolly, 1995), as well as having the advantage of reducing local and systemic side effects of high-dose inhaled steroids (Selroos and Halme, 1981). In addition, the use of a large volume spacer, as well as improving acquisition of technique, also improves its retention (Connolly, 1995) and allows carers to assist with technique for those patients with cognitive impairment or physical disabilities affecting hand function. Of the breath-actuated devices available, the Turbohaler and the Autohaler appear preferable while the Rotahaler and Diskhaler are particularly problematic for the elderly (Diggory *et al.*, 1991; Harvey and Williams, 1992). A recent study by Allen and Ragarb (2002) has shown that this is probably due to dyspraxia or previously unrecognized cognitive impairment. In clinical practice, a pragmatic approach is needed however, with patients being tried on a variety of inhalers until the one "best for them" is found. Their inhaler technique should then be reassessed at regular intervals and they should preferably have all their inhaled drugs administered through the same type of inhaler device.

While nebulizers do have a place for inhaled drug administration in COPD, they have too frequently been prescribed without objective evidence of benefit, and even more frequently employed in an unsupervised fashion (*Lancet*, 1984). In some patients, however, nebulizers may be an alternative to inhalers, particularly for those small numbers of patients with poor and uncorrectable inhaler technique. Nebulizers as well as inhalers require adequate cognition and manipulative skill on the part of the patient, though when these are lacking, carers can often be trained to provide support (Teale *et al.*, 1995). Nebulizers need regular servicing and filter replacement and patients or carers need a contact telephone number for this. There are now national guidelines in the United Kingdom for nebulizer provision and assessment (Muers and Corris, 1997).

Theophyllines are beneficial both as bronchodilators and in improving respiratory muscle strength. Unfortunately, the side effects are often prohibitive in elderly patients, particularly as clinically significant benefit is only obtained when plasma concentrations are at the upper end of the "therapeutic range" (McKay *et al.*, 1993). Sustained release preparations reduce the incidence of side effects. Both theophyllines and oral β_2-agonists preparation may be useful in small numbers of patients (often the demented) who are unable to use any form of inhaled bronchodilator. However, the NICE Guidelines recommend the "addition" of theophylline to either inhaled β_2-agonist or inhaled anticholinergic therapy where patients remain symptomatic (and indeed the guidelines recommend combinations of drugs from different classes in this regard). There is a strong evidence base for their effectiveness in this manner and also that the addition of a different class of drug to existing medication produces fewer side effects than intensifying the dose of the first line drug (β_2-agonists or anticholinergics).

Mucolytic therapy has until recently been regarded as ineffective in the management of COPD and indeed in the United Kingdom, mucolytics were withdrawn from the National Health Service (NHS) drug tariff some years ago. Recently, meta-analysis of previously reported studies has in fact revealed that mucolytics (in the United Kingdom, carbocisteine which is once again on the NHS drug tariff) reduce symptoms of cough and sputum production in patients with COPD troubled by these symptoms. There is also some (though less) evidence of a reduction in severity and/or frequency of exacerbations in sputum producers. The NICE guidelines thus recommend consideration of the use of mucolytic therapy in patients with chronic productive cough. There is no evidence base for the use of antioxidant therapy or of cough suppressants in COPD.

Oxygen

Many patients with more severe COPD become hypoxemic. When baseline (resting) pO_2 falls below 8 kPa, many patients will develop signs of cor pulmonale secondary to pulmonary hypertension. The most usual manifestation of this is peripheral edema. Cor pulmonale is a very adverse prognostic feature and when untreated has a 5-year survival of less than 50%.

In addition, many COPD patients also become transiently hypoxic on exercise, and in these patients, ambulatory oxygen can be used to reduce symptoms and improve exercise capacity. Yet others find symptomatic relief from the use of fixed (nonambulatory) oxygen for short periods. Oxygen should clearly be used cautiously in patients with COPD because of the possibility of respiratory depression.

This review will not consider the use of ambulatory or symptomatic oxygen in detail. The reader is however strongly advised to consult the NICE Guidelines on this topic.

Long-term Oxygen Therapy (LTOT)

Apart from smoking cessation which improves prognosis in all COPD patients, Long-term Oxygen Therapy (LTOT) is the only intervention proven to prolong life in some patients with COPD (the chronically hypoxic; see above). LTOT is known to prevent or alleviate cor pulmonale if oxygen is used for 12–15 hours per day or more. The evidence base for the use of LTOT in the elderly is poor. The two chief studies which indicated a reduction in mortality on LTOT did not include large numbers of elderly subjects, and one, the MRC (Medical Research Council) LTOT Trial, specifically excluded patients over the age of 70 (Nocturnal Oxygen Therapy Trial Group, 1980; Report of the Medical Research Council Oxygen Working Party, 1981). Nonetheless, provided assessment follows established criteria, there is no reason to suppose that the elderly would be less likely to benefit. In brief, the need for LTOT should be assessed in:

- all patients with severe airflow obstruction (FEV_1 less than 30% predicted);
- patients with cyanosis;
- patients with polycythemia;
- patients with peripheral edema;
- patients with a raised JVP;
- patients with oxygen saturation less than or equal to 92% breathing room air.

LTOT is *indicated* in patients who have a pO_2 less than 7.3 kPa when clinically stable or pO_2 greater than 7.3 and less than 8.0 kPa when stable plus one of (1) secondary polycythemia, (2) nocturnal hypoxemia – SAO_2 less than 90% for more than 30% of the time, and (3) peripheral edema or pulmonary hypertension.

Patient assessment for LTOT should ideally comprise measurement of blood gases on two separate occasions at least 3 weeks apart in stable patients receiving optimum medical treatment. On receiving LTOT, patients should be reviewed at least once yearly and this review should include pulse oximetry.

To gain benefit from LTOT, patients should be using their oxygen for at least 15 hours per day.

Nonpharmacological Management (*see* Chapter 62, Pulmonary Rehabilitation)

Pulmonary Rehabilitation (PR) has been the subject of enormous recent and current research, much of which has not given prominence to elderly patients. Pulmonary rehabilitation programs are a multidisciplinary effort comprising education, optimization of medical therapy, nutritional assessment and modification, psychological evaluation and support, relaxation techniques, smoking cessation advice and support, and (essentially) "exercise training and reconditioning". Such programs are increasingly becoming widespread in the United Kingdom, particularly in the secondary care sector, and although their ability to improve exercise capacity in very elderly patients is now proven (Roomi *et al.*, 1996; Sudo *et al.*, 1997), there remains clinically a reluctance to refer elderly patients for PR (Yohannes and Connolly, 2004). When elderly patients are referred and accepted onto PR programs, it is essential to individualize the exercise-training arm of the program to the level of disability of the patient and recognize that severe end-stage disability may be more common in the elderly. Conversely, many elderly patients decline the offer of PR, though even they should be advised to stay as physically active as possible and provided with further advice and support on weight reduction (if obese), nutritional support (if malnourished – including dietician assessment), and smoking cessation (see above).

The value of PR in improving exercise capacity, quality of life, and in reducing the frequency of hospital admission, is summarized in the NICE COPD Guidelines.

Influenza vaccination and pneumococcal vaccination should be offered to all patients with COPD (and indeed to elderly people in general). The evidence for this is reviewed in a later section.

Wheeled walking frames may improve exercise tolerance in those severely disabled by breathlessness (Grant and Kapel, 1972; Yohannes and Connolly, 2003). It should in addition be remembered that COPD is often a terminal illness and indeed the 1-year mortality of patients discharged after acute exacerbation is up to 45% in some studies (see below). Palliative care and end-of-life planning should therefore play a large role in the management of many of these patients. However, anecdotal evidence suggests that this is rarely the case. More research is needed to identify which patients would most benefit from the interventions of palliative care teams.

Psychological Factors

The point prevalence of depression in disabling COPD in the elderly is up to 40% (Light *et al.*, 1985; Yohannes *et al.*, 1998a, 2000). Probably in no small part because of the overlap between symptoms of COPD and depression (particularly, the somatic symptoms or lethargy, poor sleep quality, and anorexia, but also other symptoms including low mood, and in particular, anxiety), the problem is difficult to detect without the use of validated screening questionnaires (Yohannes *et al.*, 2000). Depression predictors include patient-perceived quality of life and (importantly) level of disability, but do *not* include age and lung function. Anxiety may also be a marker, as clinical anxiety is only common in disabled COPD patients who are also depressed (Yohannes *et al.*, 2000). Even when identified, however, treatment of depression remains problematic as many patients have difficulty accepting the diagnosis and decline pharmacological treatment (Yohannes *et al.*, 2001).

Quality of life in the COPD population as a whole is definitely impaired compared to that of age matched controls without airways obstruction (Renwick and Connolly, 1996b). However, in the COPD population, the factors affecting quality of life are not clear. FEV_1 (in this population all of whom have low FEV_1s) does not seem to be a predictor and our own group had agreed with others in finding that quality of life seems to be mainly determined by level of disability and by depressive ideation (Yohannes *et al.*, 1998b).

Management – The Acute Exacerbation

Although most acute exacerbations are managed effectively in the community, it is during such episodes that patients are most likely to present to hospital. The mean age for hospital admissions due to acute exacerbations of COPD (AECOPD) is approximately 70–73 years in the United Kingdom and indeed admissions are relatively rare under the age of 65 (Vilkman *et al.*, 1996; Roberts *et al.*, 2002). The 2004 NICE Guidelines (The National Collaborating Centre for Chronic Conditions, 2004) define an exacerbation as "..... *a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough and increased sputum production and change in sputum colour. The change in these symptoms often necessitates a change in medication"*. The consequences of an exacerbation severe enough to precipitate hospital admission are grave. Nearly a third of patients are readmitted, and one in seven has died within 3 months of index admission (Roberts *et al.*, 2002). The figures from our own unit have revealed that over a third of patients who survive and are discharged from hospital admission for AECOPD are dead within 12 months (Yohannes and Connolly, 2002) and other authors reveal 12-month mortality rates of between 25 and 45% (Seneff *et al.*, 1995; Connors *et al.*, 1996; Sin and Tu, 2000a).

It is generally only patients with moderate or severe COPD who need admission to hospital during infective or other exacerbations. Even in the absence of short-term mortality, once patients have reached the stage of needing admission for AECOPD, the chances of repeated and frequent admissions are high. The NICE Guidelines has reviewed the evidence in this area and suggested that nearly two-thirds of patients admitted with AECOPD are admitted again within 12 months. The economic cost to have care providers of an exacerbation severe enough to result in hospital admission is approximately £1500 per event (2002 figures based on data from the Organisation for Economic Cooperation and Development (www.oecd.org)).

Many but not all exacerbations are the results of bacterial infection (acute infective bronchitis, pneumonia (this will be considered separately)). Common bacterial pathogens comprise *Streptococcus pneumoniae*, *Hemophilus Influenzae*, *Chlamydia pneumoniae*, *Moxarella catarrhalis* and (less frequently) *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Other causes include viral infection mainly from the Rhinovirus (common cold), influenza, parainfluenza, coronavirus and respiratory syncytial virus, and adenovirus. Exposure to pollutants such as particulates, sulphur dioxide, nitrogen dioxide, and ozone may also cause exacerbation, and other medical illness, particularly pulmonary embolism and exacerbations of congestive cardiac failure may present with symptoms of exacerbation. It is estimated that in nearly a third of exacerbations, no cause is found.

Symptoms may include increase in breathlessness, cough or sputum volume, or tenacity. Increased wheeze or chest tightness, fluid retention, acute confusion, and coryzal symptoms may also be present.

Many exacerbations are mild (particularly in patients with less severe underlying COPD). By no means all exacerbations require hospital admission and indeed many patients with mild exacerbations may not consult their doctor. Nonetheless, given the potential implications, assessment of severity is vital. The NICE Guidelines provide criteria on which to base a decision to recommend admission or home management. Hospital should be strongly considered if any of the following factors are present: inability to cope at home; severe breathlessness; poor or deteriorating general condition; poor level of activity (e.g. confined to bed); cyanosis; worsening peripheral edema; any impairment of level of consciousness; patients already receiving LTOT; patients living alone or not coping; acute confusion; rapid onset; significant comorbidity. In addition, if during initial hospital assessment, the patient is shown to have changes on chest radiograph, an arterial pH of less than 7.35 or an arterial pO_2 of less than 7 kPa, admission is recommended.

Investigations during exacerbation are not essential for the diagnosis (although they may be needed to exclude other pathologies – coincident or alternative) but they are often necessary in terms of guiding treatment. There is some evidence from preliminary analysis of a recent UK national audit that elderly patients are less likely to receive appropriate investigation during exacerbation than their younger counterparts (Connolly, 2004). However, more detailed analysis

of this data is needed. The NICE Guidelines recommend that in primary care, pulse oximetry is of value if there are clinical features of a severe exacerbation, but that sputum samples are not normally needed. In both primary and secondary care, spirometry at the time of the exacerbation is probably not helpful but in secondary care, the following investigations are usually required: chest radiography (exclude pneumonia and other coincident or alternative pathologies); arterial blood gases measured and inspired oxygen at the time recorded; ECG (exclude comorbidity); full blood count and urea and electrolyte estimation; theophylline level if patients on theophylline treatment at admission; sputum microscopy and culture if purulent; blood cultures if patient pyrexial.

Following these initial assessments in hospital it may be possible to discharge a patient to the care of a hospital-at-home team with intensive specialist nurse support. Alternatively, similar assessments within the first day or so of the patient's hospital admission may enable early discharge and shorter length of stay. Such hospital-at-home teams are a relatively new development in the United Kingdom and are strongly evidence based. This chapter does not attempt to review the evidence in detail but again the reader is referred to the NICE Guidelines. Decisions on admission or discharge to a hospital-at-home or assisted discharge scheme are based on the same criteria given above for deciding whether to admit or not. Such schemes are becoming widespread throughout the United Kingdom and have been shown to reduce admissions without increasing readmission rate or mortality or producing an additional burden on primary care. GP and patient satisfaction with the schemes is high.

Whether admitted or not, the NICE Guidelines provide a detailed review of recommended management of acute exacerbation. The evidence base for these recommendations is variable with strong evidence for some aspects and weaker evidence (often consensus based) for others. For each area of the NICE recommendations on AECOPD treatment an estimate of the grading of recommendations will be given, but for the purpose of brevity, the literature will not be reviewed in detail here. The interested reader is once again encouraged to consult the NICE guidelines directly.

Nebulized (as opposed to inhaled) bronchodilators are generally administered during exacerbations. There is, however, Grade A evidence that inhalers can be used effectively during exacerbations, provided multiple doses are given. Bronchodilators should be given four-hourly, driven by compressed air and not by oxygen. Standard doses comprise Salbutamol 2.5–5 mg and Ipratropium 0.5 mg, but the latter should be omitted in patients with glaucoma because of the risk of anticholinergic-precipitated acute episodes. If nebulizers have been used, the treatment should be changed to inhalers (unless the patient uses home nebulizers) at least 2 days before discharge to allow time for monitoring of inhaler technique and excluding deterioration on dosage reduction (Grade D evidence).

It is common practice to administer systemic corticosteroids to AECOPD patients. However, for some years, their value in this area has been unclear. More recently, randomized controlled trials have shown a significant benefit against placebo in terms of rapidity of improvement in lung function and in arterial oxygenation, as well as a reduction in hospitalization time (Grade A evidence). However, no difference in mortality has been demonstrated in five randomized controlled trials analyzed. Data on dose and duration is lacking, though it is recommended that Prednisolone 30 mg daily should be administered for 10–14 days (Grade D evidence) and not longer than this (Grade A evidence). Osteoporosis prophylaxis should be considered (Grade D evidence) particularly in patients needing frequent course of oral steroids (Grade D evidence). Corticosteroid response during an acute episode does not indicate the need for maintenance treatment and patients should be given clear instruction about when and how to stop their corticosteroids *and* the reasons why this is done (Grade D evidence).

There has, in recent years, been a controversy about whether antibiotics should be routinely administered to patients with acute exacerbations of COPD – the danger being not only risk of side effects to patients, but also the risk to the general population of production of antibiotic-resistant strains of bacteria. The NICE Guidelines recommend (on Grade A evidence) that antibiotics should be used to treat exacerbations of COPD associated with a history of newly purulent or more purulent sputum. They further suggest that antibiotics are not needed in other circumstances unless there are radiographic or clinical signs of pneumonia (Grade B evidence). There is less hard data when it comes to recommendation of *which* antibiotic to use. The general basis for these recommendations on the use of antibiotics is based on several studies (largely placebo-controlled trials), which have shown an increased rate of resolution of symptoms in patients with moderate to severe exacerbations and reduced death rate in patients with severe exacerbations requiring ventilation when given antibiotics. In addition, reduced mortality has been shown in a retrospective population-based study of over 26 000 patients (Sin and Tu, 2000b). The NICE Guidelines recommend that an aminopenicillin, a macrolide or a tetracycline be administered and that clinicians take the advice of local microbiologists (Grade D evidence). They further recommend that sputum cultures should be used to guide changes in therapy when necessary (Grade D evidence).

For severely bronchoconstricted patients who fail to respond to nebulized bronchodilators, intravenous aminophylline (usually given in a dose of 0.5 mg per kg per hour) may be valuable, although the studies are contradictory and many have been performed in acutely ill asthmatics rather than in patients with AECOPD. NICE Guideline evidence in this area is all Grade D. Nonetheless, the guidelines recommend that intravenous theophylline should only be used as an adjunct to the management of exacerbations if there is an inadequate response to nebulized bronchodilators, care should be taken over potential toxicity and that theophylline levels should be monitored within 24 hours of starting treatment. It is this author's recommendation that intravenous

aminophylline should be avoided in patients already receiving methylxanthine therapy unless serum theophylline levels are available. I would also suggest that intravenous β_2-agonists may be an alternative in the severely bronchoconstricted when nebulized drugs may penetrate poorly. Clinical experience suggests their usefulness but controlled trials in the elderly are lacking.

Oxygen is routinely administered to patients hospitalized with acute exacerbations of COPD. The commonest cause of death in AECOPD is hypoxia and the aim of oxygen therapy is to achieve adequate oxygenation without precipitating acute carbon dioxide retention and respiratory acidosis. The NICE Guidelines recommend the assessment of arterial blood gasses (on a recorded inspired oxygen concentration) in all patients assessed in hospital for exacerbations. They also recommend regular repetition of blood gas measurements to monitor response to the treatment (Grade D evidence). Oxygen saturation measurements may be useful as a guideline to oxygenation aiming to achieve an SaO_2 of 90–93%, titrating inspired oxygen upwards if saturation falls below 90% and downwards if the patient becomes drowsy or saturation exceeds 93–94%. Patients with an arterial pH of less than 7.35 should be considered for noninvasive or possibly invasive ventilatory support (see following text – Grade D evidence). There has been particular concern about oxygen supplementation given to patients during ambulance transfer to hospital. The guidelines recommend (again Grade D evidence) that all ambulances should be fitted with oxygen saturation monitors and that oxygen should be given to keep the SaO_2 above 90%.

Noninvasive ventilation (NIV) services are rapidly expanding for hospitalized patients with AECOPD across the United Kingdom and elsewhere. NIV is delivered by portable ventilators using a mask which either covers the mouth and nose, or the nose only. The evidence base for noninvasive ventilation in AECOPD is good. Systemic reviews and meta-analyses have confirmed a reduction in mortality, a decreased need for intubation, a more rapid improvement in blood gases, fewer complications, and reduced duration of hospital stay when compared to normal medical care. There is also health economic evidence that this treatment is cost-effective. As a result of analysis of these studies, the NICE Guidelines recommend that NIV should be the treatment of choice for persistent hypercapnic ventilatory failure (usually regarded as a pH of less than 7.35 which has not improved with standard treatment) during exacerbations. The guidelines also recommend (Grade D evidence) that NIV is delivered in a dedicated setting with staff experienced in its use but not necessarily in an intensive care or high dependency unit. When patients are started on NIV, it is important that a plan outlining what is to be done in the event of deterioration should be agreed upon (Grade D evidence). Where possible, this plan should be discussed with the patient as well as the patient's relatives.

Some patients fail to respond to NIV, and where invasive ventilation via intubation is appropriate, advanced age alone is not a contraindication. However, the evidence base for the use of intubation and invasive ventilation is surprisingly poor. It is largely based on descriptive case series rather than randomized trials. The NICE Guidelines recommend consideration of invasive ventilation only at Grade C level although they do confirm a Grade A recommendation for the use of NIV in patients slow to wean from invasive ventilation.

The NICE Guidelines also recommend (Grade D) the use of respiratory stimulants (Doxapram) only where NIV is inappropriate or unavailable.

During recovery from an exacerbation, patients should be monitored carefully by clinical assessment, pulse oximetry, and intermittent blood gas measurement together with daily peak flow or spirometry (all Grade D evidence). *Objective* assessment of severity of airways obstruction is essential in all age-groups but most particularly in the elderly. The absence of pulsus paradoxus and of tachycardia are common in severe airways obstruction in the elderly and are not reassuring. Similarly, the assertion by patients that their dyspnea is not particularly troublesome or is improving, may be unreliable (Petheram *et al.*, 1982).

Discharge planning is of particular importance, especially as there is a higher mortality in the first 3–6 months after discharge than during the admission itself (see above). The NICE Guidelines recommend that spirometry is checked in all patients before discharge; patients are stabilized on their optimum maintenance bronchodilator therapy; have satisfactory oximetry or blood gas measurements; patients or their carers are given appropriate information regarding medication (including oxygen); and where there is any doubt about patient functional ability, a formal ADL (activities of daily living) assessment should be performed (all Grade D recommendations).

ASTHMA

Epidemiology

The true prevalence of asthma in old people is complicated by problems with diagnostic labelling. Nonetheless, epidemiological studies suggest a prevalence of between 6.5 and 17% with one recent preliminary report suggesting a prevalence of 25% (Renwick and Connolly, 1996a; Burr *et al.*, 1979; Dodge and Burrows, 1980; Braman *et al.*, 1991b; Parameswaran *et al.*, 1998). Most of the subjects revealed by these studies as having asthma, were symptomatic of their condition. Nonetheless, in clinical practice, the prevalence of *diagnosed* asthma falls after the age of 65, suggesting underdiagnosis and undertreatment (Renwick and Connolly, 1996a; Roberts and Bateman, 1994), probably for reasons akin to those detailed above for COPD.

Pathogenesis

Most elderly asthmatics have "late-onset" disease (that is, have developed the disease as adults and not in childhood (Burr *et al.*, 1979; Rackemann, 1927)) and in contrast to

those with juvenile-onset, rarely have atopic disease. The pathogenesis of such "intrinsic" disease is hotly debated. Lack of clinical atopy does not imply absence of the airway inflammation, which is pathognomonic of asthma at all ages. The pathology underlying asthma in elderly patients has been less studied, but intrinsic disease in younger patients displays similar patterns of eosinophil activation and cellular immune response to those in atopic asthma (Walker *et al.*, 1992; Bentley *et al.*, 1992).

The search for the trigger for such inflammatory responses has produced several theories of pathogenesis which are not necessarily mutually exclusive. Firstly, despite lack of obvious clinical atopic disease, including atopic-related exacerbations and elevated serum immunoglobulin E ([IgE] levels), an atopic etiology cannot be entirely dismissed. IgE levels are recognized to fall with age (Barbee *et al.*, 1987; Dow *et al.*, 1992a), but remain a predictor of lung function in elderly populations independent of the presence or absence of asthma (Dow *et al.*, 1992a). Although the possibility of relationship between IgE levels and bronchial responsiveness (airway irritability – high levels of which characterize asthma) is not as clear in studies of elderly subjects as it is in the young, such a relationship may indeed exist (Dow *et al.*, 1992a; Burrows *et al.*, 1989).

Other putative etiologies include imbalance between β-adrenergic, α-adrenergic and cholinergic receptor pathways. Most of the work in this area has concentrated on β-adrenergic receptors with evidence of exaggeration of the "normal" age-related changes in the β-adrenoceptor activity being seen in elderly late-onset asthmatics (Connolly *et al.*, 1994, 1995a), and being directly associated not only with imbalance in autonomic regulation of airway smooth muscle (Connolly *et al.*, 1995a) but also with increased leucocyte activity necessary for airway inflammation (Nielson *et al.*, 1992). Down-regulation of glucocorticoid receptors in the elderly (Chang and Roth, 1980) may also be implicated, as the β-adrenoceptor adenylyl cyclase pathway is modulated by corticosteroid activity.

Interest in recent years has concentrated on genetic markers of bronchial irritability, atopy, and asthma. A variety of linkage markers have been identified in young subjects (Ramo *et al.*, 1978; Cookson *et al.*, 1989; Young *et al.*, 1994; Shirakawa *et al.*, 1994; Moffat *et al.*, 1994). Whether late-onset asthma is in fact a delayed phenotypic expression of the same genotype that leads to juvenile-onset disease is as yet unclear. Our own group is pursuing collaborative studies in the area and initial results are encouraging (Ruse *et al.*, 2002, 2003).

There is debate in both the medical and lay press about the relevance of atmospheric pollution in the *pathogenesis* of asthma (as opposed to merely exacerbating asthma in those with the condition). This debate is no less relevant to the elderly, especially in view of their greater lifelong exposure to a greater variety of potentially harmful respirable particles and gases. Agents hypothesized in this regard include smoke particulates (indoors from heating systems and outdoors from diesel engines), nitrogen dioxide (indoors from gas cookers (Doggon, 1996) and outdoors from car exhausts) sulphur dioxide (car exhausts), domestic cleaning products, and even "new" crops such as oil-seed rape and soya bean.

Mortality from Asthma in Old Age

Asthma mortality in the elderly is a persistent problem. Asthma mortality figures for England and Wales which were published in 1997 showed a decline of 6% per year in mortality in young patients for the 13-year period ending in 1995, but only a 2% decline for those aged 65–74 years and no fall in mortality at all for those over 75 years of age during the same period (Campbell *et al.*, 1997). Some of this discrepancy may relate to improvements in accuracy in diagnosis (deaths from asthma in old age that would previously have been regarded as being due to COPD). However, there are likely to be many other causes including age-related differences in presenting symptoms and in the approach of physicians to investigation, as well as differences in treatment response (see below). Whatever the reasons for the increasing age-related discrepancy in asthma mortality, it is surprising that the recently published revision of the British Guideline on Asthma Management (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2003) does not refer at all to the particular problems associated with asthma in old age. This is arguably a retrograde step from the revision of the previous guideline (British Thoracic Society *et al.*, 1997a).

Presentation

The classical presenting symptoms of asthma seen in young patients (intermittent breathlessness, wheezing, chest tightness, and cough, often in association with exercise, emotion, viral infection, and nonspecific respirable irritants) are also seen in the elderly asthmatic (Banerjee *et al.*, 1987; Lee and Stretton, 1972; Allen, 1988; Bailey *et al.*, 1992; Burrows *et al.*, 1991). However, because of the problems of diagnostic confusion (specificity) caused by other coexisting conditions common in this age-group (COPD, cardiac failure, angina), the sensitivity of symptoms is reduced in the elderly. Acute bronchoconstriction is less well perceived in this age-group (Connolly *et al.*, 1992a; Ekici *et al.*, 2001), as are other symptoms characteristic of asthma (Bailey *et al.*, 1992) and the predictive value of the so-called "bronchial irritability syndrome" (wheeze, cough, and chest tightness on exposure to respirable irritants such as cold air and traffic fumes) is much less in the elderly than in the young (Dow *et al.*, 1992b). Furthermore, the intrinsic (nonallergic) nature of asthma in old people, together with reduced tendency to diurnal variation, "reverse" seasonal variation (elderly asthmatics tend to be worse in the winter), and the chronic nature of the condition (i.e. even with maximal treatment, bronchoconstriction is rarely completely reversible) result in considerable diagnostic confusion with COPD. (Braman *et al.*, 1991b) As both asthma and COPD are common conditions, they are not mutually exclusive (Burrows *et al.*, 1991;

Renwick and Connolly, 1996a), but misdiagnosis and bias based on social class, age, and sex are proven phenomena. Elderly men (Dodge *et al.*, 1986) and those of lower social class (Littlejohns *et al.*, 1989a) seem more likely to receive a diagnosis of emphysema or COPD than one of asthma, irrespective of clinical features. This is very likely to influence treatment as patients under general care who have the label of 'asthma' have been much more likely to have received inhaled bronchodilators than those with a label of 'COPD' (Littlejohns *et al.*, 1989b), although it is expected that this disparity may have lessened in recent times. However, in contrast to a strong relationship between primary care prescribing and hospital admission in young adults with asthma, there is some evidence that lack of appropriate primary care prescribing in elderly patients with asthma does not increase the risk of hospital admission, although this in itself may reflect lack of diagnostic accuracy in the elderly (Renwick and Connolly, 1996a; Griffiths *et al.*, 1996).

MANAGEMENT

The first step is thus accurate diagnosis and assessment of severity. Spirometry with assessment of reversibility to inhaled or nebulized bronchodilators is essential and although the amount of reversibility detected may be less than in the young, it is usually in excess of 20% (or 200 ml). For those without significant immediate reversibility, a course of inhaled or oral corticosteroids followed by repeat reversibility assessment may be helpful. It is possible that diurnal peak flow monitoring with reversibility (at least 4 times daily (British Thoracic Society and others, 1993)) may be useful but, in addition to potential problems of unsupervised inhaler technique, the meters may also prove difficult to read for elderly people with poor vision. Assessment of bronchial responsiveness to methacholine or histamine may be helpful in a few cases (especially those in whom pulmonary function is normal or equivocal), but in addition to the lack of an accepted normal range of responsiveness in the elderly, the test is not generally available and will remain chiefly a research tool. Chest radiography and electrocardiography should be performed to exclude pulmonary edema and help exclude ischemic heart disease. Allergy testing (skin testing or serum immunology) is usually unhelpful and rarely necessary.

Unfortunately, the limited evidence available gives the impression that geriatricians pursue the above investigations in only a small percentage of wheezy elderly patients (Ghosh *et al.*, 1992). Although, the situation may have improved in the United Kingdom since the publication of the first national guidelines on the management of asthma (Connolly *et al.*, 2002), it unfortunately remains a frequent misapprehension that the elderly are unable to perform reliable spirometry. In fact, a very recent study has shown that over 80% of an unselected patient population aged 65–94 years (715 patients in total) were able to perform spirometry according to the guidelines of the American Thoracic Society. In this population, age was only an influence on performance of spirometry when associated with cognitive or functional deficits (Pezzoli *et al.*, 2003).

Management of the Chronic Condition

As mentioned above, the latest revision of the United Kingdom national guidelines on asthma management (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2003) pay no specific attention to the needs of the elderly asthmatic. However, they are widely accepted and respected and with relatively minor modifications, are generally applicable to elderly patients. This chapter does not attempt to review the guidelines in detail and the reader is strongly advised to become familiar with them. The stepwise and symptom based approach to treatment is usually a self-evident process to follow, though it may be complicated by a poorer appreciation of symptoms in old age. The guidelines suggest that the first step should be "on demand" use of regular bronchodilators. This is probably inappropriate and the prophylactic use of regular low-dose corticosteroids should be considered as a first step. Whether in addition to this, one should prescribe regular or "on demand" inhaled bronchodilators is unclear. Subsequent incremental steps are generally appropriate though emphasis should be placed on objective monitoring of severity (e.g. home peak flow measurements) over subjective complaints (or more likely the lack of these) by patients. The value of leukotriene antagonist therapy (step 3 or 4) is uncertain in the elderly. Trials of these drugs have included very few elderly patients, although in a recent systemic review of 12 randomized control trials of leukotriene antagonists versus inhaled corticosteroids in adults of all ages, the latter was superior in terms of improvement in lung function, nocturnal waking, use of rescue medication, asymptomatic days, and prevention of exacerbation (Ducharme, 2003). In "young elderly" patients, leukotriene antagonists *may* have more value (Price *et al.*, 2003).

The use of maintenance regular oral corticosteroids (Step 5) is rarely indicated in the elderly and indeed is of some concern in this subpopulation who are particularly prone to the side effects of hypertension, diabetes, osteoporosis, and supra-added infection (Braman *et al.*, 1991a). Any perception that regular oral corticosteroids are needed more commonly in elderly asthmatics comes from a small study in a highly specialist clinic population (Braman *et al.*, 1991a), probably unrepresentative of most elderly asthmatics. Where oral corticosteroids are indicated (either for exacerbations or as regular maintenance therapy) monitoring for common side effects is mandatory and prescribers should consider the need for prophylaxis against corticosteroid-induced osteoporosis (National Osteoporosis Society, 1998). It is also mandatory to regularly review symptomatology against treatment in order to prevent unnecessary prolongation of oral corticosteroid therapy. Patients on regular oral corticosteroids should carry a steroid card and be warned about sudden discontinuation and likely side effects.

In the wider sense, elderly patients need to be fully informed and educated about their asthma and for many, it is possible that involving relatives and carers in this process will improve disease control. There is no evidence that the elderly, unless cognitively impaired, are less able to cope with personal action plans for asthma management (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2003) though more research is needed in this area. It is a sad indictment of the physician's reduced ability to interact positively with vulnerable patients that asthmatics with psychotic illness have greater risk of asthma death (Joseph *et al.*, 1996). This presumably relates to poor personal control of the condition among patients with psychiatric problems. It is likely that some of the same difficulties in control are found in the chronically or acutely confused for reasons other than their asthma. In addition, the demented may subjectively perceive their asthma symptoms less well (Connolly *et al.*, 1990). These factors may also go part of the way to explain the increased differential mortality from asthma in old people. Particular care must be taken over the chronic management of the condition in the elderly psychotic or chronically confused.

Assessment and Management of Acute Condition

Age-specific mortality rates for asthma are much higher in the elderly (Lung and Asthma Information Agency, 1992a). Most asthma mortality occurs during acute exacerbations and is frequently due to potentially avoidable factors (Model, 1995). The likelihood that elderly asthmatics underestimate the degree of bronchoconstriction (see above) and thus the severity of exacerbations is reinforced by the fact that the elderly with status asthmaticus take on average three times as long to get to hospital as their young counterparts (Petheram *et al.*, 1982). The elderly also develop less tachycardia and pulsus paradoxus than the young with the same degree of bronchoconstriction (Petheram *et al.*, 1982). The latest revision of the UK asthma guidelines is appropriate for the elderly in terms of assessment and treatment of acute exacerbation. Indeed, their emphasis on objective assessment of severity should be especially welcomed by any physician dealing with elderly patients. All patients should have peak flow estimated and compared to their previous known best or to their predicted level (Cook *et al.*, 1991). All those attending hospital should have blood gas estimations (preferably when breathing room air). Chest radiography should look for evidence of pneumothorax, pulmonary edema, or infection. Unsuspected acute abnormality (often of immediate clinical significance) occurs on the majority of chest radiographs in elderly acute asthmatics admitted to hospital (Connolly *et al.*, 1995b).

Immediate treatment should include high flow oxygen (bearing in mind, however, the increased possibility of diagnostic confusion with COPD in old age and the concerns about high flow oxygen in acute exacerbations of the latter), and nebulized beta agonists and ipratropium. Oxygen treatment should be accompanied by regular assessment of blood gases as overreliance on oxygen saturation assessment may lead to increased likelihood of type II respiratory failure in patients who in fact are suffering from COPD. Conversely, if misdiagnosis is in the other direction the physician may mistakenly "tolerate" eucapnia or even mild hypercapnia in an asthmatic misdiagnosed as suffering from AECOPD. For those who do not respond to the above, intravenous salbutamol and/or aminophylline should be considered. Decisions regarding noninvasive or invasive ventilation should not be based simply on age, but need to consider functional status previous ventilatory episodes, comorbidity, and the wishes of the patient and family (see above for COPD). Mechanical ventilation may be more often considered for elderly asthmatics than the elderly patient with end-stage COPD. A detailed discussion of this area is beyond the scope of this chapter but may be found in a recent review (Nielson and Connolly, 2003).

Respiratory infection may or may not be present in patients with severe asthma. Mildly purulent sputum is common in the absence of infection due to high percentage of eosinophils (even in the elderly), but if there is objective evidence of infection (raised white blood cell count pyrexia, infiltration on chest X ray) then antibiotics should be chosen as discussed above for AECOPD. Many patients will need intravenous rehydration which must be done carefully to avoid fluid overload.

LOWER RESPIRATORY TRACT INFECTION (*see* Chapter 58, Epidemiology of Respiratory Infection)

Epidemiology and Pathogenesis

Respiratory infection is probably commoner in older people. Certainly, death from respiratory infection is commoner in the elderly than young adults. However, epidemiological studies are patchy and many such studies specifically exclude elderly people. The best estimate is that death rate from lower respiratory tract infection for over 65 years of age approaches 500 per 10 000 people per annum, perhaps 50 times higher than that in young adults.

Factors which tend to increase the risk of respiratory infection in the elderly have been detailed earlier. Briefly, these comprise a depressed immune response, an increased closing volume, an increased prevalence of chronic lung disease (in turn producing impairment of the mucociliary escalator, impaired respiratory muscle strength and endurance, breaches of the respiratory epithelium, and alteration in the mucous layer), institutionalization leading to greater proximity to other potentially infected individuals, and colonization of the upper respiratory tract by potential pathogens (gram-negative enterobacteria are particularly likely in some circumstances (Valenti *et al.*, 1978)). In addition, the increasing prevalence of comorbidities with age also predispose to increased infection (stroke and other neurological conditions increasing the risk of aspiration, achlorhydria, and impaired nutritional status, further depressing immunity, and diabetes mellitus being

the most important). It is these age-related factors, rather than factors directly relating to the process of aging itself, that are probably most important in the increased prevalence of mortality from lower respiratory tract infections with increasing age. Polypharmacy may also play a part in impairing defenses against bacterial assault (Esposito, 1987; Curwan *et al.*, 1990).

Influenza and Other Respiratory Viruses (*see* Chapter 145, Infectious Diseases)

Influenza and the common cold (usually rhinovirus) are not more common in the elderly than in young adults. However, their complication rate, morbidity, and mortality are much greater. The commonest causes of viral pneumonia are influenza viruses, especially Influenza B (Venkatesan *et al.*, 1990), and Respiratory Syncytial Virus (Vikerfors *et al.*, 1987). Hospitalization as a result of influenza is up to 20 times commoner in old people and even more so in those with other chronic illnesses (Barker and Mullooly, 1980; Gelezen *et al.*, 1987; Menec *et al.*, 2003). This poses vast strain on both primary and secondary health-care services (Menec *et al.*, 2003). Excess mortality during influenza epidemics results not only from pneumonia but also indirectly from exacerbations of COPD and asthma and from ischemic disease and stroke. A recent study from the United States has shown that mortality related to influenza in the elderly is still rising, in large part because of the rise in the elderly population overall (Thompson *et al.*, 2003). Nearly a quarter of the elderly with influenza suffer complications, most commonly acute infective bronchitis, and although this does not greatly impinge upon secondary care, it does put enormous strain on primary care provision.

The well-recognized complication of staphylococcal pneumonia following influenza in fact only accounts for about a quarter of pneumonias, even during epidemic periods, and the commonest bacterial pathogen following influenza is *Streptococcus pneumoniae* (Schwarzmann *et al.*, 1971).

Influenza vaccination using a vaccine modified each year to cover serotypic changes is usually available in the United Kingdom in late September or early October and within a month of immunization produces a 60–80% reduction in hospitalization and mortality (Barker and Mullooly, 1980; Gelezen *et al.*, 1987; Menec *et al.*, 2003; Thompson *et al.*, 2003; Schwarzmann *et al.*, 1971; Howells *et al.*, 1985). It is now offered in the United Kingdom to everyone over the age of 65 as well as to all people regardless of age with chronic renal failure, diabetes, ischemic heart disease, cerebrovascular disease, and chronic respiratory conditions. Average uptake in the United Kingdom has improved recently and now approaches 70% of those eligible (Donaldson *et al.*, 2002). However, there remain among our patients many erroneous beliefs regarding side effects (Gupta *et al.*, 2000; Findlay *et al.*, 2000; Cornford and Morgan, 1999). Perhaps surprisingly, lifestyle factors, particularly the regular participation in vigorous exercise but also self perception of optimism, and social activity and absence of "stress" are associated with enhanced immune response to the influenza vaccination in older adults (Kohut *et al.*, 2002). Apart from producing specific protection against influenza, the vaccine also produces a nonspecific stimulant effect on the type I immune response (Mysliwska, 2002).

There are four drugs licensed around the world for the treatment of established influenza. The Amantadine group (Amantadine and Ramantadine) which have been available for some time are active against only Influenza A and even here, resistance develops quickly. Furthermore, the elderly and patients with impaired renal function commonly experience adverse side effects. The neuraminidase inhibitors, Zanamivir and Oseltamivir are effective against both Influenza A and Influenza B without the common development of viral resistance. Oseltamivir has the additional benefit of being given by dry powder inhalation. Both accelerate the resolution of clinical symptoms of influenza by up to 48 hours and are most effective when given within 24–36 hours of symptom onset. They may be indicated in the treatment of the disease, particularly in the frail elderly and those with comorbidity, and may also have a role in prophylaxis of outbreaks, particularly in residential and nursing homes and in hospitals (Hirji *et al.*, 2002). However, the treatment of established "influenza" with such drugs is complicated by the problem of correctly identifying the illness. Respiratory syncytial virus produces a clinical picture almost indistinguishable from that produced by the influenza virus (Zambon *et al.*, 2001b). Nonetheless, primary care physicians are able to correctly diagnose influenza in over three-quarters of cases during epidemics, on clinical grounds (van Elden *et al.*, 2001; Zambon *et al.*, 2001a). There is current interest in rapid-result viral testing for the influenza virus with one Canadian nursing home study showing the practicability and cost-effectiveness of this approach (Church *et al.*, 2002).

As already stated, the incidence of the common cold is low in old age; however, the complication rate is much higher, particularly in terms of AECOPD with a doubling in the rate of hospitalization (Greenberg, 2002). It is estimated that vaccination against parainfluenza virus and respiratory syncytial virus may be available within 10 years. If so, it is likely to be of greatest benefit in the elderly and the very young (Olszewska *et al.*, 2002).

Pneumonia

Pneumonia is much commoner in the elderly than in younger adults. UK studies suggest an incidence of over 120 cases per 1000 population per year in the 70–79 age-group compared with 30 cases per 1000 population per year in the 20–29 age-group (Macfarlane *et al.*, 1993). The vast majority (over 90%) of deaths from pneumonia in developed countries occur in the older age-group. UK national figures suggest pneumonia as a primary cause in over 5% of deaths in people over 65 years of age (Office of Population Censuses and Surveys, 1990). In association with bacteremia, the prognosis for pneumonia in the elderly has changed

little since the 1950s (Esposito, 1987; Macfarlane, 1987; Venkatesan *et al.*, 1990).

In most of Europe, including the United Kingdom, *Hemophilus Influenzae* and *Pneumococcus* (*Streptococcus pneumoniae*) are the commonest of community-acquired pneumonias in the old (Venkatesan *et al.*, 1990; Lim *et al.*, 2000; Myint *et al.*, 2005; Zalacain *et al.*, 2003). Pneumococci, however, are becoming a less common cause in the United States. "Atypical" pneumonias in the elderly seem rare in the United Kingdom (Venkatesan *et al.*, 1990), though less so in the United States. The relative exception to this is that Mycoplasma infection is common during epidemics, which tend to occur approximately every 4 years and peak between January and March. Influenza in the elderly is not uncommonly complicated by pneumonia, which, contrary to popular medical myth, tends to be viral pneumonia secondary to the influenza virus itself or pneumonia caused by Pneumococcus or Hemophilus. Postinfluenza Staphylococcal pneumonia is however not uncommonly seen. Despite the rarity of atypical pneumonias in Britain, when outbreaks do occur in the population, it is the elderly that have by far the greatest mortality rate. Community-acquired Legionella pneumonia is rare in Britain and Europe, particularly low levels being seen in Ireland (Smith *et al.*, 2002). This has raised concerns about possible underdiagnosis (Smith *et al.*, 2002) which may not be a uniquely Irish phenomenon. Gram-negative bacilli are not an uncommon cause of community-acquired pneumonia in the US elderly population (Farr *et al.*, 1991), but this is not the experience in the United Kingdom (Venkatesan *et al.*, 1990). Similarly, multiple pathogens are said to be involved in more than 10% of cases in the United States (Marrie *et al.*, 1985), a phenomenon not reported in the United Kingdom.

Nosocomial pneumonia is the second commonest cause of hospital-acquired infection in old age after urinary tract infection. This remains true even after corrections are applied for length of stay (Saviteer *et al.*, 1988). The incidence varies from 1.5–85% in acute wards to about 8% in long-term care facilities (Connolly *et al.*, 1992b; Harkness *et al.*, 1990). Risk factors for nosocomial pneumonia vary between acute and long-term care settings. Current respiratory disease and antibiotic use do not (counterintuitively) appear to be associated with an increased risk of nosocomial pneumonia (Harkness *et al.*, 1990). However, the majority of the literature on nosocomial pneumonia comes from the United States where studies have generally included only the younger elderly (patients aged below 75 years) hospitalized following elective surgical procedures. Such patients are likely to be poorly representative of those elderly hospitalized in the United Kingdom and our own early data suggests that antibiotic use pre- or postadmission, chronic respiratory disease, low body mass index and nasopharyngeal instrumentation all significantly predict increased likelihood of nosocomial respiratory infection (Shaw *et al.*, 2002). Indeed, others have shown a high rate of oropharyngeal colonization in patients with nasogastric tubes *in situ* (Liebovitz *et al.*, 2003). Age itself as a risk factor in the acute setting may be less important than the other variables listed above. If confirmed, these findings may allow prospective identification of at risk individuals with the aim of prophylaxis. More work is thus needed here.

Nosocomial pneumonia doubles the mortality of a hospital admission and increases length of stay significantly (Shaw *et al.*, 2002). In the United States, pneumonia developing in residents of long-term care (particularly nursing homes) is often also classified as nosocomial in origin and with the increasing level of dependency and intensification of the nursing home sector in the United Kingdom, this classification may be appropriate here also. Indeed, mortality is higher in those developing pneumonia in long-term care even when they are subsequently admitted to the acute sector (Myint *et al.*, 2005). In the long stay sector, there are no identified particular risk factors apart from possibly the use of recent antibiotics (Brennen *et al.*, 1987). Pneumococcus and Hemophilus are the cause of the majority of nosocomial respiratory infections but Staphylococcus (including methicillin resistant strains) (Rello *et al.*, 1990), Pseudomonas and other gram-negative organisms may be a problem in patients with severe underlying lung disease, mechanical ventilation, or the prolonged use of antibiotics. Gram-negatives are also becoming an increasing cause of nosocomial pneumonia in general (Horan *et al.*, 1986). "Atypical" infection, particularly Legionella, may cause outbreaks or apparently random cases of infection in both acute and long stay sectors (Brennen *et al.*, 1987).

The prophylaxis of nosocomial pneumonia is an area in need of further research. It is unclear whether described "risk factors" are genuine or are merely associated variables. Nonetheless, swallowing assessment is mandatory in patients with stroke and other neurological impairments and should include monitoring of oxygen desaturation on swallowing (Smith *et al.*, 2000). As tachypnea has been shown to be an extremely sensitive method of early identification of respiratory infection in hospitalized elderly patients, respiratory rate charts should be used as a screening tool in those at risk (McFadden *et al.*, 1982).

The historical consensus from studies of pneumonia in adults over a wide age range is that mortality correlates well with age (independently) and is predicted by the following variables: diastolic hypotension, acute or worsening confusion, leucopenia, high leucocytosis, previous digoxin treatment, dehydration, vomiting, renal impairment, number of involved lobes, admission from long-term care, previous antibiotic use (and number of antibiotics), and the necessity of a ventilatory support (Zalacain *et al.*, 2003; Farr *et al.*, 1991). In addition, confirming the clinical experience of many geriatricians, a recent study from Japan has shown that mortality in elderly patients hospitalized for infection in general (including pneumonia) relates to both initial serum albumin concentration and to the rate of fall of serum albumin during acute illness (Ueno, 2003). Similar, though not identical, prognostic factors for risk of hospitalization and/or mortality have been found in studies confined to elderly patients with pneumonia. The predictive factors for increased mortality include acute or chronic confusion,

absent or delayed pyrexial response, new urinary incontinence, increasing hypoxia, systolic hypotension, atypical presentation, delay in diagnosis, and diabetes (in females only).

Two recent studies have however simplified matters, at least as far as prediction of mortality in community-acquired pneumonia is concerned. A cooperative group from United Kingdom, Dutch, and New Zealand (Lim *et al.*, 2000) has shown that in community-acquired pneumonia in adults of all ages assigning the patient "one point" each for any of: confusion; plasma urea $>7\,\text{mmol}\,l^{-1}$; respiratory rate $\geq$ 30/min; low systolic (<90 mmHg) or diastolic (≤ 60 mmHg) blood pressure; age ≥ 65 years, results in a mortality score for each point gained as follows: $0 = 0.7\%$; $1 = 3.2\%$; $2 = 3\%$; $3 = 17\%$; $4 = 41.5\%$; $5 = 57\%$. This has become known as the *CURB65* score. Very recently, the CURB score has been applied to elderly (>65 years) patients alone in a prospective UK study and shown to be almost as sensitive but less specific as when applied to all age-groups (Myint *et al.*, 2005).

Factors predicting hospitalization in contrast, comprise male gender, current smoking, chronic lung disease (particularly COPD), previous history of myocardial infarction (males only), and hypertension (females only) (Venkatesan *et al.*, 1990; Starczewski *et al.*, 1988; LaCroix *et al.*, 1989). Of all the above factors, the most amenable to intervention is delay in diagnosis which in turn is likely to be related to atypical presentation (Starczewski *et al.*, 1988).

A history of the regular or constant production of purulent sputum even between exacerbations should alert the physician to the diagnosis of bronchiectasis. Diagnosis may be confirmed by CT or high-resolution CT (HRCT) scanning (McGuinness and Naidich, 2002). Recent evidence has however shown an effect of normal aging on the relative diameter of the bronchial lumen and its accompanying artery such that the normal elderly lung may be misinterpreted as bronchiectatic (Matsuoka *et al.*, 2003). Preventative therapy comprises regular postural drainage. Supportive treatment for established exacerbation is similar to that discussed above for pneumonia with the addition of increased postural drainage (possibly using oxygen via nasal cannulae as postural drainage may produce hypoxia). For effective drainage, CT scanning to confirm affected lobes and segments is extremely useful. Even in the absence of pseudomonas infection, there is a need for broad-spectrum antibiotics with β-lactamase activity and high-dose therapy may be needed to achieve adequate sputum penetration (Hill *et al.*, 1986). There is some evidence that using such supranormal doses also increases the exacerbation-free interval (Hill *et al.*, 1986; Cole and Roberts, 1983). Recurrent infection with P. aeruginosa is particularly problematic. Oral ciprofloxacin is a first line treatment but in most cases the organism develops early resistance to this agent. Frequent relapses may respond to maintenance low-dose oral antibiotics or even to inhaled antibiotics (Hill *et al.*, 1986). Hemoptysis is usually relatively minor and self-limiting. If it is more severe however and especially where the patient is at poor anesthetic risk (a not uncommon scenario), embolectomy is a possible therapeutic alternative. Embolization of the bronchial arteries is now possible percutaneously (Wong *et al.*, 2002). Surgical excision (not during exacerbations) is less commonly performed in recent years, but it may still have a place in an otherwise fit elderly patient with localized but troublesome disease (Kutlay *et al.*, 2002).

Tuberculosis and Other Mycobacterial Infections (*see* Chapter 47, Valvular Disease in the Elderly)

The prevalence of tuberculosis is once more increasing in the western world with a disproportionate increase in prevalence in the elderly (Powell and Farer, 1980; Teale *et al.*, 1993; Duffield *et al.*, 1996; Leitch *et al.*, 1996). This may be partly due to increasing urban deprivation which disproportionately affects the elderly (Kearney *et al.*, 1994), and to the relative ease of transmission in residential and nursing homes (Morris and Nell, 1988) (semiclosed environments populated by immunocompromised individuals). Whatever the reason for the increase, tuberculosis is commoner in the elderly with notification rates approximately 5 times that of younger adults in the 65–75 age range (approximately, 20 per 10 000 population), and up to 12 times that of young adults in those over 75 years of age in the United Kingdom (approximately, 60 per 10 000 population) (Duffield *et al.*, 1996; Leitch *et al.*, 1996).

Presentation

Of further concern is the relative difficulty in diagnosis in this age-group. Most cases of tuberculosis in the elderly represent reactivation of previous (often unrecognized) disease. This may be precipitated by the depressed immunocompetence of normal aging, malnutrition (often in association with alcohol excess), HIV infection, diabetes mellitus, corticosteroid therapy, gastrectomy (Snider, 1985) and even cigarette smoking (Doll and Peto, 1976).

Both the clinical presentation and radiological manifestations of tuberculosis in the elderly may cause confusion. Presenting features of tuberculosis are often similar to those in younger patients with weight loss, cough, hemoptysis and pyrexia, and night sweats. However, in addition, older people are more likely to have hyponatremia, hypokalemia, hypoalbuminemia, and abnormal liver function tests (Morris *et al.*, 1989). Miliary tuberculosis is commoner in elderly people; this presentation occurring in up to 1 in 20 cases (Teale *et al.*, 1993). Clinical presentation in such cases may be atypical and subacute. Conversely, renal and genitourinary tuberculosis seems less common in older people (Teale *et al.*, 1993) but when present, is often asymptomatic. Bone and joint tuberculosis is recognized to affect approximately 5% of elderly with the disease (Teale *et al.*, 1993). It most commonly involves the spine, often with paravertebral infection.

Worryingly, a failure to diagnose the condition during life in the elderly is evidenced by an up to 20-fold disparity

(versus the young) in the number of cases diagnosed post mortem (Teale *et al.*, 1993; Counsell *et al.*, 1989) with nearly 60% of patients with active disease not diagnosed during life. While this, in part, may reflect a reluctance on the part of elderly patients and their physicians to undergo invasive diagnostic procedures such as bone marrow aspiration, and bronchoscopy, it also suggests a low index of suspicion amongst physicians, which in turn may be in part a reflection of atypical *clinical* presentation and in part due to the increased likelihood of atypical *radiological* presentation.

The radiological features of tuberculosis in the elderly are not entirely dissimilar to those in younger patients, but there is a greater prevalence of mid- and lower-zone shadowing (Teale *et al.*, 1993; Morris and Nell, 1988). Indeed, less than 10% of chest radiographs have isolated apical shadowing. Cavitation is present in only a third (Morris *et al.*, 1989). Disseminated tuberculosis in old age may present as pyrexia of unknown origin, a negative tuberculin test and a normal chest radiograph – "cryptic TB". The commonest radiological appearance, however, is that of old healed tuberculosis with a peripheral calcified primary complex and calcified hilar nodes together with upper zone patchy calcification and possibly pleural thickening ("capping"). Pleural effusions are present in approximately 15% (Teale *et al.*, 1993; Morris and Nell, 1988). Aside from disseminated cryptic TB, a normal chest X ray almost excludes tuberculosis with the very rare exception of endobronchial postprimary disease (Ip *et al.*, 1986).

Besides radiography, other useful screening investigations include CRP (C-reactive protein) or ESR (erythrocyte sedimentation rate) estimation and tuberculin skin testing, although the latter must be interpreted with caution in elderly patients with possible postprimary disease. Biochemical abnormalities (as discussed above) are common, as is a normochromic normocytic anemia and mildly raised peripheral white blood cell count.

A grade 3 or 4 positive Heaf skin test (a ring of six confluent papules filled in the center with induration with or without ulceration) or a >10 mm reaction on Mantoux skin testing is diagnostic of present *or past* tuberculosis infection. Thus, the emergence or "conversion" from skin test negativity to skin test positivity suggests active disease. However, repeated skin testing is known to produce a "booster" effect. This phenomenon occurs in those who have suffered previous (often asymptomatic) infection but their skin test reactivity has fallen over many years and is subsequently stimulated once again by skin testing so that a first test is negative but a second or subsequent test may be positive (Snider, 1982). More commonly, a tuberculin skin test may be falsely negative in association with other infection (bacterial or viral), corticosteroid use, sarcoidosis, lymphoma, malnutrition, or even massive overwhelming tuberculous infection.

Isolation of mycobacterium tuberculosis is the only *absolute* confirmation of active infection. The organism is isolated from approximately two-thirds of elderly patients treated for active disease, a slightly lower percentage than that in younger patients (Teale *et al.*, 1993). Smear positivity (identification of the organism by simple Ziehl–Neelsen or Kinyoun staining of sputum) in an untreated patient is very highly suggestive of infectivity. More commonly, sputum culture in a Lowenstein–Jensen medium is necessary and may require up to 8 weeks (or longer for atypical mycobacteria). Common practice is to send at least three good sputum samples for microscopy and culture before any antituberculous therapy is given. This is important not only for confirmation of diagnosis but also to establish antimicrobial sensitivities. When sputum production is difficult, this may be aided by physiotherapy and inhalation of ultrasonically nebulized saline. Bacterial examination of *induced* sputum in smear negative patients or in those who are unable to produce sputum is a useful technique that may avoid the need for bronchoscopy and washing (McWilliams *et al.*, 2002). The diagnostic yield from this technique is high even when parenchymal involvement is absent from the chest radiograph (Conde *et al.*, 2003). Bronchoscopy and washing of radiologically affected areas however may still be occasionally required, as may aspiration of pleural fluid together with pleural biopsy. When renal or genitourinary infection is suspected, three samples of early morning urine should be sent for microscopy and culture. Bone marrow aspiration, liver biopsy, synovial aspiration, or lymph node biopsy may be helpful in disseminated disease.

Treatment

The BTS has published revised guidelines for the treatment of tuberculosis (Joint Tuberculosis Committee of the British Thoracic Society, 1998), and separate recommendations for the treatment of opportunistic mycobacterial infection (Sub Committee of the Joint Tuberculosis Committee of the British Thoracic Society, 2000) as well as the prevention and control of tuberculosis (Joint Tuberculosis Committee of the British Thoracic Society, 2000). Perhaps the most important point to note is that "*the assessment and treatment of tuberculosis and of atypical mycobacterial disease is a specialist area, and all patients of whatever age with proven disease or in whom the diagnosis is suspected should be referred to respiratory physicians*". The evidence base for this recommendation is good. Nonetheless, it is appropriate to summarize current recommendations. For pulmonary disease, a 6-month course of chemotherapy comprising isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months followed by isoniazid and rifampicin for another 4 months is generally advised irrespective of the bacterial status of the sputum. Ethambutol is often omitted unless there is strong suspicion clinically of resistant mycobacteria (e.g. in patients from the Asian subcontinent or those recently returned from areas of the world where resistance is common). In the absence of valid susceptibility data, pyrazinamide and ethambutol should be continued with rifampicin and isoniazid for the whole 6-month period. Routine pyridoxine treatment is not recommended except for those at particular risk of peripheral neuropathy. Visual acuity should be checked prior to starting

treatment with Ethambutol. Renal function should be checked similarly before ethambutol is commenced and liver function ascertained before commencing isoniazid, rifampicin, or pyrazinamide. Liver and renal function should be monitored regularly during treatment. However, a transient hepatic enzyme rise is common and does not indicate the need for modification of treatment unless hepatitis or jaundice also occurs. Treatment side effects seem to be commoner in older people (Teale *et al.*, 1993; The British Thoracic Society Research Committee and the Medical Research Council Cardio-thoracic Epidemiology Research Group, 1991). Overall, almost one in five elderly people will experience treatment side effects. Smear positive patients or those suspected of being infective should be hospitalized until they have received adequate chemotherapy for at least 2 weeks. Local infection control policies should be adhered to and these will include patient isolation in rooms with active ventilation to the external environment where possible.

The treatment of tuberculosis is not complete without contact tracing which is performed by Public Health Departments. Tuberculosis is a notifiable condition. The details of contact tracing are given in the BTS Guidelines (Joint Tuberculosis Committee of the British Thoracic Society, 2000).

Atypical mycobacterial infection is relatively rare in Britain. There is no direct evidence that it is common in older people though some atypical mycobacteria seem to be more likely to cause infection in patients with preexisting respiratory conditions which may be commoner in the elderly (Connolly *et al.*, 1985). Clinical features of atypical mycobacterial disease are summarized in the BTS guidelines (Sub Committee of the Joint Tuberculosis Committee of the British Thoracic Society, 2000) but are generally similar to those of "true" tuberculosis, although upper lobe and pleural involvement appears commoner (American Thoracic Society, 1990). As already mentioned, culture of nontuberculous mycobacteria may take longer than that of mycobacterium tuberculosis and sensitivity patterns are often unusual.

LUNG CANCER AND OTHER THORACIC NEOPLASMS (*see* Chapter 128, Cancer and Aging and Chapter 129, Oncological Emergencies and Urgencies)

Aging is a major and an independent risk factor for development of malignant disease. Both lung cancer and pleural mesothelioma are commonest in older people. However, partly because of nihilistic attitude toward diagnosis and treatment, the management of thoracic neoplasms in the elderly has not advanced at the same rate as that of the same conditions in younger patients.

Bronchogenic Carcinoma

The prevalence and mortality of lung cancer is highest in the elderly reaching a peak at 80 years in men and 70 years in women. In elderly men mortality has, in common with that in younger men, fallen slightly in the last decade though mortality continues to rise in women over the age of 60 (Lung and Asthma Information Agency, 1993; Woll and Thatcher, 1995). Almost 95% of lung cancer is caused by cigarette smoking with the highest rates not surprisingly occurring in those with the highest uptake of smoking habit (men born between 1910 and 1930) (Lee *et al.*, 1990). Smoking remains a risk factor for a bronchogenic carcinoma for as much as 30 years after proven cessation, but it is important in clinical terms to understand that the beneficial effect on cancer risk begins soon after cessation and gradually increases over many years (Ebbert *et al.*, 2003). It is also recognized that active smoking is a risk factor for more extensive disease at presentation (Kobrinsky *et al.*, 2003). Asbestos exposure is a further contributing factor in a minority of cases and is multiplicative to the risk caused by cigarette smoking (Muscat and Wynder, 1991). Despite increasing interest in the possible role of lung cancer screening in older smokers, the cost-effectiveness of such an approach is not yet established (Mahadevia *et al.*, 2003).

Presentation

The presenting symptoms of lung cancer in the elderly do not differ from those in younger patients (chest pain, cough, hemoptysis, breathlessness, weight loss, etc). However, elderly patients tend to present with more advanced disease (O'Rourke *et al.*, 1987). In contrast with many other respiratory and nonrespiratory conditions in elderly people, nonspecific presentation is unusual unless patients present with infective complications. On the other hand, the existence of multiple pathology in many elderly patients means that lung cancer may be discovered as a coincidental finding during investigation of other conditions.

Appropriate investigation is essential and should not depend upon age even if curative treatment is not contemplated (histological confirmation of cancer type may be invaluable in management [see below]). The first step is a cytological examination of expectorated sputum. Success however is critically dependent upon not only the patient's ability to expectorate but also the skill and experience of the cytologist. The use of nebulized saline may aid sputum expectoration. Cytological examination of fine needle aspirates under computed tomographic (CT) scan control may also be helpful. Flexible bronchoscopy is safe and well tolerated even in the very elderly (Knox *et al.*, 1988; Davies *et al.*, 1997; Matot *et al.*, 1997). The advantages of accurate histological diagnosis are discussed below but in at least one series, 60% of bronchoscopies resulted in the exclusion of a tumor and the diagnosis of insignificant or curable pathology (e.g. tuberculosis) instead (Knox *et al.*, 1988). An alternative and noninvasive approach in the very frail or those who refuse bronchoscopy may be the use of computerized tomography though this will clearly never identify histological type.

Apart from histological diagnosis, the other indication for bronchoscopy or computerized tomography may be for tumor staging.

There is considerable evidence that elderly patients are less likely to be *referred* for bronchoscopy. One (admittedly rather elderly) study showed rates of histological confirmation of 40–60% in the elderly compared to 80% in younger patients (Joslin and Rider, 1993). Patients with suspected lung cancer who are seen or reviewed by chest physicians are more likely to have histological confirmation and active treatment than those under the care of geriatricians or general physicians (Brown *et al.*, 1996). The older patients in the same study were also less likely to be reviewed by a chest physician. It may however be that some of this discrepancy is not inappropriate as relatively fit elderly patients with possible lung cancer as a single pathology are more likely (appropriately) to be referred to respiratory physicians or even thoracic surgeons, whereas, those with multiple pathology who are perhaps less fit for investigation or treatment are more likely (appropriately) to be referred to geriatricians – that is, a case-mix effect. Nonetheless, a recently published survey by the Royal College of Physicians in the United Kingdom has shown large age-related differences in both management and survival of patients with bronchogenic carcinoma irrespective of case-mix, even when managed by respiratory physicians (Peak *et al.*, 2003). It is thus incumbent upon both respiratory physicians and geriatricians to have an active approach to investigation and management. Unfortunately, elderly patients with lung cancer are also less likely to find themselves directed to therapeutic trials of lung cancer treatment (Trimble *et al.*, 1994).

Recent studies have revealed that patients (not exclusive to, but including the elderly) with lung cancer feel that their worries and concerns are being poorly met. This is particularly true of worries about psychosocial issues rather than physical symptoms (Hill *et al.*, 2003; Murray *et al.*, 2003). These studies reemphasize the need for an "old-fashioned" caring professional attitude in the management of this patient group.

Non–small Cell Lung Cancer (NSCLC)

Squamous cell carcinoma is the commonest form of lung cancer in old age, accounting for 45–70% of cases (Knox *et al.*, 1978). Other non–small cell types (adenocarcinoma, bronchoalveolar carcinoma, and large cell carcinoma) together account for 20–25% of all cases.

As surgical resection is at present the only chance of cure for non–small cell lung cancer, staging is vital in assessment. Approximately, half of non–small cell carcinoma is resectable at presentation. Full details of staging criteria are beyond the scope of this chapter, however, the single most important factor in staging is mediastinal lymph node involvement. Mediastinal node *size* can be assessed by CT or MR scanning and/or by bronchoscopy although enlarged mediastinal nodes should, if possible, be biopsied if there is no other evidence that the tumor is inoperable as lymphadenopathy does not always indicate metastatic spread. The role of positron-emission tomographic (PET) scanning remains to be established.

Distant (extrathoracic) spread is in theory a contraindication to surgical intervention. However, there is no evidence that ultrasonic or invasive search for distant metastases is valuable unless physical examination or simple biochemical or hematological testing suggests distant metastases.

Staging by uncomfortable and/or invasive methods is difficult to justify if the patient is unfit for surgical intervention. Age alone, however, is not a contraindication to surgery. The presence of comorbid multiple pathology should be assessed in the same way as in younger patients (Hasse *et al.*, 1998). Particularly, attention must be given to respiratory function and in borderline cases lung isotope scanning may help determine whether the patient has sufficient respiratory reserve to undergo pneumonectomy (is the involved lung contributing a significant proportion of the patient's vital capacity or FEV_1?). In most centers, elderly patients are much less likely to undergo pneumonectomy or indeed any form of surgical intervention. However, studies from several centers have indicated 5-year survival of between 35–50%, a little different from that in younger patients (Sherman and Guido, 1982; Shirakusa *et al.*, 1989; Mane *et al.*, 1994). A more recent retrospective study of prognostic factors for survival in surgically treated non–small cell lung cancer, advanced age (over 70 years) was not an independent prognostic factor. Survival was over 50% in both groups, the only survival predictor being tumor size (Yamamoto *et al.*, 2003). Despite all the above evidence, there remains recent data to suggest that older patients are less likely to be referred for surgery even when the tumor is operable (Turner *et al.*, 1999).

Radiotherapy for nonsmall cell lung cancer is usually used for palliation (chiefly for hemoptysis and bony pain) although radical radiotherapy may occasionally be curative. Some elderly patients with cardiac respiratory or musculoskeletal conditions may find difficulties with the prolonged supine position needed for radiotherapy (Pignon and Scalliet, 1998) however, no excess of acute or late toxicity from radiotherapy has been found in elderly patients (Pignon and Scalliet, 1998). Radiation pneumonitis occurs in up to 15% of patients irrespective of age though there is some suggestion that its severity may be greater in the elderly (Koga *et al.*, 1998). The use of postoperative radiotherapy (PORT) after radical surgery has recently been called into question, as a large meta-analysis suggested worse outcomes in postsurgical patients treated with radiotherapy (PORT Meta-analysis Trialists Group, 1998). Radical radiotherapy in isolation can be very effective for small tumors and may be used as an alternative to surgery in the very frail elderly patient or those with extensive comorbidity (Dosoratz *et al.*, 1993). Continuous hyperfractionated accelerated radiotherapy (CHART) may have survival advantage for the elderly with unresectable disease and can be delivered over 12 days as opposed to 6 weeks. Two studies have shown such survival advantages even in octogenarians with nonsmall cell lung cancer (Saunders *et al.*, 1997; Bonner *et al.*, 1998). Chemotherapy has traditionally had little part to play in the treatment of non–small cell lung cancer. However, as palliation, it may be useful in patients with advanced disease and age is not a

prognostic factor in such cases. Current research is addressing whether combination chemotherapy is more effective than single agent treatment in such circumstances (Hickish *et al.*, 1998).

Small Cell Carcinoma (SCLC)

Small cell lung cancer accounts for 20–25% of all lung cancers in the elderly. It is currently increasing as a proportion of all bronchogenic carcinoma. The over 70s comprise about 20% of all small cell lung cancer patients (Smit *et al.*, 1989). SCLC has very different growth patterns and clinical characteristics from non–small cell lung cancer (NSCLC), it is a rapidly growing tumor and has almost always metastasized by the time of diagnosis: Thus, surgery has little or no place in its management. Conversely, it is highly sensitive to therapeutic agents but responders have a very high relapse rate. Combination chemotherapy has improved median survival but produces long-term survival in only a minority of patients. Staging should be performed as for NSCLC.

There are few randomized trials of chemotherapy for SCLC in the elderly. Treatment is therefore often guided by local experience or by case reports (Ueda *et al.*, 2002). Once again, age alone is a poor predictor of either response to treatment or of the occurrence or tolerability of side effects. Approximately, two-thirds of the elderly when first diagnosed with SCLC have detectable metastatic disease. Small cell lung cancer usually responds to cisplatin, vincristine, etoposide, cyclophosphamide, and doxorubicin. However, the use of multiple agent "high intensity" chemotherapy has produced a high level of toxicity (even in the young) without much evidence of extra survival benefit (Kelly *et al.*, 1991), and is associated with increased likelihood of bone marrow toxicity in the elderly.

However, untreated SCLC has a median survival of approximately 3 months and most patients will respond well to chemotherapy the prolongation of life and an increase in quality of life. In the last 15–20 years, both research and clinical practice has generally focused on single agent etoposide (Carney *et al.*, 1990; Clark *et al.*, 1994). This produces a response rate of over 70% with an increase in median survival to about 7 months. Etoposide is administered orally therefore reducing the need for hospitalization and frequent outpatient attendance. Teniposide produces similar or slightly better results than etoposide in the elderly. Carboplatin has also been shown to be valuable (Tummarello *et al.*, 1992; Raghaven *et al.*, 1992).

The combination of radiotherapy and chemotherapy may be used for palliation in SCLC without excessive toxicity (Geremic *et al.*, 1998). Prophylactic cranial radiotherapy (the brain being a common site for early recurrence) may be added to multiagent or single agent chemotherapy to produce remission in patients with limited disease. In a very small number of patients with very limited disease, surgical resection is occasionally employed despite the absence of trial data. Relapse occurs in the vast majority of patients and has a uniformly poor prognosis in all age-groups.

Pleural Mesothelioma

Pleural Mesothelioma is caused by airborne respirable asbestos (particularly blue asbestos) dust usually over a period of years. Time lapse between exposure and disease is 20–40 years. In the United Kingdom, it primarily occurs in response to occupational exposure (shipyard workers, plumbers and central heating engineers, asbestos factory workers, demolition workers, etc.). However, in view of the latent period between exposure and presentation, it is most common in the elderly, particularly the 65–74 year age-group (Lung and Asthma Information Agency, 1992b).

Presentation

Mesothelioma most commonly presents with breathlessness due to pleural effusion or with chest wall pain, which may or may not be pleuritic. Conventional pleural biopsy and aspiration only yield positive diagnostic results in about 50% of patients (Boutin and Rey, 1993). Thoracoscopy with direct visualization of the pleura and hence the tumor (well tolerated in the elderly) almost always provides diagnostic material on biopsy (Boutin *et al.*, 1993).

Mesothelioma is uniformly fatal but more rapidly so in the elderly in whom median survival is less than 12 months (De Pangher *et al.*, 1993). Indeed, in one recent series, median survival was less than 8 months and was inversely related to age (Magnani *et al.*, 2002).

As mesothelioma is a compensatable industrial disease (and because of the possibility of alternative treatable conditions) even in a patient with previous asbestos exposure and typical presentation (van Hengel *et al.*, 2001), where diagnosis is not achieved by pleural aspiration biopsy, thoracoscopy is indicated.

Mesothelioma is uniformly insensitive to chemotherapy and radiotherapy and hardly ever resectable. Treatment is palliative – chiefly alleviation of breathlessness and chest pain. Pain relief may be by pharmacological means including opiates and nonsteroidal anti-inflammatory agents often with adjuvant low dose major tranquilizers. Pharmacologically intractable pain is however not unusual but can very often be controlled by nerve blocks or surgical techniques such as CT – guided cordotomy (Kanpolat *et al.*, 2002).

In a small number of patients fit enough for radical surgery (either pneumonectomy or pleurectomy) and postoperative chemotherapy, survival may reach a mean of nearly 3 years (Aziz *et al.*, 2002). Despite historical resistance to chemotherapeutic agents, research efforts have focused on combination chemotherapy with cisplatin, oxaliplatin, gemcitabine, ralitraxed, and pemetrexed and also on the single agent ranpirnase, and on postoperative intensity-modulated radiotherapy (Masano *et al.*, 2001; Nowak *et al.*, 2002; Hughes *et al.*, 2002; Mikulski *et al.*, 2002; Ahamad *et al.*, 2003).

Even without histological confirmation, mesothelioma is a compensatable industrial disease in the United Kingdom. However, histological confirmation will aid separate claims

through the courts, which usually results in much higher levels of settlement. Local trade union representatives can offer advice and support in the pursuit of legal claims.

Other Lung Tumors

Lymphomas

Although lymphomas are rarely confined to the thorax, mediastinal involvement, and parenchymal infiltration are not uncommon. There has been a rise in incidence of lymphomas since the 1960s. The incidence of non-Hodgkin's lymphoma increases directly with age with about a third of patients being over the age of 70. Conversely, Hodgkin's disease has a bimodal incidence with peaks at about 30 years and 65 years (Cartwright *et al.*, 1987). Increasing age adversely affects survival (Guinee *et al.*, 1991; Vose *et al.*, 1988).

There have been promising advances in the development of intensive therapy regimes specific to the elderly with Hodgkin's disease though elderly patients seem less able to tolerate standard regimes (Levis, 1993; Urkamp *et al.*, 1992).

Non-Hodgkin's lymphomas can be divided into three subgroups in terms of prognosis. High-grade disease responds well to multiagent chemotherapy in younger patients but the elderly treated with similar combinations suffer unacceptable levels of toxicity. Regimens including podophyllotoxins have been developed for the elderly and seem to produce useful response with minimal toxicity (Tiralli *et al.*, 1992).

Carcinoid Tumors

About 20% of all cases of carcinoid tumors occur in the elderly. However, they are rare and account for less than 1% of all thoracic tumors. Age adversely affects prognosis (Greenberg *et al.*, 1987). Occasionally, carcinoid tumors may metastasize. In such cases, there is no effective treatment.

Squamous Papillomas

These are relatively rare tumors usually occurring in smokers. They may be solitary or multiple and vary in histology from completely noninvasive to invasive and metastatic carcinoma. Endoscopic removal is a treatment of choice.

Other Thoracic Tumors

These comprise hamartomas and other benign lung tumors, mediastinal tumors (mainly teratomas and neurogenic tumors), salivary gland tumors and thymomas. All are rare in the elderly and will not be discussed further.

Palliative Therapy and Quality of Life in Lung Neoplasms in the Elderly

It is logical to assume that response to chemotherapy or radiotherapy (as assessed by radiological tumor shrinkage) will be associated with improved quality of life and levels of activity. However, this has not been carefully assessed in the elderly. Performance scores used to measure activity and quality of life in cancer are usually not appropriate for elderly patients and there is need for appropriate methods of assessment and therefore for validation of ADL and quality of life scores.

The palliative use of radiotherapy for treatment of bony pain and hemoptysis has already been discussed. Laser photocoagulation of large endobronchial tumors may improve stridor and breathlessness. The judicious use of nonsteroidal anti-inflammatory agents may improve bone pain. There is a wealth of literature on pain control in cancer which is beyond the scope of this chapter. However, it is a damning indictment that approximately one-third of cancer patients still suffer pain and other distressing physical symptoms such as nausea in the latter stages of their illness. Referral to pain-control teams, palliative care teams and inpatient or outpatient hospice care should always be considered. Macmillan nurses play an invaluable role in both physical palliation and emotional support.

As in many aspects of care in elderly patients, the physician often needs to communicate not only with the patient themselves but also with their relatives. The request that the doctor does "not tell the patient the bad news" is frequently heard from caring relatives. Such a request must always of course be taken seriously as the relatives usually have deep insights into the emotional needs and capabilities of the patient. However, it is essential to remember that the primary relationship is between physician and patient and should the physician be seen by the patient to be withholding information, this will seriously damage the doctor–patient relationship and erode trust. A general policy of open access to (without insistence upon) information from doctor to patient should operate regardless of patient age.

PULMONARY EMBOLIC DISEASE

Pulmonary embolic disease is common in the elderly, particularly among those who are ill. It is estimated that over half of subjects with pulmonary embolism are over 65 years of age (PIOPED Investigators, 1990). Age-related factors include immobility, hemiplegia, cancer, recent surgery, and hip fracture. Typical features of pulmonary embolism in the elderly differ little from those in the young (Stein *et al.*, 1991). These are usually acute, and comprise breathlessness, severe central constricting chest pain (in large hemodynamically compromising pulmonary emboli), pleuritic chest pain (in more peripheral emboli) and hemoptysis. Occasionally, symptoms may be chronic or subacute due to multiple emboli and comprise gradual onset of breathlessness and right-sided cardiac failure. Only about one-fifth of patients present atypically (usually with radiological abnormalities most commonly linear atelectasis). Patients with very large emboli will present with chest pain, breathlessness, and severe hypotension often

with a right ventricular heave, a high jugular venous pressure, and a prominent pulmonary second sound (signs of right cardiac strain).

Physical signs as well as those of right-sided strain include tachypnea, cyanosis, tachycardia, localized crepitations, pleural rub, and (particularly in a patient with preexisting asthma or COPD) wheeze. Atrial fibrillation may be precipitated, particularly in the elderly.

Unfortunately, diagnosis based on clinical features or on investigations short of pulmonary angiography (or more commonly these days CT pulmonary angiography) is inaccurate with both high false positive and high false negative rates (PIOPED Investigators, 1990; Dalen, 1991). Diagnosis may be particularly difficult in patients (often the elderly) with previous respiratory disease. The accuracy of the ventilation/perfusion (V/Q scan) may be particularly compromised by this. Simple screening tests may do little other than enhance clinical suspicion. Electrocardiogram will show right-sided strain in a minority of cases. Abnormalities include right bundle branch block, "P pulmonale", S wave in lead 1, and Q wave and T wave inversion in lead 3 ($S_1Q_3T_3$). Atrial fibrillation may be present. Blood gas estimation frequently reveals hypoxia in association with hypocapnia. These findings are not specific. The chest X ray may be normal (thus helping exclude other pathologies) or occasionally may show effusions, atelectasis, or wedge-shaped areas of hypoperfusion.

An entirely normal V/Q scan essentially excludes pulmonary embolism. The presence of single or multiple perfusion defects with normal ventilation (a mismatched scan) is highly suggestive of pulmonary embolic disease. However, matched ventilation perfusion defect(s) will occur if the scan has been delayed for 24 hours or more. Such a scan may be classified as having a low or intermediate probability for pulmonary embolism, but up to a third of patients with scans so classified will indeed have pulmonary embolism (PIOPED Investigators, 1990).

Arguably, the absolute diagnosis of pulmonary embolism is less critical in the presence of a proven diagnosis of deep vein thrombosis (DVT). Ultrasound and impedance plethysmography is an investigation of choice for potential DVT. It is as accurate as venography without the complications (Stein *et al.*, 1991).

However, the only absolutely definitive diagnostic investigation for pulmonary embolism is angiography (including CT angiography). This may be difficult or impossible in ill frail elderly patients and is not without risk, although the limited evidence available suggests the risks are no higher in the normal elderly as compared with younger age-groups (Stein *et al.*, 1991; Raskob and Hull, 1990).

National guidelines exist for the diagnosis and management of pulmonary embolic disease and the reader is strongly referred to these (British Thoracic Society, 1997b).

Treatment

Immediate supportive therapy comprises supplemental oxygen (usually high inspired percentage as dictated by blood gas measurement) and analgesia in patients with pleuritic chest pain. Anticoagulation should be instigated with low molecular weight heparin (which does not require monitoring). Following 5–7 days of heparinization, maintenance therapy should be with oral anticoagulation usually aiming for an International Normalized Ratio (INR) of between 2 and 3. There should be 2 or 3 days overlap between establishment of a therapeutic INR and the discontinuation of low molecular weight heparin. Recent evidence suggests that the classical duration of oral anticoagulation is excessive and that for pulmonary embolism 3 months anticoagulation is adequate, 1 month being adequate for DVT, provided there are no persisting risk factors (British Thoracic Society, 1997b; Research Committee for the British Thoracic Society, 1992).

Anticoagulation will need frequent hematological monitoring. Patients should receive written and verbal information regarding side effects and what is to be done should these arise, as well as information on drug interactions and which drugs are to be avoided. Access to outpatient warfarin clinics may prove difficult for elderly patients and domiciliary phlebotomy may need to be provided in some cases.

A small proportion of patients who suffer recurrent pulmonary embolism despite anticoagulation may benefit from the insertion of a filter device into the inferior vena cava. These can now be inserted by a minimally invasive percutaneous procedure.

In patients with catastrophic acute pulmonary emboli associated with hemodynamic compromise, the prognosis is dire with a mortality rate of over 80% (Research Committee for the British Thoracic Society, 1992). Thrombolysis may be beneficial and is recommended in National Guidelines in these circumstances (Research Committee for the British Thoracic Society, 1992), and a minority of patients may be appropriate for surgical pulmonary embolectomy. This latter surgery can be performed as an open procedure or by percutaneous suction catheterization. It is clear that many frail elderly patients may not be suitable for such aggressive invasive measures. This is probably particularly true of those with medical conditions, which put them at the highest risk of pulmonary embolism (stroke, cancers, a frail elderly female patient with fractured neck of femur). Prophylaxis of pulmonary embolism in the context of immobility, stroke, and surgery is discussed in **Chapter 55, Venous Thromboembolism**.

FIBROTIC (INTERSTITIAL) LUNG DISEASES

These conditions comprise a wide variety of pathologies and etiologies and are generally taken to exclude malignant conditions and infection.

Epidemiology

Many fibrotic interstitial diseases have a higher prevalence in elderly people. These include the commoner conditions of fibrosing alveolitis in association with connective tissue

disorders, cryptogenic fibrosing alveolitis, and the pneumoconioses associated with industrial dust exposures. Some of the rarer conditions are also commoner in the elderly. These include Wegener's granulomatosis, amyloidosis, and cryptogenic organizing pneumonia. Conversely, sarcoidosis is extremely rare *as a primary presentation* in elderly people and chronic eosinophilic pneumonia is less common than in younger adults. Mortality from interstitial lung disease as a whole is increasing in the western world and is highest in the elderly, most particularly among those in the 75–84 age-group (Mannino *et al.*, 1996).

Although details of presentation, investigation, and treatment of the specific conditions are given below, it is important to emphasize that these conditions are not common enough for geriatricians or general physicians to become experienced in their management. Thus, all diagnosed or suspected cases, regardless of age, should be referred to respiratory physicians. National guidelines exist for the diagnosis and treatment of these conditions and the reader is once again strongly referred to them (British Thoracic Society, 1999).

Investigations

Patients' main initial complaint is usually breathlessness on exertion. Given the large number of more common causes of this symptoms, interstitial lung disease is not usually at the top of the average physician's differential diagnosis and, thus, many patients undergo a variety of investigations before interstitial lung disease is considered a significant possibility or probability. Thereafter, the investigatory route is similar, whatever the eventual specific diagnosis. This will thus be outlined first followed by more details of particular conditions.

Interstitial lung diseases classically produce a restrictive ventilatory defect on spirometry (relatively preserved FEV_1 with a reduced FVC and thus a normal or raised FEV_1/FVC ratio). Wegener's granulomatosis however produces an obstructive pattern (low FEV_1/FVC ratio). Total lung capacity is reduced, as is the transfer factor (TL_{CO}). The transfer coefficient (K_{CO}), which is essentially transfer factor corrected for lung volumes, is generally affected later than TL_{CO}. However, measurement of transfer factor and transfer coefficient may prove difficult for the elderly, those with very low FEV_1, or those unable to hold their breath for the required period.

Blood gas analysis commonly reveals hypoxia, often with hypocapnia secondary to hyperventilation. Chest radiography may be normal in early disease and even in some more advanced cases (Epler *et al.*, 1978). Commonly, characteristic shadowing in the form of reticular, nodular, reticulonodular, linear, or ground-glass appearances may be present. In the early stages, such abnormalities may be subtle and indeed may only be discovered in retrospect some months or years later. The distribution of such shadowing is often a clue to diagnosis. For example, a "reversed bat wing" appearance, that is, peripheral shadowing, is commonly seen in chronic pulmonary eosinophilia and cryptogenic organizing pneumonia. In addition, the presence of nonparenchymal abnormalities on the chest X ray for example, eggshell calcification of hilar lymph nodes in silicosis or pleural involvement in association with asbestosis may be helpful. However, diagnosis based on the type and distribution of shadows on a simple chest radiograph is possible in less than 20% of cases (Mathiesom *et al.*, 1989).

Conversely, CT scanning (or more recently high-resolution CT scanning – HRCT) has a high diagnostic accuracy so much so as to be diagnostic for specific conditions in over 90% of cases. It can also give information on severity and activity of disease, thus obviating the need for lung biopsy (Muller and Miller, 1990; Padley *et al.*, 1992, 1993; DuBois, 1994; Akira, 2002); diagnosis in this area depends on both the site and type of infiltrate, details of which are beyond the scope of this chapter.

Lung biopsy may remain unnecessary even in the absence of an accurate HRCT diagnosis if the condition is only slowly progressive (particularly if the patient is very elderly). Where lung biopsy is needed, then a transbronchial method gives high diagnostic accuracy with the lowest mortality rate (0.2% in one large series) and lowest significant morbidity (up to 10%) (Herf and Suratt, 1978; Poe *et al.*, 1979).

Occasionally, bronchoalveolar lavage may be indicated for differential diagnosis, and characteristic patterns of cellular abnormalities have been described in different conditions. However, bronchial lavage remains more commonly a research tool.

In the small number of cases where transbronchial biopsy (which uses multiple samples) fails to achieve diagnosis, open lung biopsy (a surgical procedure requiring general anesthetic) may be needed. As well as producing sufficient material for increased diagnostic yield, a larger sample is usually able to produce a good estimate of disease activity. Mortality however is appreciable at 1–2%. Other complications include infection and persistent pneumothorax. They occur in approximately one out of six patients (Warner *et al.*, 1988).

Specific Conditions

Pneumoconioses

Pneumoconiosis results from an abnormal lung parenchymal reaction to respirable *inorganic* dusts. There is usually an occupational context. The commonest dusts involved are coal (producing coal workers' pneumoconiosis), silica (producing silicosis), and asbestos (producing asbestosis). Coal workers' pneumoconiosis is the result of fibrosis in alveoli and in the interlobular septa with compensatory dilatation of other alveoli producing centrilobular emphysema. This may progress (even after cessation of occupational exposure) to insidious complicated pneumoconiosis or progressive massive fibrosis (PMF). PMF mainly affects the upper lobes which contain large fibrotic masses several centimeters across, often with necrotic centers. PMF is associated with

the increased likelihood of autoimmune antibodies such as antinuclear antibody and rheumatoid factor (Soutar *et al.*, 1974). Occasionally, in patients with rheumatoid arthritis, Caplan's syndrome may result. This takes the form of flitting radiological lesions in the lung which occasionally necrose or calcify. These may be associated with pleural effusion. An obstructive ventilatory pattern is common in patients with simple pneumoconiosis, especially where there is associated central alveolar emphysema. PMF produces both restrictive and obstructive defects, the restrictive defects in part being the result of reduced lung volume. Progression to cor pulmonale is not uncommon.

With the decline in the underground coal mining industry in the United Kingdom, new cases are rare but stable or progressive disease is still seen, particularly in elderly patients. Symptoms usually comprise those of chronic bronchitis and COPD together with the production of coal stained black sputum (melanoptysis). Patients often erroneously feel that they have coughed up blood. True hemoptysis is however common in PMF. Patients are not clubbed. Complicated pneumoconiosis is a compensatable industrial disease. There is no specific treatment other than supportive therapy and bronchodilators for any reversibility of airways obstruction. Smoking cessation should be encouraged and supported.

Occupational exposure to silica in sand blasting quarrying, some forms of mining, boiler making, and some forms of brick manufacture may result in silicosis. Apart from a few cases of acute illness after intense exposure (essentially unheard of in the elderly), silicosis has a similar clinical picture and pathological features to coal workers' pneumoconiosis with fibrosis of lymphatics, blood vessels and bronchi, and some degree of secondary emphysema. Silicosis predisposes to pulmonary tuberculosis.

There are usually mixed obstructive and restrictive ventilatory defects, hypoxia, and cor pulmonale in the later stages. Radiological abnormalities usually comprise nodular or miliary lesions throughout all the lung fields especially in the middle and upper zones. There may in addition be larger, sometimes cavitated shadowing. "Eggshell" calcification of the hilar lymph nodes is pathognomonic but not particularly common.

Symptoms can occasionally appear acutely but are usually gradually progressive over several years. They are those of chronic bronchitis and COPD together with occasional hemoptysis, cachexia, and weight loss. In such circumstances, tuberculosis and bronchogenic carcinoma need to be actively excluded.

Treatment is once again supportive and the disease is notifiable and compensatable. Smoking cessation should again be encouraged and supported as, apart from the association with tuberculosis, there is also an association between silicosis and both COPD and lung cancer (Calvert *et al.*, 2003).

Asbestosis is almost exclusively due to prolonged exposure to asbestos dust. There is a "lifetime" of 20–30 years between exposure and clinical presentation, with the result that the disease has its peak prevalence in the elderly. Asbestosis must be distinguished from asbestos-related pleural thickening and calcification, mesothelioma, and bronchogenic carcinoma – all of which can also be precipitated by asbestos exposure. Occupations at risk are the same as those at risk of pleural mesothelioma (see earlier section). Fibrosis originates in the alveoli and bronchioles; It is most marked in the lung bases, but may spread to involve the whole of the lungs. Progressive massive fibrosis is not a common feature.

History is usually of a relatively prolonged unprotected exposure but relatively short-term exposure is also a risk (Wright *et al.*, 2002).

The major ventilatory defect is restrictive with reduced transfer factor and reduced total lung compliance. Radiological appearances include fine mottling and patchy streaky fibrosis superimposed on pleural lesions most commonly on the diaphragm (coin lesions).

Symptoms usually comprise breathlessness on exertion and later cough, weight loss, and fatigue. Patients are usually clubbed and have fine bilateral basal crepitations. Tuberculosis may complicate the picture. Asbestosis is a notifiable and compensatable disease.

Perhaps, as a result of the lack of any effective treatment for asbestosis, there is evidence that previous asbestos workers who present with symptoms, signs, and radiographic features of interstitial lung disease, are poorly investigated and that full investigation may reveal other treatable pathology (most commonly other interstitial lung diseases) in up to 5% of cases (Gaensler *et al.*, 1991). Treatment is again essentially symptomatic and colchicine may be helpful in this regard (Addrizzo-Harris *et al.*, 2002) in some individuals, but once again because of the strong association with bronchogenic carcinoma, patients should be advised and supported in smoking cessation. In the United States, over 16% of asbestos workers are current smokers and few of these have plans to quit (Osinibi *et al.*, 2002). Similar data is not available from the United Kingdom, though there seems little reason to believe that the situation is any different here. There is current debate as to whether screening of previous asbestos workers for detection of lung cancer and other asbestos-related conditions may be helpful (Tiitola *et al.*, 2002).

Extrinsic Allergic Alveolitis

Extrinsic allergic alveolitis is the result of an immunological reaction (type III) to respirable *organic* dusts. An acute form (type I reaction) can occur with acute dyspnea, cough and pyrexia. Budgerigar fancier's lung is probably the commonest form, particularly in the elderly (Hendrick *et al.*, 1978). Essentially the same condition can occur in pigeon fanciers and keepers of parrots. Irrespective of the cause, age is an important prognostic factor (Allen *et al.*, 1976).

Symptoms comprise exertional breathlessness progressing to breathlessness at rest with the production of sputum. Clubbing is uncommon but when it is present it may be associated with a poorer prognosis (Sansores *et al.*, 1990). Weight loss is common. Crepitations on auscultation are present in only about 25% of patients at presentation. In

addition to the investigations discussed above, etiological diagnosis is aided by identification of serum precipitins.

Treatment comprises removal of or from the offending antigen (budgerigar, pigeon, or fungal spores in the case of farmer's lung). This may prove difficult in a patient who is particularly attached to his/her pet. Furthermore, it is recognized that in some affected patients, the disease is not progressive despite continued exposure to the offending antigen whereas, in others, removal of the antigen does not prevent progression (Kokkarinen *et al.*, 1992). Some patients may require corticosteroid or immunosuppressive therapy as discussed below for cryptogenic fibrosing alveolitis. However, the evidence base for their use is poor, particularly in the elderly.

Cryptogenic Fibrosing Alveolitis

This is the commonest interstitial lung disease in the elderly. Estimates of peak age at presentation have increased recently to a mean of about 60 years (Crystal *et al.*, 1984). Overall prevalence is approximately five cases per hundred thousand population with a slight male predominance (Crystal *et al.*, 1984). There is a rare familial form of the disease, but otherwise its etiology is unknown. Histological appearances are many and varied. The two ends of the spectrum of histology are a fibrotic pattern in which the alveoli are replaced by collagen and there is very little active inflammation, and a cellular pattern with infiltration of lymphocytes, neutrophils, and eosinophils into the interstitium with the alveolar spaces containing larger numbers of macrophages. It is possible but not certain that the cellular form *progresses* to the fibrotic form. However, the cellular appearance is certainly associated with an increased chance of steroid responsiveness and with a better prognosis (Wright *et al.*, 1981; Stack *et al.*, 1972).

Typical presentation is with breathlessness on exertion, progressing to breathlessness at rest. There is some suspicion that elderly patients present later than younger patients, possibly because of reduced appreciation of breathlessness. Many patients complain of a productive cough and certainly the volume of sputum relates negatively to prognosis (Hiwitari *et al.*, 1991). Patients will have fine crepitations ("Velcro" crepitations) at the bases, possibly extended to mid and even upper zones. The majority have clubbing. Cyanosis is so common as to be almost universal. In most patients, the disease progresses slowly and insidiously with an untreated 50% mortality at about 5 years (Sansores *et al.*, 1990). There is a strong association with progression to bronchogenic carcinoma (usually a peripheral squamous cell carcinoma (Aubry *et al.*, 2002)). Patients who are current smokers should be made aware of this and given smoking cessation advice and support. When lung cancer does occur in association with cryptogenic fibrosing alveolitis, the overall prognosis and the prognosis of surgical intervention for cancer is much poorer than that of the same cancer in the absence of fibrosing alveolitis (Aubry *et al.*, 2002; Kawasaki *et al.*, 2002). Advanced age seems to be associated with a poorer prognosis and with a recently recognized rise in overall mortality from the condition (Turner-Warwick *et al.*, 1980). There is a suggestion that elderly patients present later in the course of the disease. This may in part explain the adverse prognostic factor of advanced age, but there is also evidence that the disease progresses more rapidly in the elderly after diagnosis (Kawasaki *et al.*, 2002).

Treatment should be supervised by a respiratory physician. The evidence base, however, for corticosteroid treatment in cryptogenic fibrosing alveolitis is poor and entirely dependent upon anecdote and retrospective review rather than prospective blinded controlled trials. There is limited consensus on when to start treatment, even in younger patients, although in practice the decision is often based on evidence of progressive disease. A relatively old survey suggested that elderly patients tend to receive less corticosteroid therapy than the young (Turner-Warwick *et al.*, 1980). A clinical response to corticosteroids (usually beginning at 100 mg of Prednisolone daily for up to 8 weeks and then reducing gradually to a maintenance dose of 10 mg daily) is seen up to 35% (though perhaps a little less in the elderly) and usually within the first 3 months. The addition of azathioprine to high-dose corticosteroid therapy anecdotally increases the response rate to perhaps as much as 50% but there seems to be little benefit is using immunosuppressives in a steroid-sparing role (Johnson *et al.*, 1989, Ragu *et al.*, 1991). Patients on corticosteroid treatment should receive osteoporosis protection as recommended by national guidelines (National Osteoporosis Society, 1998). Colchicine produces symptomatic improvement in some patients, possibly by inhibiting the formation of collagen (Addrizzo-Harris *et al.*, 2002).

Fibrosing Alveolitis in Association with Autoimmune Disorders

Autoimmune disorders, particularly rheumatoid arthritis and systemic sclerosis can lead to fibrotic lung disease in up to 5% of cases. In Sjorgren's syndrome and celiac disease, lung complications are almost as common. There is a 2 : 1 male : female predominance. The association with rheumatoid arthritis and fibrotic lung disease seems stronger for elderly rheumatoid patients. Pathology and clinical features are very similar to those of cryptogenic fibrosing alveolitis, though with a slower rate of progression and a better prognosis. A transfer factor below 55% has been shown to be highly predictive of progressive lung involvement (Dawson *et al.*, 2002; Morgan *et al.*, 2003). There is evidence, at least in scleroderma, that progression to end-stage lung disease is uncommon even over an extended period of time, though lung involvement in the condition lends an adverse prognosis overall (Simeon *et al.*, 2003).

Treatment regimens and response rates are very similar to those in cryptogenic fibrosing alveolitis, though again controlled trial evidence is lacking. There seems to be less evidence for the value of cyclophosphamide and azathioprine. The possibility that lung involvement is an adverse reaction to therapy administered for the autoimmune disorder (particularly methotrexate and gold salts but others also

(Mehandru *et al.*, 2002)) is always worthy of consideration. A discontinuation of therapy on a temporary basis may be indicated.

Wegener's Granulomatosis

This relatively rare condition is common in the elderly with a peak age of onset of about 55 years. It is a granulomatous and vasculitic condition principally affecting the lung, upper respiratory tract, and kidneys. It follows a relapsing and remitting pattern with breathlessness, wheeze, hemoptysis, rhinitis, epistaxis, otitis, sinusitis, and pleuritic chest pain.

In elderly people, renal involvement is more common and upper respiratory tract involvement less common (Krafcik *et al.*, 1996). In elderly patients, acute or subacute confusion (due to direct central nervous system involvement) not uncommonly occurs (Mehandru *et al.*, 2002). Infective complications are no commoner in the elderly than in the young although *mortality* from infection is commoner in old age (Krafcik *et al.*, 1996).

Absolute diagnosis can only be obtained by renal biopsy, lung biopsy, or biopsy of the upper respiratory tract. Diagnosis may be helped by the presence of circulating antineutrophil cytoplasmic antibodies (cANCA).

Usual treatment regimens comprise cyclophosphamide and high corticosteroids with an initial response rate of up to 90% at about 6–12 months. However, relapse rates are high at up to 50% (Fauci *et al.*, 1983). The disease is no less aggressive in the elderly who should thus be treated with the same therapeutic regimes as the young. There is no convincing evidence that the elderly suffer more treatment complications.

Drug-induced Interstitial Lung Disease

There is little evidence that the elderly are more prone to adverse drug reactions producing inflammatory lung disease. However, such iatrogenic disease is more common in the elderly, probably by virtue of their increased exposure to multiple drugs. Perhaps, the most commonly prescribed are carbamazepine, phenytoin, nitrofurantoin, amiodarone, and (perhaps surprisingly) aspirin. Others comprise the cytotoxic agents methotrexate, bleomycin, and busulphan together with gold salts, penicillamine, and sulphasalazine. Patients with interstitial reactions to cyclophosphamide and amiodarone may have received these drugs for many years before problems become apparent. Treatment comprises withdrawal of the offending agent with occasional recourse to specific anti-inflammatory therapies.

Cryptogenic Organizing Pneumonia

This is a rare condition, but again is slightly more common in the elderly with a peak age of onset at 55–60 years. It is characterized by the appearance of buds of connective tissue in the alveoli and small bronchioles. Presenting features comprise breathlessness on exertion and cough, and in the majority of patients, pyrexia, weight loss, and general malaise. Clubbing is unusual. Plain radiological appearances are usually patchy and peripheral. Its importance lies in its rapid (sometimes within days) and frequent (60% or more) response to high-dose corticosteroid therapy. However, over half of the respondents will relapse on stopping corticosteroids.

Chronic Eosinophilic Pneumonia

Once again, this is a rare disease and probably even rarer in the elderly. Most patients have an atopic history.

Sarcoid Lung Disease

Over the whole population, sarcoidosis is the commonest idiopathic interstitial lung disease. However, the appearance of sarcoidosis for the first time in an elderly patient is extremely unusual. There is limited evidence that when this does occur the prognosis is slightly worse. Routine estimation of serum angiotensin-converting enzyme (ACE) is not recommended in the BTS Guidelines (British Thoracic Society, 1999), because of its poor sensitivity and specificity.

Lung Transplantation in Interstitial Lung Disease in Old Age

The upper age limit for lung transplantation is 65 years (British Thoracic Society, 1999). There is no evidence base for lung transplantation in patients older than this despite the fact that most interstitial lung diseases are more common in the elderly. Further research is clearly indicated.

VENTILATORY AND INTENSIVE CARE SUPPORT FOR THE ELDERLY PATIENT WITH ACUTE RESPIRATORY DISEASE

This is a controversial area with evidence of widely different practice in different western countries. It has been the subject of a recent review (Nielson and Connolly, 2003) to which the reader is directed for more information. Given the increase in the elderly population together with the increase in patient's and relative's expectation, it is likely that in the near future larger numbers of elderly patients will be considered for and referred to intensivists for respiratory support. Over and above all other considerations, the most relevant must remain patient preference and in this regard elderly people are known to be less likely to want intensive resuscitation and "aggressive" management than younger patients (Hamel *et al.*, 2000). In discussions with family and carers, it is important to emphasize that age alone is not an adverse prognostic factor in the intensive care situation (Thomas and Brennan, 2000). Nonetheless, the elderly are more likely to have multiple comorbidity, functional problems, and

nutritional deficits that do indeed have adverse prognostic effects. The elderly are also at greater risk of complications from intensive care support, particularly with the use of invasive medical procedures and multiple drugs. Decisions regarding ventilation in elderly patients should be guided in large part by a previous disability and functional status as elderly patients in general (including those with respiratory disease) recover well from periods of ventilatory support, provided their premorbid functional level is good. Indeed, in one series, the survival *at 1 year* after care support was 56% in the over 70s and 27% even in the over 85s age-group (Djaini and Ridley, 1996). The outcome of invasive ventilation for AECOPD in the very elderly is significantly better than that for intensive care support for pneumonia, stroke and other brain injury, multisystem disorder, and sepsis in general.

Perhaps the best recognized classification system for advanced prediction of survival risk is the APACHE (Acute Physiology and Chronic Health Evaluation) score which has now been revised (APACHE III) (Zimmerman *et al.*, 1998).

KEY POINTS

- Age-related disease is much more important than the physiological changes of 'normal aging' in terms of respiratory capacity in old age.
- Chronic obstructive pulmonary disease is underdiagnosed and undertreated in old age.
- Tuberculosis is occurring more commonly in the elderly and its treatment should be supervised by a respiratory physician.
- There has been a nihilistic attitude (both in clinical and research terms) to the problem of bronchogenic carcinoma in older people.
- Age per se is not a barrier to invasive ventilation.

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Pulmonary Rehabilitation

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INTRODUCTION

Pulmonary rehabilitation is "a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy" (Statement of The American Thoracic Society, 1999). While pulmonary rehabilitation has been utilized for decades, interest has grown in recent years, along with the renewed interest in lung-volume reduction surgery (LVRS) for chronic obstructive pulmonary disease (COPD). In fact, owing to the significant benefits of pulmonary rehabilitation, it has become virtually mandatory for patients prior to undergoing LVRS. As a result of the experience with pulmonary rehabilitation in the National Emphysema Treatment Trial (NETT), it has become accepted as standard therapy for COPD. In addition, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines have stated with the strongest level of evidence (level A recommendation) that pulmonary rehabilitation can benefit all patients with COPD, with improvements in exercise tolerance and dyspnea.

The majority of patients entering a pulmonary rehabilitation program have a diagnosis of COPD. COPD currently affects almost 24 million people in the United States (National Center for Health Statistics, 1994), almost half of whom are asymptomatic. It is the fourth leading cause of death in the United States (Arias and Smith, 2003). Despite this, COPD remains underrecognized. The primary risk factor for COPD is smoking, which accounts for 80 to 90% of cases. Between 10 and 15% of all smokers will develop symptomatic COPD during their lifetimes.

Dyspnea in patients with COPD is often multifactorial. As the disease progresses, patients often decrease their level of exercise since exertion often worsens their dyspnea. Deconditioning results which further exacerbates their shortness of breath. On a microscopic level, structural changes in skeletal muscle occur, which leads to easy muscle fatigability. There is a shift from predominantly type I, high-oxidative capacity fibers to type II fibers, compared to age- and height-matched controls (Whittom *et al.*, 1998). Steroid myopathy, electrolyte imbalance, and tissue hypoxia may also contribute to skeletal muscle dysfunction. The increased work of breathing may lead to increased protein catabolism and muscle wasting. Progressive hyperinflation leads to a mechanical disadvantage for diaphragmatic shortening. It can also impair right ventricular filling and cardiac output. With severe disease, the development of right heart failure and cor pulmonale may ensue.

Treatment of COPD includes smoking cessation, bronchodilator therapy, and supplement oxygen for patients with either resting or exercise-induced desaturation. Treatment with inhaled corticosteroids remains controversial (*see* **Chapter 61, Respiratory Disease in the Elderly**). There is renewed interest in surgical treatment of COPD; however, this is indicated for only a minority of patients (National Emphysema Treatment Trial Research Group, 2003). Pulmonary rehabilitation, on the other hand, can improve exercise tolerance and quality of life in most patients with symptomatic COPD as well as in patients suffering from other chronic respiratory disorders.

ORGANIZATION

There are no specific guidelines for the organization or structure of a pulmonary rehabilitation program. A multidisciplinary approach is required with involvement from nursing, physical therapist, occupational therapist and respiratory therapist. Psychologists or social workers are often employed, as are nutritionists and recreational therapists. A physician serves as the medical director, performs the initial medical screening, writes the exercise prescription, and monitors

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patients' progress through the program. The medical director is also involved as an educator and research coordinator. One member of the team functions as the program director and is responsible for the day-to-day management of the program, recruitment, and marketing.

The location of the program varies. While it is most often based in the outpatient setting as either a hospital-based or free-standing facility, it can also be performed in an inpatient setting or even at the patient's home. A typical program lasts for six to eight weeks with two-to-three two-hour sessions each week. Components of a pulmonary rehabilitation program include breathing retraining, exercise, education, and psychosocial support.

Breathing Retraining

Respiratory muscle function is impaired in COPD. Hyperinflation places the diaphragm in a disadvantageous position for inspiration. Muscle weakness, including ventilatory muscle weakness, can occur for a variety of reasons as outlined above. Inspiratory muscle training leads to improvements in muscle strength and dyspnea (Hamilton *et al.*, 1995). However, the apparatus used is cumbersome and it is not clear how effective these methods would be when incorporated into a pulmonary rehabilitation program. As a result, these techniques are not routinely employed.

Other techniques used are pursed-lip breathing and diaphragmatic breathing. Pursed-lip breathing involves nasal inspiration followed by exhalation through partially closed lips. This causes improvement in oxygenation with a decrease in respiratory rate and minute ventilation with a shift in the pattern of ventilatory muscle recruitment from the diaphragm to intercostals muscles (Breslin, 1992). Diaphragmatic breathing is performed in a supine position with the patients' hand on their abdomen during inspiration. Patients exhale through pursed lips and use the abdominal muscles to return the diaphragm to a resting position. This attempts to shift the breathing pattern from a chest wall to a diaphragmatic pattern. While this can achieve improvements in dyspnea, contrary to what might be expected, increased chest wall asynchrony, abdominal paradox, and increased work of breathing may occur (Vitacca *et al.*, 1998). As a result, diaphragmatic is no longer a routine part of pulmonary rehabilitation.

Exercise

Exercise training is an essential component of pulmonary rehabilitation. Numerous studies have demonstrated improvements in dyspnea in patients with COPD, without changes in lung function, highlighting the importance of skeletal muscle deconditioning contributing to exercise intolerance in COPD. Preenrollment cardiopulmonary exercise testing is helpful in designing an exercise program for patients. Many programs focus on endurance training with exercise session usually lasting from 20 to 40 minutes, two-to-three times weekly. Lower extremity training is very effective in improving endurance. There is some debate as to the optimal intensity of exercise. High-intensity exercise (at about 60% of maximal work rate as determined by exercise testing, which is usually above the onset of anaerobic metabolism) achieves greater improvements in maximal and submaximal exercise response (Casaburi *et al.*, 1991). Our experience has been that patients usually do not tolerate such high levels of exercise. We usually target exercise intensity at just below anaerobic threshold. This still results in improvement in exercise parameters and dyspnea but with better compliance than at higher levels of exercise intensity.

Many elderly patients may have limited shoulder mobility or tremor due to age, neurologic disorders, or medications; this can increase ventilatory demand and lead to significant functional limitation. Upper extremity training along with occupational therapy is helpful for these patients. Upper extremity training leads to benefits specific to the muscle groups exercised and is useful for specific tasks, but does not lead to improved exercise tolerance.

Education

Education is an integral component of pulmonary rehabilitation. Patients benefit from an understanding of their disease and learn how to recognize symptoms of an exacerbation. Better coping skills, better understanding of the physiological and psychological aspects of chronic pulmonary disease, better adherence and understanding of medications and other treatments, and smoking cessation are all potential benefits of the educational component of pulmonary rehabilitation. Unfortunately, education has become such an integral component of pulmonary rehabilitation that few studies isolating this component alone have been performed. Thus, the American College of Chest physicians (ACCP)/American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) has given the education component of pulmonary rehabilitation a level C recommendation (expert opinion supports the guideline recommendation, though the available research does not have consistent results and controlled trials are lacking).

Education is no substitute for exercise in pulmonary rehabilitation. A number of randomized studies have compared education and exercise in COPD patients. In all studies, the sense of dyspnea and exercise tolerance and endurance was much greater in the exercise treatment arm, and little, if any, improvement, was seen in the arm receiving education alone.

End-of-life issues are an important topic to include in pulmonary rehabilitation programs. Almost all patients have expressed a desire to discuss these issues during the course of a pulmonary rehabilitation program (Sullivan *et al.*, 1996). Reluctance by some to include these topics in their curriculum, because of concerns of extinguishing hope, seems to be unfounded. Pulmonary rehabilitation provides a unique opportunity to discuss issues such as advanced directives,

health-care proxies, living wills, palliative care, and physician–patient communication regarding end-of-life issues.

Psychosocial Support

Anxiety, depression, and difficulties in coping with the progressive, debilitating nature of COPD are common in these patients. In part, this is due to loss of independence as dyspnea worsens. This can lead to progressive social isolation and a sense of hopelessness. The elderly are particularly at risk, since their spouses may themselves be disabled or no longer surviving. In addition, their children may be grown and not available to help with daily activities. Chronic dyspnea can lead to both anxiety and panic. A common concern among patients is not having immediate access to treatment should dyspnea worsen while away from home. This can further lead to social isolation and patients being housebound.

There has been increased interest in using pulmonary rehabilitation programs to identify patients with depression. The effect of pulmonary rehabilitation on psychological outcomes, however, has not been clearly defined. The GOLD guidelines state that psychosocial intervention is helpful and gives this an evidence grade of C (nonrandomized trials and observational studies). Similarly, the ACCP/AACVPR recommendations consider group psychosocial, behavioral, and educational interventions and outcomes together and give them an evidence grade of C (expert opinion supports the recommendation though the available research does not have consistent results, and controlled trials are lacking). More recently however, it has been recognized that targeting treatment of anxiety and depression during a rehabilitation program can lead to improvements in anxiety and depression scores with psychotherapy (De Godoy and de Godoy, 2003). This was independent of any effect on exercise capacity.

Psychological support during pulmonary rehabilitation can be in the form of regularly scheduled support groups focusing on specific topics such as stress reduction, coping skills, or panic control. Family sessions are often included in these programs as well. Group sessions, progressive relaxation techniques, and hypnosis have all been tried in these with anecdotal reports of success.

PATIENT SELECTION

Pulmonary rehabilitation should be considered in all patients with COPD who have functional limitations that persist despite the use medications to treat their disease. Pulmonary rehabilitation is considered by most to be essential both before and after lung-volume reduction surgery or lung transplantation. The benefits of pulmonary rehabilitation occur independent of lung function (Niederman *et al.*, 1991), even in patients with severe disease. Furthermore, the magnitude of benefit was inversely correlated with the baseline 12-minute walk (ZuWallack *et al.*, 1991). These studies highlight the importance of identifying the disability that COPD causes, rather than focusing on impairment as measured by the forced expiratory volume in one second (FEV_1). Therefore, even patients with only mild disease (as identified on pulmonary function testing) who are symptomatic will benefit from pulmonary rehabilitation. Unlike lung-volume reduction surgery or transplantation, which is appropriate for a very select group of patients, pulmonary rehabilitation can benefit the majority of patients with COPD. Certainly while patients with advanced COPD can certainly benefit from pulmonary rehabilitation, referral earlier in their disease course might allow earlier preventive strategies such as smoking cessation, nutritional therapy, and a more vigorous exercise prescription.

Certain patients may not be candidates for the exercise component of pulmonary rehabilitation. Orthopedic problems may prevent the use of certain exercise apparatus. Often consultation between a physical therapist and orthopedist can allow some patients to participate in an individualized manner; for example, upper arm exercise only in a patient with severe aseptic necrosis of the hips. Severe coronary artery disease and unstable angina would also preclude exercise in this group of patients.

While most studies of pulmonary rehabilitation have focused on patients with COPD, anecdotal reports suggest that pulmonary rehabilitation may play a role in diseases other than COPD. Potential candidates for pulmonary rehabilitation include patients with impaired lung function needing thoracic surgery, patients with interstitial lung disease, and those with chest wall or neuromuscular disease. Pulmonary vascular disease is considered to be a relative contraindication for pulmonary rehabilitation but without good supporting evidence. Certainly many patients with COPD or interstitial lung disease, who have successfully completed pulmonary rehabilitation have cor pulmonale. It is not known what to do with patients suffering from primary pulmonary hypertension or pulmonary hypertension associated with systemic sclerosis in which the primary pathophysiology is obliteration of the pulmonary vasculature and not hypoxic vasoconstriction or mechanical compression of vessels from hyperinflation or fibrosis. There is no current evidence indicating what degree of pulmonary hypertension would make exercise unsafe, nor how treatments to modulate vascular tone such as epoprostenol or bosentan will affect this risk. More research is needed in these areas.

OUTCOMES

Studies of pulmonary rehabilitation have consistently shown improvements in exercise tolerance, quality of life, dyspnea, and in many, reductions in anxiety and depression. Measures of peak exercise capacity, such as maximal oxygen consumption with exercise, are not clearly improved with pulmonary rehabilitation, but sustainable exercise, reflected by the 6-minute walk, does seem to correlate with improved quality of life. Most of these improvements can be accounted

for by changes in muscle strength and oxidative capacity, but some improvements in dyspnea and exercise tolerance can be due to both a reduction in fear and desensitization to dyspnea, which occur independently of any training effect (Belman and Kendregan, 1991). Pulmonary rehabilitation does not improve overall lung function, need for supplemental oxygen, or mortality. Thus, pulmonary rehabilitation should be viewed as adjunctive therapy and does not replace pharmacologic therapy for COPD.

Perhaps the most complete study of pulmonary rehabilitation involved 119 patients who were randomized to either a formal program consisting of supervised exercise, education, physical, and respiratory care instruction, and psychosocial support or to education alone (Ries *et al.*, 1995). The patients undergoing exercise had significant improvements in exercise capacity and reduced dyspnea.

While there is no effect on mortality, there has been increased interest on how pulmonary rehabilitation affects health-care utilization. In a single center in Wales, patients completing pulmonary rehabilitation had fewer hospital days (10.4 vs 21 for the year following rehabilitation) compared to patients not undergoing rehabilitation (Griffiths *et al.*, 2000). In the United States, under a different health-care system, similar results were found (California Pulmonary Rehabilitation Collaborative Group, 2004). At 10 sites there was a significant reduction in hospital days the year after rehabilitation compared to the year before (3.4 vs 10). There were also fewer physician visits, telephone calls, and urgent care visits the year following pulmonary rehabilitation.

MAINTENANCE OF BENEFITS

The benefits of pulmonary rehabilitation, while significant, are generally lost over time. On average, exercise tolerance, breathlessness, and quality of life return to baseline over approximately 12 to 18 months following completion of pulmonary rehabilitation. The effect on dyspnea and quality of life are generally somewhat more prolonged than on exercise tolerance. This is likely due to the fact that the education and sense of mastery that a patient acquires is longer lasting than any physiologic effect of exercise training that occurs during a rehabilitation program. It is very common for patients after a short-term, high-intensity program to return to their previously sedentary lifestyles. The occasional, highly motivated patient will follow an exercise program and have sustained benefit but most patients gradually return to their prior functioning.

As a result, many pulmonary rehabilitation centers have started maintenance programs to allow patients to exercise in a structured program, which also maintains the motivating social structure of the rehabilitation environment. Maintenance programs are not as well standardized and can be performed either at home or in a facility. Exercise regimes are typically not as rigorous as the formal rehabilitation program. Education and psychological support are usually not included in maintenance. The data on these programs have shown variable success. In general, the long-term effects of maintenance correlate with the intensity of the program.

Pulmonary rehabilitation ultimately is an attempt to achieve a lifestyle change for patients utilizing education and exercise designed specifically to maximally benefit those with chronic respiratory disease. Unfortunately, it is difficult to achieve changes in lifestyle during a short, 6 to 12 week program. Inpatients who underwent repeated pulmonary rehabilitation programs on a yearly basis had similar benefits compared to the first cycle; however, these benefits dissipated over the following year. Long-term lifestyle modification requires a short-term, high-intensity intervention followed by continued reinforcement. Therefore, while rehabilitation has significant effects on quality of life and exercise tolerance, without maintenance afterwards, patients are likely to gradually return to their previous level of disability.

SUMMARY

Pulmonary rehabilitation causes improvement in exercise capacity and symptoms in patients with COPD, even in those receiving optimal medical therapy. There has been increasing recognition of the benefits of pulmonary rehabilitation along with the renewed interest in lung-volume reduction surgery; despite this, pulmonary rehabilitation remains underutilized. Unlike surgical treatment of COPD, pulmonary rehabilitation can be applied to a wide spectrum of patients with pulmonary disease. This noninvasive, nonpharmacologic treatment should be considered for all patients with symptomatic respiratory disease.

KEY POINTS

- COPD is a common cause of disability in the elderly.
- Dyspnea is multifactorial and is not necessarily related to loss of lung function alone. Other factors including deconditioning, changes in skeletal muscle function and structure, electrolyte imbalance, and cardiovascular effects of hyperinflation contribute to exercise intolerance.
- Pulmonary rehabilitation is a multidisciplinary tool which specifically addresses many of these issues in patients with chronic respiratory disease.
- Unlike surgical treatments for COPD, pulmonary rehabilitation can be used for the vast majority of patients with COPD.
- Pulmonary rehabilitation improves exercise tolerance, symptoms of dyspnea, and seems to decrease overall health-care utilization. The effects of pulmonary rehabilitation however dissipate over time without continued reinforcement of new habits learned during the rehabilitation program.

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Sleep Disorders in Elderly People

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BACKGROUND

Prevalence

The prevalence of sleep problems in adulthood increases with age (Ford and Kamerow, 1989; Bliwise, 1993; Brabbins *et al.*, 1993; NCSDR, 1993; Foley *et al.*, 1995). In the general population, the most common types of sleep problems reported are insomnia (both difficulties in initiating and/or maintaining sleep), and early morning waking with an inability to return to sleep. Older adults primarily report difficulty in maintaining sleep and, while not all sleep changes are pathological in later life, severe sleep disturbances may lead to depression (see below), cognitive impairments, and stress to partners (Morin and Gramling, 1989; Bliwise, 1993).

Prevalence rates of insomnia in people aged 65 and over range between 12 and 40% (Morin *et al.*, 1999). Prevalence rates of insomnia are higher when coexisting medical or psychiatric illness is taken into account (Ford and Kamerow, 1989; Mellinger *et al.*, 1995). Lifestyle changes related to retirement, the increased incidence of health problems, and the use of medication all place older people at increased risk of disrupted sleep (Morgan *et al.*, 1988). The relationship between sleep problems and depression in the elderly is strong, but prone to confounding influences (Ford and Kamerow, 1989). Sleep disturbances may also be comorbid with (but not necessarily causative of) dementia, while Alzheimer-related deterioration of suprachiasmatic nucleus neurons could cause still further disturbance in sleep–wake cycle disorders (Kripke, 2001).

Basic Issues Concerning Sleep in the Elderly

In spite of the high prevalence of sleep disorders in the elderly, relatively little is known about them. This may be because gerontologists, in common with many other clinicians, are taught very little about sleep either at undergraduate or postgraduate levels (Stores and Crawford, 1998; Stores and Wiggs, 1998).

In short, sleep is a reversible state of reduced awareness of and responsiveness to the environment, which usually occurs when lying down quietly with little movement. The functions of sleep are still being debated, with a range of theories postulating physical and psychological restoration and recovery, energy conservation, and a range of biological purposes. No single theory encapsulates all of these functions, and it is likely that sleep serves many purposes. For most people, a significant lack of sleep impairs both physical and psychological functioning.

Sleep problems may relate to the quality, duration, or timing of sleep. Asking patients whether they feel sleepy during the day, whether they feel refreshed in the morning, and whether they are sleeping at socially appropriate times are all good indicators of whether these important aspects of sleep are acceptable.

There are essentially three main sleep problems: too much, too little, and the so-called *parasomnias* (things that go bump in the night). However, the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 1990) lists more than 80 sleep disorders. This chapter will focus on the most common sleep disorders faced by people aged over 65 and will consider diagnostic and treatment issues relevant to each of them.

A variety of factors may give rise to the sleep problems reported (and often underreported) by the elderly (Bliwise, 1993; Neubauer, 1999). Principally, these are: medical illnesses, both chronic and acute; the effects of medication; psychiatric problems; primary sleep disorders; social changes; and behavior patterns that are not conducive to good sleep. These problems may be exacerbated by poor handling of these problems by the patient, his or her family, medics, and other health-care workers.

The consequences of sleep problems can be serious. Lack of sleep and sedative medications have been shown to be associated with falls and accidents (Tinetti *et al.*, 1988; Hemmelgarn *et al.*, 1997). Sleep-related breathing problems have serious cardiovascular, pulmonary, and central nervous system (CNS) effects (Hla *et al.*, 1994). In patients with

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dementia, sleep disorders frequently lead to nursing-home placement. Experimental studies of total sleep loss indicate that this is associated with a negative impact on mood and cognitive functioning, although as with most sleep problems, individual variations can be substantial. For ethical reasons, the number of studies in this area is limited. Partial sleep loss has been better researched and these studies are likely to be more relevant to daily life and clinical practice. A loss of sleep between 1 and 2 hours per night has been shown to lead to irritability and poor concentration. When sleep loss is prolonged, disorientation, hallucinations, and inappropriate behavior may be reported (Bonnet, 1993; Bonnet and Arand, 1995; Bonnet and Arand, 1996; Bonnet and Arand, 1998; Bonnet and Arand, 2003).

It is important that sleep disorders be diagnosed properly and treated accordingly in view of their consequences to patients as well as carers. These problems also impact health-care costs (Stoller, 1994), further justifying medical attention. (Please see Table 1 for a guide to these problems and their treatments.)

Sleep Structure

Normal sleep consists of a number of stages that can be simplified into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. REM sleep is generally associated with dreaming as well as lability of heart rate, blood pressure, and respiration. Brain metabolism is highest in this stage of sleep, with a low voltage, mixed frequency non-α electroencephalogram (EEG). Spontaneous rapid eye movements are seen and skeletal muscle tone is virtually absent. REM sleep makes up approximately 25% of total sleep time in adults and it is when most dreaming occurs. REM-sleep episodes occur at approximately 90-minute cycles, with each episode increasing in duration as the night progresses. It is sometimes known as paradoxical sleep since the EEG is most like wakefulness and yet there is very little physical activity.

NREM sleep is subdivided into four stages of increasing depth, and dominates the first half of a normal night. Stage 1 occurs at sleep onset or following arousal from another stage of sleep. The EEG is low voltage with mixed frequencies and reduced α-activity compared with the awake state. It makes up about 5% of the total sleep time. Stage 2 contains more slow-wave activity, and sleep spindles and K complexes are seen. It makes up around 50% of overnight sleep. Stage 3, also about 5% of sleep time, is yet more slow-wave EEG activity and Stage 4 is the slowest activity and makes up about 15% of sleep. Together, Stages 3 and 4 are known as slow-wave sleep. These are the deepest forms of sleep from which awakening is especially difficult. Arousal disorders such as sleep-walking and confusional arousals arise in slow-wave sleep. These sleep stages are summarized in Figure 1, which shows a summative hypnogram for a 25-year-old adult and an otherwise healthy 80-year-old elderly person for comparison.

The most striking differences are that the younger person sleeps for a longer time, with fewer wakes during the night. The elderly person sleeps less, and this sleep is highly fragmented with many arousals, some of which are for a considerable time. The older person also has very much less deep NREM sleep. Whether the older person needs less sleep at night or simply cannot get it is not currently known, but it may go some way in explaining why high levels of daytime sleepiness in the elderly is so common (Bliwise, 1993). Overall, it can be seen that sleep efficiency (the ratio of time asleep to time in bed) has fallen. The reduction in deep sleep and its replacement with lighter Stage 2 sleep is of clinical significance as it is reflected in perception of sleep quality (Riedel and Lichstein, 1998).

Table 1 Common sleep problems and their treatments in the elderly

Sleep disorder	Clinical features	Diagnostic method	Treatments	Comments
Sleep apnea	Reports of stopping breathing for short periods during sleep; daytime sleepiness; loud snoring; obesity	History; physical examination; polysomnography	CPAP; weight loss;	Intermittent airway closure; more common in men; sedatives unhelpful
Restless legs syndrome	Motor restlessness; pacing at night	History	Dopaminergics; benzodiazepines	More common with iron deficiency; PLMD often also present
Periodic limb movement disorder	Legs kicking in sleep, arousals from sleep, daytime sleepiness	Polysomnography	Dopaminergics	May extend to other muscle groups; may occur during wakefulness also
REM-sleep behavior disorder	Apparent acting-out of dreams	History and Polysomnography	Clonazepam	Mostly idiopathic; injury to bed- partner should be considered
Advanced sleep phase	Falling asleep and waking too early	History/diary (with actigraphy)	Psychological; bright light; (melatonin)	More common in institutionalized elderly
The insomnias	Difficulty initiating or maintaining sleep	History/diary (with actigraphy)	Psychological; medication (for acute insomnia only)	Consider the type of insomnia with medication

PMLD, periodic limb movement disorder.

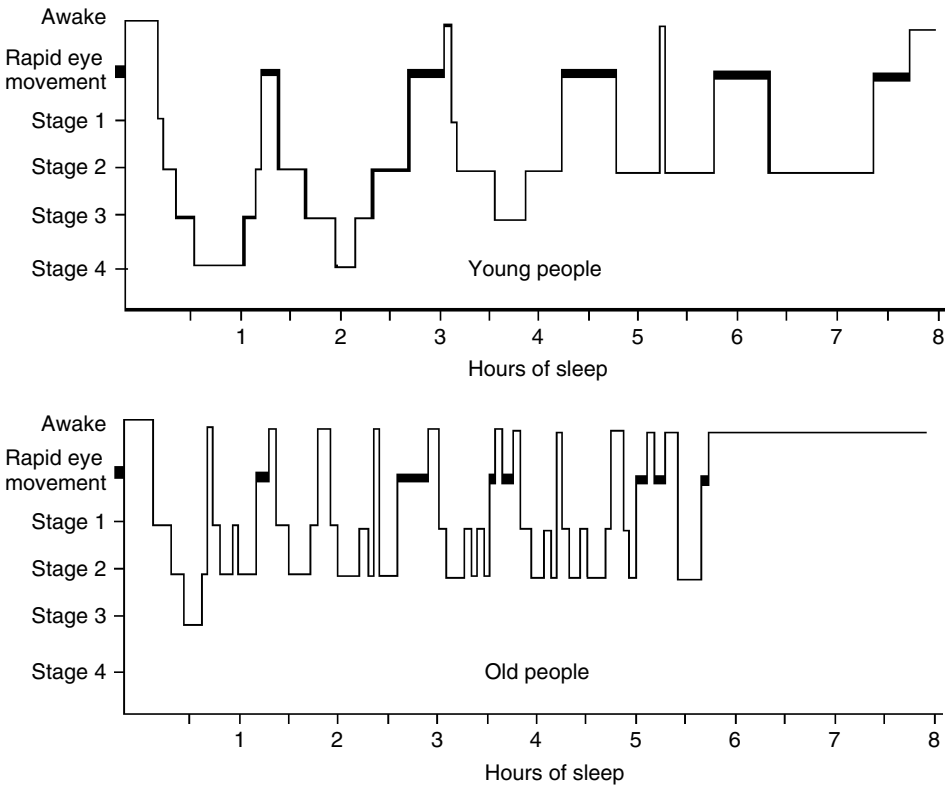

Figure 1 Sleep hypnogram for a young adult and an 80-year-old. Horizontal axis = time, vertical axis = sleep stage. These subjects fall from wakefulness into slow-wave non-REM sleep in stages 1 to 4 before their first REM phase where most dreaming occurs. The first half of the night is dominated by slow-wave sleep and the second half by REM sleep. Thus, a patient who is limiting their sleep is more likely to be deficient in REM sleep and, thus, more likely to have cognitive difficulties. Note the shorter, more fragmented sleep in the elderly compared with the young adult

The noise threshold required to waken an older person appears lower than in younger adults despite reductions in hearing sensitivity (Zepelin *et al.*, 1984), although a study looking at this issue in people living near Heathrow airport indicated that bed-partner behavior was more influential than noise (Horne *et al.*, 1994). Perhaps the elderly have a general increase in sensitivity to external stimuli, which decreases sleep quality.

Whether these sleep problems are related to gender is not yet properly understood. It appears that women report more sleep problems, although men have objectively more disordered sleep. This may be due to women reporting their sleep problems more frequently (Rediehs *et al.*, 1990).

The timing of sleep in the elderly is often phase-advanced, that is, they generally go to sleep early and wake up earlier than they would like. The early morning waking may lead to sleep deprivation and excessive daytime sleepiness. Conversely, some older people may develop a phase-delay, that is, becoming "night owls" with bedtime delayed until late. This behavior may have been accommodated in youth when the cues of bright morning light and other environmental influences were stronger; however, deterioration of light perception has weakened these cues. These patients may go on to develop very irregular sleep–wake cycles, which can be difficult to treat.

Dementia

Dementia presents additional challenges to physicians because many of the sleep changes seen in the normal aging population are amplified. Compared with controls, older people with dementia have a longer sleep latency (time between going to bed and getting to sleep); wake up in the night more frequently and for longer periods; and are more likely to fall asleep during the day (Allen *et al.*, 1987; Prinz *et al.*, 1982). Circadian rhythm problems are also more common, and 10% of older people with dementia actually sleep more during the day than during the night. These changes are often accompanied by episodes of nighttime agitation and sundowning, which are among the most common reasons for admission to a nursing home (Pollak and Perlick, 1991). While there is some evidence of a possible link between sleep problems and dementia (Prinz *et al.*, 1982), individual differences are great and do not discriminate between dementia and non-dementia patients effectively. The possible causal mechanism is thought to include a degeneration of the neurons in the suprachiasmatic nuclei. Whatever the organic origin, it is likely that behavioral factors will influence sleep problems. There is good evidence that a regular day–night pattern of activity with minimal naps and optimal daytime stimulation is helpful. An exhausted carer leaving their demented relative

to sleep during the day in order to give themselves a much-needed break may make life considerably worse in both the short and the medium term.

Institutionalization

The link between institutionalized living and sleep disturbance is perhaps best demonstrated by the high levels of hypnotic drug consumption that have been found in hospitals and nursing homes (Alessi *et al.*, 1995). Within these institutions, sleep disturbance may be related to the act of admission itself. A period of adjustment may be required (3–4 days), as is common in many other settings where people do not sleep normally when their usual night time environment changes. Hypnotics should not be prescribed for people who cannot sleep in a new institution unless they have other problems as well. Moving to an institution is likely to be contemporaneous with a life event such as the death of a partner, discomfort, or pain, any of which may have a negative effect on sleep. Noise has been shown to be a significant factor in the sleep of the institutionalized elderly and, often, noise levels in such homes are excessive. Institutions that fail to stimulate residents during the day and that have routines that are not conducive to sleep may be more likely to have sleep-disordered residents.

Assessment

Subjective enquiries about the sleep of elderly patients should be done routinely as they are at special risk of sleep disorders, which they tend to under-report and see as normal and untreatable. More detail on the assessment of sleep disorders is given elsewhere (Kryger *et al.*, 2005).

All patients should be screened by being asked whether they sleep enough and whether their sleep is of good quality. They should be asked if they are sleepy during the day and whether their nocturnal sleep is disturbed at all. Information may be corroborated by carers or bed-partners. If any of these enquiries are positive, a fuller sleep history should be taken. This should include details of the nature of the sleep complaint, its onset, and so on. Contributing factors and patterns of occurrence should be explored. The impacts of both sleep problems and previous treatments on patients and their families should be assessed. Patients should be taken through their 24-hour schedules, which may elicit helpful information about timing and other aspects of their sleep. If justified, clinicians may then consider giving patients sleep diaries to complete. Sleep diaries can be helpful in understanding the times a patient goes to bed, gets to sleep, wakes in the night, wakes in the morning, and gets up. Using sleep diaries, estimates can be made of sleep latency and efficiency (times between getting to bed and getting to sleep, and ratio of time asleep to time in bed, respectively). There are many versions of sleep diaries available (for an example, see http://www.sleepfoundation.org/publications/sleepdiary.cfm), but it may be helpful to customize one to attend to the particularly relevant points raised in the clinical interview. An example diary is given as Figure 2.

From the physical examination, attention should be paid to any systemic illness including cardiorespiratory disease or neurological disorder such as Parkinson's disease or stroke, which may disturb sleep. Obesity or craniofacial abnormalities may suggest upper airway obstruction and any psychiatric problems (particularly depression and anxiety) should be noted during the physical examination.

Objective investigations of sleep are not justified for all sleep disorders (ASDA, 1997). The main indications for them are sleep apnea, narcolepsy, or periodic limb movements (PLMs). If details of parasomnias (such as REM-Sleep Behavior Disorder) are unclear from clinical interview, an objective check on the clinical impression is required. Generally, objective investigation is in the form of polysomnography (PSG) in a sleep laboratory, although home PSG is becoming better established and validated. When this is more accepted and widely available, home PSG may diminish the so-called *first night effect*, which is common when patients

Sleep diary

Day of the week	Example day
When did you rise from bed this morning?	8 A.M.
What time did you get into bed last night?	Midnight
How long did it take you to fall asleep? (mins)	45 min
How many times did you wake *during* the night?	3
How long was each awaking *during* the night?	10, 10, 20
How long did you sleep altogether? (hours:mins)	6 h 35-min
How much alcohol (if any) did you drink last night?	1 glass wine
How many sleeping pills, if any, did you take to help you sleep last night?	None
How much caffeine did you consume yesterday? (tea, coffee, coke etc.)	2 cappuccinos, 1 tin coke

Figure 2 Sleep diary

spend their first night in a sleep laboratory. PSG studies should include an EEG, an electrooculogram, and an electromyogram in order to compile an overnight hypnogram such as Figure 1. Commonly, PSG is extended to include respiratory variables where sleep-related breathing disorders (SRBD) are suspected, and anterior tibialis electromyogram if period limb movements of restless leg syndrome (RLS) are suspected.

Alternative objective measurement of sleep can be made using actigraphy, small wrist-watch-sized motion detectors that distinguish wake and sleep and so are useful for circadian rhythm disorders (Sadeh *et al.*, 1995).

Sleep-related Breathing Disorders (SRBD)

The most common sleep-related breathing problems are apneas (temporary cessations of breathing) and hypopneas (a form of shallow rapid breathing). They can be due to an occlusion of the airway (obstructive sleep apnea) or reduced respiratory drive (central sleep apnea). The most obvious features of these are stopping of breathing followed by gasps for breath during sleep episodes, and excessive daytime sleepiness, both of which increase with age. These events can occur hundreds of time each night and commonly impair daytime functioning significantly because the patient is aroused during each episode and is, therefore, deprived of sleep and deep NREM sleep. The main risk factors for apnea are male sex and obesity.

The clinical importance of SRBD is substantially demonstrated by numerous studies over the past 30 years. The presence of five or more apneic episodes per hour is generally considered pathological. It has been reported that one in 10 adults aged between 30 and 60 stop breathing 10 or more times per hour, whereas 60% of people aged over 65 do this (Young *et al.*, 1993; Ancoli Israel *et al.*, 1991a). The reasons for this may be due to the elderly having physiological changes such as longer soft palates, larger pharyngeal fat pads, and lower response of genioglossal muscle to negative pressure stimulation (Malhotra *et al.*, 2000). An Australian study (Mant *et al.*, 1988) reported that 72% of patients with dementia had clinically significant apnea (>5 events per hour) compared to 46% of controls. Oxygen desaturation experienced during apneas may compromise neuropsychological functioning in dementing illness, although reports of this vary in the literature (Hoch *et al.*, 1989). Sleep apnea patients who also have congestive heart failure have a mean survival time of less than 2.71 years compared to 4.04 years in patients with congestive heart failure alone (Ancoli Israel *et al.*, 2003).

Patients suspected of having sleep apnea may be evaluated in a sleep laboratory where monitoring of the electroencephalogram, blood oxygen saturation, airflow, and chest and abdomen respiratory efforts can be performed to confirm the diagnosis.

The treatment of choice for sleep apnea is continuous positive airways pressure (CPAP), which requires a device that pushes air into the airway to keep it open at night. These devices have been found acceptable in older patients, including those with mild Alzheimer's disease. In this latter group, snoring and daytime sleepiness were reduced; depressive symptoms in both patients and carers improved.

Oral appliances that move the mandible forward or pull the tongue forward during the night may also be used to treat sleep apnea. However, these do not always work well with dentures and may not be appropriate for all older adults. Avoiding alcohol and hypnotics can be helpful as these are respiratory depressants. Weight loss may be an effective intervention since obesity is one of the biggest predictors of apnea. Changing sleep position from the back to the side can be effective if it can be shown that the apneas occur only when patients sleep on their backs. Surgical interventions are not usually recommended because of the possible complications.

Periodic Limb Movements in Sleep (PLMs) and Restless Leg Syndrome (RLS)

PLMs is a condition in which the legs kick or jerk for between 0.5 and 5 seconds at 4 to 90 second intervals throughout the night. PLMs causes fragmented sleep (especially the loss of deeper slow-wave sleep) and patients report insomnia and excessive daytime sleepiness. This idiopathic disorder also increases with increasing age (Ancoli Israel *et al.*, 1991b) with prevalence among elderly people living at home at about 45%. However, not all people with PLMs experience disturbed sleep, although the quality of their sleep can be greatly impaired by this disorder, which usually comes to light from partner complaints.

RLS is a related disorder where patients experience irritating "creepy–crawly" leg sensations that are relieved only by moving the legs. It can occur prior to sleep onset and in the daytime when the person is relaxed. RLS can significantly interfere with the onset of sleep. Risk factors for both PLMs and RLS include not only increasing age but also renal failure and iron deficiency (serum ferritin level less than $50\,\mathrm{ng\,ml^{-1}}$). Both disorders can be diagnosed from patient and partner report of these clinical symptoms and confirmed by electromyography in a sleep laboratory if necessary.

PLMs and RLS can both be treated with medication, usually carbidopa–levodopa (25–100 mg) and other dopaminergic agents. Comorbid low iron level may need to be corrected for a satisfactory response. Pergolide, at a very low dose (0.05–0.5 mg) has also been used for these disorders. Some patients report that soaking the legs and feet in a warm bath or taking regular exercise provides some relief.

REM-sleep Behavior Disorder (RBD)

REM-sleep behavior disorder is a rare condition that occurs mostly in the elderly. In patients with RBD, muscle tone is preserved in REM sleep; patients may be able to act out their dreams. In suspected cases, patients should be seen urgently

because they risk harming themselves and those around them. Treatment at bedtime with a low dose of a long-acting benzodiazepine such as clonazepam is generally effective.

Circadian Rhythm Disorders

In adults with normal circadian rhythms, sleepiness occurs around 11 P.M. and persists for around 8 hours. This period is associated with a drop in core body temperature, which is thought to be a cause of sleepiness. These cycles are thought to be related to changes in the levels of light. As aging occurs, the circadian rhythm seems to advance so that sleepiness occurs earlier in the evening and morning waking occurs correspondingly earlier. Most older adults try to stay awake even though they feel sleepy in the early part of the evening. However, they still wake up earlier as their core body temperature rises, leading to sleep deficiency and excessive daytime sleepiness and/or naps during the day. Some elderly people doze off in the early evening, have sleep onset problems at bedtime, and wake early; this cycle may impair their daytime functioning still further. These sleep phase problems are common in many groups of patients, notably visually impaired people, and treatment of these problems can be difficult as these dysfunctional patterns of sleep can become entrenched.

Treatment of advanced sleep phase (sleeping too early) involves delaying the sleep cycle. Strong social and environmental cues such as meals at regular times, exposure to light, and exercise are most important. This may be accomplished artificially using bright light, although evidence for this intervention is limited in patients both with and without dementia (Montgomery and Dennis, 2002a). Usually, a light source of at least 10 000 lux (which is far greater than is normal indoors) should be used late in the day (say 4 P.M.). Light exposure may delay the circadian rhythm so patients become sleepy later in the evening and sleep later in the morning. If patients continue to wake early and want to go outdoors, they should be encouraged to wear sunglasses lest the early light exposure shift their sleep phase still earlier. Bright light treatment is, however, contraindicated in patients with mania. Alternative treatments include melatonin, which is a hormone released by the pineal gland, but convincing research evidence here is even more limited.

The Insomnias

The International Classification of Sleep Disorders (American Academy of Sleep Medicine, 1990) defines 12 subtypes of insomnia, that is, disorders of initiating or maintaining sleep. However, in day-to-day practice, the technology required to precisely diagnose each of them limits the value of this system. It is, nevertheless, important to consider the type of insomnia with which the patient presents. The main types are psychophysiological insomnia (with psychosomatic arousal, excessive concern about sleep adequacy, and somatized tension), inadequate sleep hygiene (where the sleep problem appears to be caused or maintained by dysfunctional practices around sleep), and sleep-state misperception (where the insomnia diagnosis is not supported by objective findings).

A wide range of medical conditions is associated with the insomnias including arthritis and cancer. Neurological problems such as dementia, RLS, and Parkinson's disease are also associated with it and, in the elderly, congestive heart failure, asthma, gastroesophageal reflux, urinary incontinence, nocturia, and benign prostatic hyperplasia are commonly comorbid with insomnia. Depression is strongly linked with insomnia in both directions, that is, as both cause and effect. Anxiety disorders, prevalent in the elderly, may in part be caused by bereavement, social changes, and relocation, but insomnia is associated with all of them. There are several drugs that cause insomnia, including alcohol, nicotine, CNS stimulants, β-blockers, corticosteroids, bronchodilators, calcium channel blockers, and thyroid hormones. Alcohol is often used to induce sleep, but its effect is short-lived and leads to early waking. Adjusting the dose or time of day when medications are taken can improve a patient's insomnia, for example, wake promoting drugs could be taken earlier in the day and sedating drugs later.

Evaluation of insomnia should be based on a good sleep history, augmented by a sleep diary and a physical examination. Initially, medical and psychiatric problems should receive attention and, if the insomnia remains, identification of an underlying cause should be attempted before direct treatment for insomnia is indicated. Nonpharmacological treatments such as sleep hygiene and education integrated into a cognitive behavioral framework should be considered first for chronic insomnia to reduce polypharmacy especially in view of the other drugs commonly taken by the elderly (Montgomery and Dennis, 2002b). Sleep hygiene should aim to establish: regular sleep and wake times; avoidance of excessive time in bed awake (sleep restriction); stimulus control in the form of a clear routine leading up to sleep; daily activity and exercise; appropriate use of caffeine (avoidance after 4 P.M.); limited alcohol and nicotine use; elimination of loud noise, excessive light, and uncomfortable room temperature. Inaccurate attributions should be challenged and corrected about what sleep is, how common problems can be, and how sleep changes with age. Even if poor sleep habits are not responsible for insomnia, the elimination of such habits will avoid their role in the maintenance of the problem. There is some evidence from other populations that written information can be an effective way of delivering these sorts of treatments, although no good trials have been conducted with the elderly (Montgomery, 2001). Cognitive behavioral intervention for insomnia includes stimulus control, aims to set up conditions conducive to sleep for the patient. It typically involves removing any sleep-incompatible stimuli from the bedroom, and the patient is told to get up if not asleep within 20 minutes of getting into bed. It is essentially a conditioning treatment that develops strong associations between the bedroom and sleep while extinguishing associations between sleep and any other place.

Table 2 Common appropriate medications for insomnia in the elderly

Agent	Dose/timing	Comments
Non-benzodiazepine hypnotics		
Zolpidem tartrate (Ambien)	5–10 Mg at bedtime	Can be used for sleep-onset and maintenance insomnia (as half-life is 1.5–4.5 hours)
Zaleplon (Sonata)	5–10 Mg at bedtime	Can be used for sleep-onset and maintenance insomnia (as half-life is 1 hour)
Benzodiazepines		
Temazepam (Restoril)	7.5 Mg	Exclude obstructive sleep apnea before prescfribing
Antidepressants for insomnia and depression		
Sertraline HCI (Zoloft)	50 Mg in the morning	Well tolerated.
Fluoxetine HCI (Sarafem)	20 Mg in the morning	As sertraline however consider lower doses in patients aged over 65, with concurrent disease or multiple medications
Mirtazepine (Remeron)	15 Mg at bedtime	For use with depression and severe insomnia and anxiety

From Ancoli-Israel Geriatrics 2004, 59,1.

Sleep restriction limits the amount of sleep to the length of time that the person is likely to sleep. It aims to improve sleep efficiency (ratio of time asleep to time in bed) by either increasing time asleep or reducing time in bed. Most patients want to increase their time in bed, even though this may not be physiologically necessary. By asking patients to use a sleep diary carefully, sleep efficiency can be calculated and sleep compressed and, if necessary, expanded later as long as efficiency is maintained. It can be difficult to persuade elderly patients to accept this treatment as it is based on a key time when they must get up, however little sleep they may have had. In this way, their increasing tiredness will increase the drive for sleep.

Other cognitive behavioral techniques currently with less (although increasing) research evidence to support them include imagery and relaxation, paradoxical intention, and thought suppression. Daily exercise is thought to be important in promoting good sleep although firm evidence for it is again somewhat limited (Montgomery and Dennis, 2002c).

In acute insomnia, some patients may benefit from short-term use of sleep-promoting medications (Nowell *et al.*, 1997). Over-the-counter antihistamines should be used with caution because of their long duration of action and their anticholinergic effects in the elderly. These may cause confusion, constipation, and urinary retention. Among the hypnotics, the treatment of choice is a short-acting benzodiazepine receptor agonist. Short-term use and low doses are recommended. Occasional use reduces the possibility of withdrawal effects. The option to use such a drug may reduce anxiety about sleep in the patient and therefore be beneficial. In cases of excessive daytime sleepiness, referral to a sleep specialist is indicated, as this symptom can be dangerous.

The choice of sedative-hypnotic agent for insomnia should be based on issues of efficacy including whether it consolidates fragmented sleep, whether it can be administered at different times in the night, and the effect on next-day functioning. Thus, a short half-life with few withdrawal symptoms and minimal adverse events with no tolerance should be key considerations. Some common options are listed in Table 2.

It should be stressed that among a physician's first set of treatment goals should be the improvement of sleep hygiene in the patient, moving on to drug treatment only if this proves insufficient.

KEY POINTS

- It is necessary to ask directly about sleep problems lest they go unnoticed and untreated. Carefully considered sleep diaries and histories are essential diagnostic tools in this area.
- Nonpharmacological interventions such as sleep hygiene and cognitive behavioral treatments should be considered first.
- In dementia, encouraging a regular schedule including exercise and light meals (especially later in the day) but excluding alcohol and caffeine in the evening is helpful.
- Comorbid problems such as pain or depression and current medications should be considered as possible causes.
- Short half-life medications such as zolpidem and zaleplon may be considered for short-term use.

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PART III

Medicine in Old Age

Section 6

CNS Disorders

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Neurological Signs of Aging

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INTRODUCTION

Any attempt to describe the neurological signs of aging immediately prompts a number of challenging questions. Perhaps the most significant of these is how to ascribe neurological signs observed in later life to normal aging *per se*, rather than concurrent (and possibly subclinical) age-related neurological conditions such as cerebrovascular disease, Alzheimer's disease (AD), Parkinson's disease, or combinations thereof. Differing quantitatively or qualitatively from normal aging, such diseases fall within the province of geriatric neurology (Olney, 1995; Hamill and Pilgrim, 2000). From the clinical perspective, this is not merely a question of dry academic interest, since disease-related changes might be amenable to disease-specific therapeutic interventions, whereas age-related change might require acceptance as part of the human condition, perhaps abetted with sympathetic attempts at neurorehabilitation.

To define the neurological signs of normal aging, one requires a definition of "normal", which will determine the optimal requirements for a study that aims to describe such signs. The one absolute of studies of aging is substantial heterogeneity, in both control and age-related disease groups. Hence, should individuals selected for study be free of all age-related disease and medication use? Such individuals may be described as having undergone "successful" aging or "optimal" aging. By contrast, the category of "typical" aging accepts common age-associated disease (and medication use) as physiologically typical of the aging process. Such definitions may be informed by biological models of aging, such as senescence (age as a disease) or life-span (age as development) models (Smith and Ivnik, 2003). Considerations of this nature will also determine the locus of study populations (community based, hospital based, nursing home based), and whether an attempt should be made to include all relevant subjects or only those who volunteer for study.

"Successful" aging or "optimal" aging occurs in "supernormals", individuals whose function or performance clusters at the upper end of any normal distribution. Genetically, these individuals may differ from those undergoing "typical" or "normal" aging (Martin, 1998). Relatively greater or lesser vulnerability of aging tissues to disease processes (Geula *et al.*, 1998) and relative preservation or loss of neural regenerative capacities with aging (Larner and Sofroniew, 2003) may also be relevant.

Study logistics also need careful consideration. Cross-sectional studies, in which, for example, 20 year olds are compared with 50 year olds and 80 year olds, with assessment occurring at one time point, may overestimate age-related changes because of cohort effects such as differences in education or nutrition. Moreover, with lack of follow-up, it may be that "normals" in the older age-groups were in fact in the subclinical phase of age-related disease. Longitudinal studies of cohorts that might address such difficulties, by following individuals for many years with repeated examinations at successive time points, risk underestimating change due to loss of subjects to follow-up. Such studies are also expensive.

Definition of signs to be examined and standardization of testing procedures are also fundamental requirements. Disagreement between experienced examiners in the interpretation of neurological signs is well recognized (Stam and van Crevel, 1990; Maher *et al.*, 1992). Hence, prespecified operationalization of neurological examination and agreement on scoring or quantitation of signs are required for robust results (Franssen, 1993). Without specifying these parameters, it is difficult to realize a quantitative measure of the sensitivity and specificity of neurological signs with respect to aging.

Similar arguments apply to age-related changes in investigation findings, such as neuroimaging and electrodiagnostic studies, and likewise to the definition of the neuroanatomical substrates of change in neurological signs with aging. For example, cerebral atrophy on structural brain imaging or in postmortem tissue is not an uncommon finding in cognitively normal older individuals, and is not in itself an inevitable signature of AD.

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Table 1 Topographical overview of age-related neurological signs

Cognitive function
Loss of processing speed, cognitive flexibility, efficiency of working memory (sustained attention); preservation of vocabulary, remotely learned information including semantic networks, and well-encoded new information.
Cranial nerves
I: olfactory sense diminished
II: presbyopia; reduced visual acuity, depth and motion perception, contrast sensitivity
III, IV, VI: senile miosis; restricted upward conjugate gaze
VIII: presbycusis; impaired vestibulospinal reflexes
Motor system
Appearance: loss of muscle bulk; "senile tremor"
Tone: rigidity, gegenhalten/paratonia; mild parkinsonism
Power: decline in maximal muscle strength
Coordination: impaired speed of movement
Reflexes: depressed or absent phasic muscle stretch reflexes (especially ankle jerk); depressed cutaneous reflexes (e.g. abdominal); emergence of primitive or developmental reflexes (glabellar, snout, palmomental, grasp)
Sensory system
Decreased sensitivity to vibratory perception, +/− pain, temperature, proprioception

NEUROLOGICAL SIGNS OF AGING

An early and comprehensive review of the neurology of old age was given by Critchley in his three Goulstonian lectures delivered to the Royal College of Physicians of London in (Critchley, 1931). Since then many reviews have appeared, some indicating the need to revise the designation of "senile" for certain signs in favor of etiological explanations, which may carry therapeutic implications (Olney, 1995; Adams *et al.*, 1997; Hamill and Pilgrim, 2000).

Some neurological signs particularly associated with aging are briefly described (summarized in Table 1) along with details of their investigational correlates and neuroanatomical substrates where these are known. Techniques for eliciting neurological signs and their semiological value are not covered here (for further details, see Harrison, 1987; Haerer, 1992; Larner, 2001). The description follows the traditional, and somewhat arbitrary, sequence of the neurological examination.

COGNITIVE FUNCTION

A distinction may be drawn between crystallized intelligence, characterized by practical problem-solving skills, knowledge gained from experience, and vocabulary, and fluid intelligence, characterized by the ability to acquire and use new information as measured by the solution of abstract problems and speeded performance (Horn and Cattell, 1967).

Crystallized intelligence is assumed to be cumulative and longitudinal studies of, for example, vocabulary show that it does not decline through old age (Salthouse, 1982). By contrast, fluid intelligence does change with age, performance on tests such as Raven's Progressive Matrices and Digit Symbol Substitution declining marginally up to the age of 40 years and then more rapidly (Salthouse, 1982). There is general consensus that typical cognitive aging involves losses in processing speed, cognitive flexibility, and the efficiency of working memory (sustained attention). In other words, it may take more time and/or more trials to learn new information. The fact that cognitive domains such as access to remotely learned information including semantic networks and retention of well-encoded new information are spared with typical aging permits their use as sensitive indicators of disease processes (Smith and Ivnik, 2003). It may be that memory decline in healthy aging is secondary to decline in processing speed and efficiency: controlling for processing speed may attenuate or eliminate age-related differences in memory performance, unlike the situation with memory impairment in dementia (Sliwinski *et al.*, 2003).

Longitudinal studies of neuropsychological function in older Americans indicate that there is considerable variability in normal older adults across different skills, and consistency across different domains may not necessarily be observed (Smith and Ivnik, 2003). Clearly, this needs to be taken into account when assessing whether perceived cognitive decline is pathological or normal, that is, in defining neuropsychological norms for aging. Likewise, norms may need to be age-weighted rather than age-corrected to detect cognitive impairment related to AD (Sliwinski *et al.*, 2003), the prevalence of which increases exponentially with increasing age. Many other situational influences may also impact testing of cognitive skills, such as fatigue, emotional status, medication use, and stress. These need to be taken into account when considering the results of cognitive testing, as may other factors such as educational and background experience. Many norms are also culturally weighted.

It has been increasingly recognized in recent times that a degree of age-related cognitive decline may exist in individuals who do not fulfill validated criteria for the diagnosis of AD (McKhann *et al.*, 1984). Various terms have been used to describe this state, including benign senescent forgetfulness, age-associated memory impairment (AAMI), age-associated cognitive decline (AACD), cognitive impairment no dementia (CIND), and mild cognitive impairment (MCI). Consensus has developed around the concept of MCI, which may be defined by the presence of a memory complaint, preferably corroborated by an informant; evidence of objective memory impairment for age and level of education; largely normal general cognitive function; essentially intact activities of daily living; and failure to fulfill criteria for dementia (Petersen *et al.*, 1999; Ritchie and Touchon, 2000). The identification of MCI is important since longitudinal studies indicate a conversion rate to AD of around 10–15% per year.

The substrates for these changes have been examined using neuroimaging modalities and neuropathological material. Structural imaging techniques such as computed tomography (CT) and, particularly, magnetic resonance imaging (MRI) show a reduced volume of brain tissue and an increased volume of cerebrospinal fluid with increasing age.

The former consists predominantly of a decline in white matter (Albert, 1998). Hence, brain atrophy *per se* is not specific for the diagnosis of pathological change, an assumption which may lead to clinical misdiagnosis of AD if undue weight is placed on imaging findings (Larner, 2004a). Neuropathological studies have focused on both positive and negative phenomena (Albert, 1998; Hyman and Gómez-Isla, 1998). Of the former, neurofibrillary pathology (neurofibrillary tangles, neuropil threads) and senile neuritic plaques, hallmarks of the AD brain, may be seen in cognitively normal older individuals. The development of neurofibrillary pathology follows a relatively stereotyped hierarchical pattern with age, appearing first in the transentorhinal cortex (Arnold *et al.*, 1991; Braak and Braak, 1991). Spread to hippocampal and association cortex is associated with progressive appearance of cognitive decline. Senile plaques have a broader and more variable distribution; a significant burden may be associated with normal cognition. Negative phenomena include neuronal and synaptic loss. There is relative preservation of cortical and hippocampal neuronal populations with aging, although subcortical structures such as the basal forebrain, locus coeruleus, and substantia nigra do show losses. Marked cell loss has been observed in entorhinal cortex in MCI, followed later by involvement of association cortex, changes which increase in severity with increasing severity of illness. In other words, preclinical AD (MCI) and normal aging may be differentiated on a pathological basis.

A disease-modifying intervention at the stage of MCI might delay progression to, and hence reduce the incidence of, AD. A double-blind placebo-controlled trial of the cholinesterase inhibitor donepezil, licensed for use in the treatment of AD, in MCI has suggested initial delay in conversion rate in the treated group but with equalization of conversion rates by three years (Petersen *et al.*, 2004). In the future, drugs targeting specific pathogenetic processes in AD may find a role in MCI. Since the amyloid hypothesis remains the most tenable explanation of AD pathogenesis, targeting the Aβ protein by means of immunotherapy ("vaccine"; Schenk *et al.*, 1999) or secretase inhibitors (Larner, 2004b), and the consequences of its overproduction such as oxidative stress, would seem logical. However, vitamin E (α-tocopherol), which is believed to act as an antioxidant, failed to slow conversion rate of MCI to AD (Petersen *et al.*, 2004).

CRANIAL NERVES, INCLUDING SPECIAL SENSES

Olfaction (Olfactory Nerve; Cranial Nerve I)

The sense of smell diminishes with age, as does the sense of taste (which in fact depends to a great extent on olfaction). Impaired olfaction may also be an early sign of age-related disease, occurring in both Alzheimer's disease and Parkinson's disease (Hawkes and Shephard, 1998). There is early involvement of the olfactory pathways by both neurofibrillary (Braak and Braak, 1991) and α-synuclein (Braak *et al.*, 2003) pathology.

Visual System: Neuro-ophthalmology (Optic, Oculomotor, Trochlear, and Abducens Nerves; Cranial Nerves II, III, IV, VI)

Presbyopia is an age-related impairment of accommodation, attributed to increased rigidity of the lens, leading to hyperopia (far sightedness). Age-related changes have also been documented in visual acuity, visual field, depth perception, contrast sensitivity, motion perception, and perception of self-motion with reference to external space (optical flow). The pupils become progressively smaller ("senile miosis") and their reflex responses to light and accommodation become sluggish. Opacities in the lens and the vitreous may contribute to impaired visual acuity (including contrast sensitivity). Poor visual acuity may contribute to falls in the elderly (Lord *et al.*, 1999). Whether photoreceptor loss from the retina may also be a factor in these changes is uncertain, but may be relevant to diminished dark adaptation.

Eye movements may become more restricted with age, particularly upward conjugate gaze (also observed in parkinsonism) and convergence. Bell's phenomenon, the reflex upward and outward deviation of the eyes in response to attempted forced closure of the eyelids, may be lost.

Hearing and Balance (Vestibulo-cochlear Nerve; Cranial Nerve VIII)

Presbycusis is an age-related decline in hearing perception (i.e. increased auditory threshold), especially for high frequencies, which may also lead to reduced speech discrimination. It is believed to result primarily from loss of hair cells in the organ of Corti, although other structural changes in the auditory pathways may contribute, such as thickening of the basilar membrane, atrophy of the stria vascularis, and degeneration of neurones in the spiral ganglion and cochlear nuclei.

Age-related decline may occur in vestibular functions. Specifically, reductions in the ability to detect head position and motion in space, to elicit vestibulospinal reflexes, which trigger automatic postural responses when head position is changed, and to solve sensory conflicts, are not uncommon. The neuroanatomical correlate may be loss of vestibular hair cells and nerve fibers, and neuronal loss in the medial, lateral, and inferior vestibular nuclei in the brainstem.

SENSORIMOTOR FUNCTION: MOTOR SYSTEMS

Appearance

A progressive loss of muscle bulk occurs with aging, which is diffuse but most noticeable in intrinsic hand and foot muscles (Critchley, 1931). This is thought to be neurogenic, since electrophysiological studies show features of ongoing chronic partial denervation with compensatory reinnervation with aging (Howard *et al.*, 1988). Muscle fibers

deprived of the trophic support of their innervating axons will atrophy (Larner and Sofroniew, 2003). Muscle biopsies in clinically normal elderly individuals confirm neurogenic change to be more apparent than myopathic change, with variation in fiber size (type I or type I and II fiber atrophy) and fiber type grouping suggestive of reinnervation (Jennekens *et al.*, 1971). Degeneration of alpha motor neurones within the anterior (ventral) horns of the cervical and lumbar spinal cord is said to be the neuropathological correlate of these changes. However, fasciculations, a reliable sign of anterior horn cell disease, are not apparently a feature of normal aging: if fasciculations reflect motor axonal instability due to recent reinnervation and collateral axonal sprouting, rather than an effect of denervation *per se* (Desai and Swash, 1997), then the electrophysiological and histological predominance of denervation over reinnervation might explain the absence of fasciculations in the elderly. The finding of fasciculations should therefore prompt investigations for a pathological cause (motor neurone disease, compressive cervical radiculomyelopathy, multifocal motor neuropathy).

Tremor of the limbs and/or jaw has sometimes been given the label "senile", since more prevalent in the elderly. The epithet conceals ignorance of the genesis of these signs. Limb tremor may be one feature of the extrapyramidal (parkinsonian) syndrome seen with increasing age in community-dwelling healthy individuals (Bennett *et al.*, 1996, *vide infra: Tone*), although the possible diagnosis of essential tremor should also be borne in mind, particularly if these tremors are worse with volitional activity. A diagnosis of essential tremor may have implications for therapy. Jaw tremor, often associated with the loss of teeth, has sometimes been labeled edentulous tremor. Tardive dyskinesia, associated with previous neuroleptic use, enters the differential diagnosis. Other movement disorders such as athetosis and chorea in the elderly have also been labeled "senile" (Critchley, 1931) but an attempt to ascertain an etiological diagnosis should be made. Myoclonus, a common sign in advanced dementia, practically never occurs in normal old age (Hodges, 1994).

Tone

Rigidity, an increase in resistance to passive movement around a joint, which is constant throughout the range of joint displacement ("lead-pipe rigidity") and not related to the velocity of joint movement (cf. spasticity), is one feature of the extrapyramidal syndrome, or parkinsonism. Bradykinesia (slowness in initiation and performance of movement), tremor, and gait disturbance are also features of the syndrome of parkinsonism. A population-based study of 467 individuals aged over 65 years in East Boston, USA, who underwent a structured neurologic examination, found parkinsonism (defined as the presence of two or more of the following four signs: bradykinesia, gait disturbance, rigidity, and tremor) in 159 individuals (Bennett *et al.*, 1996). The prevalence of parkinsonism increased with age. Neuropathological evidence of the progressive spread of α-synuclein-immunopositive Lewy bodies and Lewy neurites in the brains of aging but asymptomatic individuals (Braak *et al.*, 2003) may be the neuropathological correlate of these clinical findings.

In addition to rigidity of extrapyramidal origin, another form of increased tone may be observed in older patients: "superadded hypertonus of a quasi-volitional nature due to the patient's failure to relax as soon as his limbs are under examination" (Critchley, 1931). This clinical finding may be described as paratonia, paratonic rigidity, or *gegenhalten*. The anatomical correlate is bilateral frontal lobe pathology, most usually diffuse (small vessel) cerebrovascular disease. Some authors classify paratonia as a release sign (Franssen, 1993).

Power

Decline in muscle strength occurs progressively with aging (Potvin *et al.*, 1980). Loss of muscle bulk (muscle wasting; *vide supra: Appearance*) is thought by some authors to be insufficient to explain the extent of weakness, although, as for wasting, neurogenic changes are thought to be the relevant neuroanatomical substrate (Howard *et al.*, 1988). The oxidative capacity of exercising old muscle is reported to be less than that of young muscle. Strength may also be dependent on the integration of central mechanisms, which may also be impaired with aging due to loss of motor cortex cells, pruning of pyramidal cell dendritic trees, and loss of synapses. Nonneurological factors such as age-related joint pain and deformity may contribute to loss of power.

Coordination

Coordination refers to the rate, range, timing, and direction of movement. Impairments in the speed of movement develop with advancing age, for example, in hand or foot tapping. Activities of daily living such as dressing take more time in older individuals (Potvin *et al.*, 1980). These findings may reflect changes in muscle strength, the bradykinesia of the extrapyramidal syndrome (parkinsonism), which becomes more prevalent with age (Bennett *et al.*, 1996), or a combination of these. Cerebellar signs per se (finger–nose, heel–shin, or gait ataxia) were noted to be rather uncommon in old age by Critchley (1931). Huff *et al.* (1987) did note cerebellar ataxia in some normal controls, although the finding was said to be more common in AD patients.

Reflexes

1. **Phasic Muscle Stretch Reflexes ("Deep Tendon Reflexes")**

Depression (hyporeflexia) or absence (areflexia) of distal reflexes, particularly of the ankle (or Achilles tendon)

jerks, with age has been noted; perhaps <20% of healthy community-dwelling individuals over 65 years have absent ankle jerks (Olney, 1995). However, Impallomeni *et al.* (1984) reported ankle jerks to be present in 94% of a cohort of hospital admissions aged 65 or over. The timing or method (plantar strike, Achilles tendon strike) of eliciting the reflexes may contribute to the variability of findings. Moreover, it should not be forgotten that there is interobserver variation in the assessment of reflexes, and a biasing effect of prior clinical knowledge (Stam and van Crevel, 1990). Slight asymmetry of reflexes seems not uncommon in normal adults, occurring in 3% in one study (Huff *et al.*, 1987).

Although typically regarded as part of the motor examination, the monosynaptic reflex arc encompasses both sensory and motor components. Both elements seem to be affected with age. Electrophysiological studies show not only reduction in the amplitude of sensory nerve action potentials with aging but also slowing of nerve conduction velocities, which reflect conduction in the large myelinated fibers that subserve the efferent limb of the monosynaptic reflex arc (Taylor, 1984).

2. **Superficial or Cutaneous Reflexes**

Included within this rubric are abdominal reflexes, cremasteric reflexes (seldom examined), and plantar responses.

It is said that abdominal reflexes may become depressed with age *per se*, but other factors such as obesity, previous abdominal surgery, and a history of multiple pregnancies, known to lead to their loss, may also contribute (Larner, 2001). Corticospinal pathway damage (upper motor neurone lesions) above T6 may lead to loss of all superficial abdominal reflexes while lesions at or below T10 lead to selective loss of the lower reflexes with preservation of the upper and middle reflexes, in which case Beevor's sign (upward movement of the umbilicus in a supine patient attempting to flex the head onto the chest against the resistance of the examiner's hand) may also be present. All abdominal reflexes are preserved with cord lesions below T12. However, long tract signs in the legs are likely to be more obvious than abdominal reflex change with cord lesions at any level.

Extension ("dorsiflexion") of the big toe when the lateral border of the foot is stroked with a blunt object, Babinski's sign, is deemed a reliable sign of upper motor neurone pathology other than in infants below about 24–36 months of age (hence this may also be regarded as a primitive or developmental reflex; *vide infra: Primitive or developmental reflexes; "frontal release" signs*). No consistent changes have been documented with normal aging (Van Gijn, 1996), although it is often difficult for even experienced practitioners to form a definite judgment on the plantar response, and its reproducibility is also questionable (Maher *et al.*, 1992). Assessment of the response may be confounded by withdrawal of the foot in ticklish individuals. Differentiation from the striatal toe seen in some parkinsonian syndromes is also important. Some studies looking at neurological signs in patients with dementia as compared to normal controls have reported up to 5% abnormality of the plantar response in the control populations (Huff *et al.*, 1987; Galasko *et al.*, 1990).

3. **Primitive or Developmental Reflexes; "Frontal Release" Signs**

A number of entities may be placed within this rubric of release signs (Franssen, 1993), including paratonia (*vide supra: Tone*). The category may be further subdivided into prehensile and nociceptive reflexes; the former includes the sucking reflex (tactile and visual), hand grasp reflex, foot grasp reflex (tonic foot response), and the rooting reflex; the latter includes the snout reflex, glabellar (blink) reflex, and palmomental (palm–chin) reflex (Franssen, 1993; Hodges, 1994; Rossor, 2001). Corneomandibular and nuchocephalic responses are also described as primitive or developmental (Franssen, 1993).

Such reflexes may occur in normal individuals with aging. For example, in a study of 2029 elderly volunteers aged 50–93 years, Jenkyn *et al.* (1985) found a significant increase in all the signs in patients over the age of 70 years. Examining glabellar, snout, palmomental, and grasp reflexes, Huff *et al.* (1987) found the prevalence of primitive reflexes to be 9% in control subjects. Similar findings are reported by others (Koller *et al.*, 1982; Galasko *et al.*, 1990; Franssen, 1993). Of course, in the absence of longitudinal follow-up, it is possible that some of these "control" patients may have had preclinical AD. Hence, although such signs occur more frequently in those with AD, their sensitivity and specificity for the diagnosis is poor.

Station and Gait: Postural Responses

No neurological examination is complete without examination of the patient's gait, and this is particularly important in the elderly, since they are more prone to falls. Although some may be ascribed to pathological processes such as cervical myelopathy, Parkinson's disease, or peripheral neuropathy (Sudarsky, 1990), or due to environmental factors such as uneven floors, obstacles, or poor lighting, many defy such explanation.

Walking has two major components, equilibrium (maintaining an upright posture) and locomotion (gait ignition and stepping). Changes in both functions occur with aging.

A framework to classify impaired gait in the elderly has been suggested (Nutt *et al.*, 1993).

Maintaining balance whilst standing on one leg with the eyes closed shows significant change with aging (Potvin *et al.*, 1980). Increased postural sway also occurs with aging. Sway may be related to sensory impairments in the feet, particularly proprioception (Lord *et al.*, 1999), with additional contributions from poor visual acuity and changes in vestibular function. Postural righting responses may be slowed and of reduced amplitude (Weiner *et al.*, 1984).

For the maintenance of static balance, somatosensory function is the most important system; if impaired, reliance on visual function becomes more prominent. When both

somatosensory and visual inputs are impaired, leaving vestibular function as the primary sense for balance control, difficulties are immediately apparent. Age-related changes in balance control subsystems are common, involving not only the sensory systems (somatosensory, visual, and vestibular function), but also motor systems (strength, range of motion, coordination) and cognitive functions (sensory adaptation, attention), all of which may contribute to balance problems and falls in the elderly. However, such changes are neither inevitable nor irreversible, permitting the possibility of improvements in balance and mobility and a reduced incidence of falls in older adults (Tang and Woollacott, 2004).

Critchley's (1931) assertion that *marche à petits pas*, characterized by loss of elasticity, shortened steps, and broadened base, was "almost characteristic of healthy old age" is no longer tenable, such changes now being thought to reflect pathological small vessel cerebrovascular disease (Nutt *et al.*, 1993). The changes in gait and stance more commonly seen with aging are akin to those of parkinsonism, with slightly stooped posture, reduced arm swing, and mild shortening of steps. In the community-based study of parkinsonism in the elderly (vide supra: Tone; Bennett *et al.*, 1996), individuals with parkinsonism showed a twofold increased risk of death over a mean follow-up of 9.2 years, and this was strongly related to gait disturbance. Other gait disorders such as frontal gait disorder, cautious gait, and isolated gait ignition failure (previously labeled gait apraxia) remain poorly understood but possibly reflect pathology within cortical motor pathways (Rossor *et al.*, 1999), perhaps in combination with other factors.

SENSORIMOTOR FUNCTION: SENSORY SYSTEMS

Somatosensory Function

A decrease in the sensitivity of vibratory perception (i.e. an increase in perceptual threshold) is the most prominent age-related finding on sensory examination, particularly distally and more so in the legs than the arms (Potvin *et al.*, 1980). Some studies also report distal diminution in perception of painful and tactile stimuli, and of proprioception (Kokmen *et al.*, 1978).

Distal degeneration of sensory axons is thought to be the neuroanatomical correlate of impaired distal sensation, reflected functionally in the reduction in amplitude of sensory nerve action potentials (Taylor, 1984). Morphologically, aging sural (i.e. sensory) nerves show a reduced density of myelinated and unmyelinated nerves and increased endoneurial collagen in individuals over the age of 60 years, as well as changes indicative of nerve regeneration and degeneration, and demyelination and remyelination. Aging is also associated with reduplication of vascular basement membranes and thickening of perineurial basement membranes (Jacobs and Love, 1985). These age-related changes may contribute to the cryptogenic sensory and sensorimotor neuropathies occurring in the elderly that tend not to progress rapidly and seldom lead to significant motor disability (Wolfe and Barohn, 1998).

CONCLUSIONS

The previous tendency to label cognitive, motor, and sensory neurological changes occurring in the elderly as "senile", implying a relationship to aging *per se* and hence not requiring further elucidation, has been rightly replaced with a desire to search for etiological explanations for such changes. Nonetheless, some common neurological signs occurring with aging defy explanation and, hence, by exclusion, may be labeled "age-related". Undoubtedly, structural and functional changes occur within the nervous system with aging, and awareness of the consequent neurological signs will guide physicians in their appropriate management of these changes.

KEY POINTS

- Aging may have various meanings (successful, optimal, typical) that should be taken into account when considering which signs may be judged representative of "normal" aging.
- Aging is associated with cognitive changes, specifically slower learning of new information and decline in delayed recall. These changes may reflect slowed processing speed and attentional function, rather than more rapid forgetting, and may be qualitatively different to the memory problems seen in pathological conditions such as AD.
- The typical motor changes seen with aging include distal muscle wasting and weakness, with diminution or loss of distal reflexes. These changes are thought to be neurogenic, since electrodiagnostic and neuropathological studies indicate denervation and reinnervation of muscle fibers.
- Parkinsonian signs insufficient to fulfill a diagnosis of idiopathic Parkinson's disease are extremely common with increased age; these signs include bradykinesia, rigidity, tremor, and gait disturbance, the last of which may be associated with falling, a factor associated with an increased risk of death. In contrast to these extrapyramidal features, pyramidal and cerebellar dysfunction is uncommon in normal aging; such findings should prompt a search for a pathological explanation.
- In the sensory system, loss of distal vibratory sensibility is common with aging; other modalities such as pain and proprioception may also be involved. These changes reflect distal degeneration of sensory axons. They may contribute to the propensity to fall in the elderly.

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65

Headache in the Elderly

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INTRODUCTION

The International Headache Society (IHS), in its newest classification, ICHD-II (Headache Classification Committee, 2004), continues to divide headaches into two broad categories: primary and secondary headache disorders. Secondary headaches are attributed to another disease and can be caused by intracranial or extracranial structural abnormalities or by systemic or metabolic conditions. In the primary headache disorders, the headache itself is the illness (Table 1). The primary headache disorders include migraine, tension-type headache (TTH), and trigeminal autonomic cephalalgias (including cluster headache). Migraine is further subdivided into two groups: migraine without aura and migraine with aura. TTH is subclassified as either episodic tension-type headache (ETTH) or chronic tension-type headache (CTTH). Cluster headache is similarly divided into the episodic and chronic varieties. Chronic daily headache (CDH), a term in common use, is subclassified by the IHS into CTTH, chronic migraine (CM), hemicrania continua (HC), and new daily persistent headache (NDPH), and is often associated with acute medication overuse.

Headache prevalence is age-dependent. Migraine prevalence peaks near age 40 and declines afterward (Figure 1). With aging, not only is there a change in prevalence of the primary headache disorder but also a shift to new or organic causes of headache (Edmeads, 2000). Migraine incidence and prevalence decrease, while brain tumors, subdural hematomas, and other structural causes of headache increase. Elderly patients have more comorbid medical illness, and some headache disorders, such as temporal arteritis, occur principally in the elderly (Table 2).

Headache is common in the elderly. The 1-year prevalence of headache in a rural elderly Italian population was 51.0%; TTH 44.5%, migraine headache 11.0%, CDH 4.4%, and symptomatic headache 2.2% (Prencipe *et al.*, 2001).

The complaint of "frequent headache" was found in 11% of elderly women and 5% of elderly men participating in a health screening program; however, these patients were commonly found to have other diseases or somatic or psychologic symptoms (Edmeads, 2000). These facts justify a lowered threshold for ordering tests when older patients present with headache, particularly if the headaches are of recent onset, are atypical, or are associated with neurologic findings. Headaches that begin after age 65 are more often due to serious conditions.

The evaluation of the elderly patient with headache must be directed to rule out serious secondary causes of headache such as tumor, subdural hematoma, stroke, transient ischemic attack, and temporal arteritis. In the elderly patient, when the diagnosis is not obvious, neuroimaging and a sedimentation rate should be considered (Edmeads, 2000) (Table 3). In this chapter, we will discuss the primary headache disorders as they relate to the older patient, some of the serious secondary headache disorders, and finally cranial neuralgias.

Diagnosis and Clinical Description of Headaches

The formal criteria for headache diagnosis were updated by the IHS in 2004 (Headache Classification Committee, 2004). The first step in establishing a diagnosis is a complete history. It should include the following information: the age at headache onset; the time of onset (day, season); the location, severity, and type of pain; the attack frequency (including any change in frequency); associated symptoms; precipitating and relieving factors; the patient's sleep habits; and the family history. In addition, a complete medication history should be taken to evaluate the doses, duration of use, and effectiveness of previous headache medications as well as to determine if any medications that could exacerbate headaches are being used or overused.

The patient should keep a diary to record any changes in headache between office visits, especially if medication was modified. A diary will make the patient more aware of the disease process as well as help the physician evaluate the effectiveness and adverse effects of treatment. Patients should bring their medications with them periodically to

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Table 1 IHS migraine classification

1. Migraine
   - 1.1 Migraine without aura
   - 1.2 Migraine with aura
     - 1.2.1 Typical aura with migraine headache
     - 1.2.2 Typical aura with non-migraine headache
     - 1.2.3 Typical aura without headache
     - 1.2.4 Familial hemiplegic migraine (FHM)
     - 1.2.5 Sporadic hemiplegic migraine
     - 1.2.6 Basilar-type migraine
   - 1.3 Childhood periodic syndromes that are commonly precursors of migraine
     - 1.3.1 Cyclical vomiting
     - 1.3.2 Abdominal migraine
     - 1.3.3 Benign paroxysmal vertigo of childhood
   - 1.4 Retinal migraine
   - 1.5 Complications of migraine
     - 1.5.1 Chronic migraine
     - 1.5.2 Status migrainosus
     - 1.5.3 Persistent aura without infarction
     - 1.5.4 Migrainous infarction
     - 1.5.5 Migraine-triggered seizures
   - 1.6 Probable migraine
     - 1.6.1 Probable migraine without aura
     - 1.6.2 Probable migraine with aura
     - 1.6.5 Probable chronic migraine

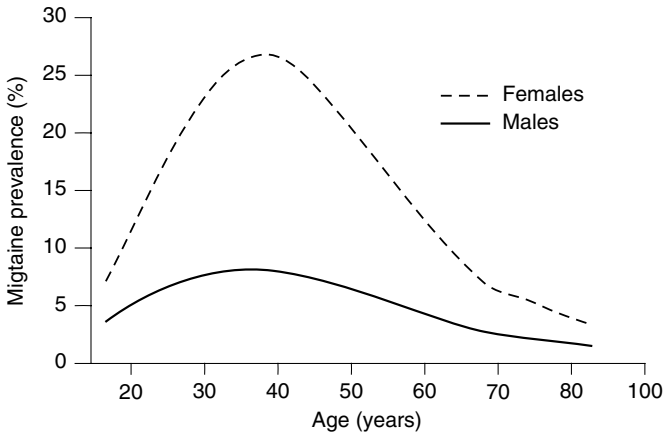

Figure 1 Migraine prevalence by age. Prevalence increased from 12 to 38 years of age in both women and men; the peak was considerably higher among women. (Reprinted from *Neurologic Clinics*, V14, Silberstein and Lipton, Headache epidemiology: emphasis on migraine, pp 421–434, Copyright 1996, with permission from Elsevier)

Table 3 Worrisome headache flags (SNOOP) (American Headache Society & American Academy of Neurology, 2001)

- **S**ystem symptoms (fever, weight loss) or **S**econdary risk factors (HIV, systemic cancer)
- **N**eurologic symptoms or abnormal signs (confusion, impaired alertness or consciousness)
- **O**nset – sudden, abrupt, or split-second
- **O**lder – new onset and progressive headache, especially in middle-age >50 (giant cell arteritis)
- **P**revious headache history – first headache or different (change in attack frequency, severity or clinical features)

check for compliance and to see if other physicians have prescribed any additional medications.

PRIMARY HEADACHES IN THE ELDERLY

Migraine

Migraine occurs in 18% of women, 6% of men, and 4% of children in the United States (Lipton *et al.*, 2001). Sixty-two percent of migraineurs also have TTH. Migraine usually begins in the first three decades of life, and prevalence peaks in the fifth decade. The prognosis for migraine sufferers is good, since migraine prevalence decreases with increasing age. While migraine can begin after age 50, a secondary organic cause must be considered when this occurs. In one study, only one of 193 patients with headache beginning after age 65 had migraine. Cull (Cull, 1995) collected 10 patients with migraine onset after age 60, two of whom had strokes on computed tomography (CT) finding. The ratio of migraine with aura to migraine without aura was reversed (86%:14%) among new onset migraine patients older than age 40. Whether this is due to referral patterns or biological factors is uncertain.

Migraine prevalence decreases with menopause, although the prevalence does not fall to premenarchal levels. The frequency of migraine aura without headache (migraine equivalents) in the elderly is unknown. In community-based studies, migraine prevalence varied from 0.3% in China (age >70) to 12% in Boston (age >65). In some, but not all studies, migraine prevalence continued to decrease in the very elderly (Lipton *et al.*, 2001).

Table 2 Headache in the elderly

Less common	Equally common	More common	Typically in the elderly
♦ Migraine	♦ Cluster headache	♦ Intracranial lesions	♦ Giant cell arteritis
♦ Tension-type headache	♦ Cervicogenic headaches	♦ Medication-induced (except rebound)	♦ Hypnic headache
		♦ "Metabolic headache"	♦ Headache of Parkinson's disease
		• anemia	
		• hypoxia	
		• hypercalcemia	
		• hyponatremia	
		• chronic renal failure	
		♦ Cerebrovascular disease	

Modified from Edmeads (2000)

Clinical Features of Migraine

Migraine is an episodic headache disorder whose diagnosis depends on the characteristics of the pain and associated features. The IHS criteria for migraine without aura (Table 4) require the patient to have at least five headache attacks (Headache Classification Committee, 2004). With time, the associated symptoms of migraine decrease, in part accounting for the decrease in migraine prevalence, since the headaches may no longer meet the IHS criteria for migraine. The migraine aura may occur without the headache, and migraine may remit or become transformed into CDH (with or without medication overuse).

A diagnosis of migraine with aura (classic migraine) requires the patient to have at least two attacks with at least three characteristics listed in Table 5. If the aura lasts longer than one hour but less than a week, the condition is called *migraine with prolonged aura* (Headache Classification Committee, 2004).

Migraine is more than just an aura and a headache. Some patients have four phases: the premonitory phase, the aura, the headache, and the postdrome. About 60% of patients have a prodrome, which occurs hours to days before the headache. During this time, patients may have various psychologic, sensory, constitutional, or autonomic symptoms. Not all patients experience a prodrome, but if they do, their prodromal symptoms are usually the same each time. The symptoms can continue into the aura and headache phases (Silberstein *et al.*, 2001).

The aura develops over 5–20 minutes, lasts from 20 to 30 minutes, and consists of focal neurologic symptoms that accompany the headache or occur up to an hour before it begins. About 20% of migraineurs experience an aura, which may be visual, sensory, or motor, or involve speech disturbances. Visual symptoms are the most common and include scintillations (fluorescent flashes of light in the visual field), fortification spectra or teichopsia (alternating light and dark lines in the visual field), photopsia (flashing lights), positive scotomata (bright geometric lights in the visual field), and negative scotomata (blind spots that may move across the visual field). Sensory symptoms include numbness, tingling, or paresthesias of the face or hand. Motor symptoms are usually hemiparetic, while language disturbances consist of difficulty in speaking (aphasia) or understanding (Silberstein *et al.*, 2001).

The headache can begin at any time during the day. The pain usually develops gradually, and then subsides after 4–72 hours. A headache lasting longer than 72 hours defines status migrainosus. The pain is usually located in the temples, but it can occur anywhere in the face or head and may radiate down the neck and shoulder. The pain is moderate to severe in intensity and usually described as throbbing or pulsating. Pain is usually unilateral, but may begin as, or become bilateral. Strictly unilateral headaches are not of concern since they occur in 20% of migraineurs. Accompanying symptoms are common: most patients are anorectic and have nausea; some vomit or have diarrhea. Photophobia and phonophobia cause patients to seek relief in a dark, quiet room to decrease sensory stimulation. Most patients have one to four attacks a month.

After the headache phase, some patients experience a postdrome or recovery phase that may last up to 24 hours. Some patients feel tired, others feel alert, some feel depressed, others feel euphoric, some feel worn out, while some feel refreshed. Some may complain of poor concentration, food intolerance, or scalp tenderness.

Medications that are more commonly used by the elderly may exacerbate or trigger migraine. Analgesic, ergotamine, or triptan overuse can cause CDH in patients of all ages. Nitroglycerin and other nitrates may exacerbate migraine. Estrogen replacement therapy may either exacerbate or ameliorate migraine. Reserpine, an antihypertensive agent, is a recognized migraine trigger.

Table 4 Migraine without aura

Diagnostic criteria

A. At least 5 attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not attributed to another disorder

Table 5 Migraine with aura

Diagnostic criteria

A. At least 2 attacks fulfilling criterion B
B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1–1.2.6
C. Not attributed to another disorder

1.2.1 Typical aura with migraine headache

Diagnostic criteria

A. At least 2 attacks fulfilling criteria B–D
B. Aura consisting of at least one of the following, but no motor weakness:
   1. Fully reversible visual symptoms including positive features (e.g., flickering lights, spots or lines) and/or negative features (i.e. loss of vision)
   2. Fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
   3. Fully reversible dysphasic speech disturbance
C. At least two of the following:
   1. Homonymous visual symptoms and/or unilateral sensory symptoms
   2. At least one aura symptom develops gradually over $\geq$5 minutes and/or different aura symptoms occur in succession over $\geq$5 minutes
   3. Each symptom lasts $\geq$5 and $\leq$60 minutes
D. Headache fulfilling criteria B–D for 1.1 *Migraine without aura* begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

Migraine Equivalents of the Elderly

In the elderly, migraine aura without headache (acephalic migraine) is also called *late-life migraine accompaniments*. It may occur for the first time in a patient over the age of

Table 6 Migraine equivalents

1. Gradual appearance of focal neurologic symptoms' spread or intensification over a period of minutes
2. Positive visual symptoms characteristic of "classic" migraine, specifically fortification spectra (scintillating scotoma), flashing lights, dazzles
3. Previous similar symptoms associated with a more severe headache
4. Serial progression from one accompaniment to another
5. The occurrence of two or more identical spells
6. A duration of 15–25 minutes
7. Occurrence of a "flurry" of accompaniments
8. A generally benign course without permanent sequelae

40 (Fisher, 1980). Its diagnosis is particularly treacherous in patients with no prior history of migraine and should be made by exclusion unless the symptoms are pathognomonic of the migraine aura (e.g. scintillating scotomata lasting 30 minutes). Features are listed in Table 6. The headaches are usually absent or, if present at all, mild, and neuroimaging is normal. The IHS diagnostic criteria are the same as in Table 5, migraine with aura, except for no headache (Headache Classification Committee, 2004).

Cerebrovascular disease (cerebral embolism or thrombosis, carotid or vertebral dissection, subclavian steal syndrome), epilepsy, polycythemia, thrombocytopenia, lupus anticoagulant, hyperviscosity syndrome, and psychiatric spells must always be considered in the differential diagnosis and must be ruled out by the appropriate studies (Edmeads, 2000; Fisher, 1986).

Treatment of Migraine Headache in the Elderly

Headache treatment begins with making the diagnosis and explaining it to the patient, since all treatment depends on establishing a therapeutic relationship. Drug treatment may be acute, preventive, or both, supplemented by nonpharmacologic treatment (Table 7). Acute migraine treatments are listed in Table 8. Because of an increased risk of cardiovascular disease, ergot alkaloids, triptans, and other vasoconstrictors, such as isometheptane mucate (present in Midrin®), must be used with caution if at all in the elderly. Benzodiazepines and barbiturates may cause excessive sedation; the long acting benzodiazepines, in particular, may cause excessive side effects due to slowed metabolic clearance. Antiemetic drugs and neuroleptics are more likely to cause tardive dyskinesia in the elderly. Even nonsteroidal anti-inflammatory drugs (NSAIDs) may cause cognitive side effects and are associated with an increased risk of gastrointestinal bleeding (Silberstein *et al.*, 2001).

Table 7 Migraine treatment

Acute (symptomatic)
- Specific – for migraine only
- Nonspecific – for any pain disorder or associated symptoms

Preventive (prophylactic)
- Preemptive – immediately prior to triggering event
- Short-term – for limited time
- Chronic – continuous

Preventive treatments (Table 9) may also cause more side effects and be less well tolerated in the elderly. Therefore, they should be started at a very low dose and increased slowly. The tertiary amine tricyclic antidepressant agents, such as amitriptyline and doxepin, which are potent anticholinergic agents, should be used with caution. They can exacerbate glaucoma, produce visual blurring, and cause problems with cognition. Nortriptyline, a secondary amine, is a reasonable alternative and generally has less pronounced side effects. The selective serotonin reuptake inhibitors, while not as effective, are very safe in the elderly. Antihypertensive drugs may cause more hypotension or lethargy in the elderly than in younger patients. Divalproex sodium and topiramate have a particularly good benefit-to-side-effect profile in the elderly. Methysergide (no longer available in the United States) and methylergonovine are relatively contraindicated because they are vasoconstrictors and may cause cardiac ischemia (Silberstein *et al.*, 2001).

Nonpharmacologic treatment in the elderly, as in all patients, is attractive because it avoids medications that may present risks or cause excessive side effects. Elimination of triggers, proper diet, regular sleep, and avoidance of excess caffeine are useful modalities for all patients. Biofeedback may not be as effective in the elderly patient. The most important nonpharmacologic approach involves the meticulous identification and treatment of comorbid medical and psychiatric conditions. Cervical triggers and other sources of pain should be treated with physical modalities if possible. Depression is extremely common and should be addressed (Silberstein *et al.*, 2001).

Tension-type Headache

TTH is the most common headache type, with a lifetime prevalence of 69% in men and 88% in women (Lipton *et al.*, 2001). TTH can begin at any age, but onset during adolescence or young adulthood is most common. Headache prevalence declines with increasing age; severity decreases in the women who continue to report headaches but does not change in men. Approximately 10% of patients acquire TTH after age 50. The IHS criteria for TTH are listed in Table 10. The headache may be shorter or longer in duration than migraine. TTH is mild or moderate in intensity and has no accompanying autonomic symptoms. The cause of this common disorder is unknown, but it is not related to muscular tension (patients with migraine have more muscle tension than patients with TTH).

TREATMENT OF TTH IN THE ELDERLY

Acute TTH often responds to nonpharmacologic treatment. If the headache does not respond to this approach and medication is needed, many patients self-medicate with over-the-counter analgesics (aspirin, acetaminophen, ibuprofen, naproxen), with or without caffeine. Combination analgesics

Table 8 Abortive medications – efficacy, side effects, relative contraindications, and indications

Drug	Efficacy[a]	Side effect[a]	Comorbid	
			Relative contraindications	Relative indication
Acetaminophen	2+	1+	Liver disease	Pregnancy
Aspirin	2+	1+	Kidney disease, ulcer disease, PUD, gastritis (age <15)	CAD, TIA
Butalbital, caffeine, and analgesics	2+	2+	Use of other sedative; history of medication overuse	
Caffeine adjuvant	2+	1+	Sensitivity to caffeine	
Isometheptene	2+	1+	Uncontrolled HTN, CAD, PVD	
Opioids	3+	3+	Drug or substance abuse	Pregnancy; rescue medication
NSAIDs	2+	1+	Kidney disease, PUD, gastritis	
Dihydroergotamine				Orthostatic hypotension, prominent nausea or vomiting
– Injections	4+	2+	CAD, PVD, uncontrolled HTN	
– Intranasal	3+	1+		
Ergotamine			Prominent nausea or vomiting, CAD, PVD, uncontrolled HTN	
– Tablets	2+	2+		
– Suppositories	3+	3+		
Triptans				
Almotriptan				
– Tablets	3+	1+	CAD, PVD, uncontrolled HTN	
Eletriptan				
– Tablets	3+	1+		
Frovatriptan				
– Tablets	2+	1+	CAD, PVD, uncontrolled HTN	
Naratriptan				
– Tablets	2+	1+	CAD, PVD, uncontrolled HTN	
Rizatriptan				
– Tablets	3+	1+	CAD, PVD, uncontrolled HTN	
Sumatriptan				
– SC injection	4+	1+	CAD, PVD, uncontrolled HTN	Prominent nausea or vomiting
– Intranasal	3+	1+	CAD, PVD, uncontrolled HTN	
– Tablets	3+	1+	CAD, PVD, uncontrolled HTN	
Zolmitriptan				
– Tablets	3+	1+	CAD, PVD, uncontrolled HTN	Prominent nausea or vomiting
– Intranasal	3+	1+	CAD, PVD, uncontrolled HTN	

PUD, Peptic ulcer disease; PVD, Peripheral vascular disease; CAD, Coronary artery disease; TIA, Transient ischemic attack; HTN, Hypertension; NSAIDs, Nonsteroidal anti-inflammatory drugs; SC, Subcutaneous.
[a]Ratings are on a scale from 1+ (lowest) to 4+ (highest) based on response rates and consistency of response in double-blind placebo-controlled trails and our clinical experience.

Table 9 Prevention

Drug	Efficacy[a]	Side effects[a]
Beta-blockers	4+	2+
Antiserotonin		
Methysergide	4+	4+
Calcium channel blockers		
Verapamil	2+	1+
Antidepressants		
Tricyclics	4+	2+
Selective serotonin reuptake inhibitors	2+	1+
Anticonvulsants		
Divalproex	4+	2+
Gabapentin	2+	2+
Topiramate	4+	2+
Nonsteroidal anti-inflammatory drugs		
Naproxen	2+	2+

[a]Ratings are on a scale from 1+ (lowest) to 4+ (highest).

contain sedatives or caffeine, and their use should be limited, as overuse may cause dependence. Narcotic analgesics and benzodiazepines should be avoided due to their abuse potential. Overusing symptomatic medications, including tranquilizers and analgesics, can cause ETTH to convert to CTTH (Silberstein and Lipton, 2001).

Preventive therapy should be administered when a patient has frequent headaches that produce disability or may lead to acute medication overuse. Antidepressants, the medication of choice, should be started at a low dose and increased slowly every three to seven days.

Chronic Daily Headache

CDH may be due to CTTH, CM, HC, or NDPH and is often associated with acute medication overuse (Table 11). It is important to determine the subtype of CDH so that the appropriate treatment can be chosen. When concurrent depression and medication dependence accompany CDH, treatment is difficult and detoxification may be required. Refractory medication overuse headaches (MOHs) may occur when analgesics or triptans are taken more frequently than three days a week or opioids or ergotamine tartrate more often

Table 10 Tension-type headache (IHS classification)

2.2 Frequent episodic tension-type headache
Diagnostic criteria
A. At least 10 episodes occurring on ≥1 but <15 days per month for at least 3 months (≥12 and <180 days per year) and fulfilling criteria B – D
B. Headache lasting from 30 minutes to 7 days
C. Headache has at least two of the following characteristics:
   1. Bilateral location
   2. Pressing/tightening (non-pulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. No nausea or vomiting (anorexia may occur)
   2. No more than one of photophobia or phonophobia
E. Not attributed to another disorder

2.3 Chronic tension-type headache
Diagnostic criteria
A. Headache occurring on ≥15 days per month on average for >3 months (≥180 days per year) and fulfilling criteria B – D
B. Headache lasts for hours or may be continuous
C. Headache has at least two of the following characteristics:
   1. Bilateral location
   2. Pressing/tightening (non-pulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. No more than one of photophobia, phonophobia, or mild nausea
   2. Neither moderate or severe nausea nor vomiting
E. Not attributed to another disorder

Table 11 Chronic daily headache

Primary
– Headache duration greater than four hours
  • Chronic migraine (CM)
  • Chronic tension-type headache (CTTH)
  • New daily persistent headache (NDPH)
  • Hemicrania continua (HC)
– Headache duration less than four hours
  • Cluster headache
  • Chronic oaroxysmal hemicrania
  • Hypnic headache
  • Idiopathic stabbing headache

Secondary
– Medication overuse headache (MOH)
– Posttraumatic headache (PTH)
– Cervical spine disorders
– Headache associated with vascular disorders (arteriovenous malformation, arteritis (including giant cell arteritis), dissection, subdural hematoma)
– Headache associated with nonvascular intracranial disorders (intracranial hypertension, infection (EBV, HIV), neoplasm)
– Other (temporomandibular joint disorder; sinus infection)

than two days a week. To avoid this situation, all acute medications must be used within defined limits (Silberstein and Lipton, 2001).

Patients overusing acute medications must be detoxified. This can be done as an outpatient by slowly tapering the offending medication if there are no risk factors, their use is not excessive, and the patient can tolerate it. If the patient cannot tolerate the taper, NSAIDs or a short course (about two weeks) of corticosteroids may be useful. Clonidine (0.1–0.3 mg bid–tid) is helpful for treating the symptoms of opioid withdrawal, and phenobarbital helps with withdrawal from short acting barbiturates. Refractory patients often require hospitalization. Repetitive intravenous (IV) DHE should be used with caution because of the potential for cardiac ischemia. High dose IV corticosteroids and neuroleptics can be used instead (Silberstein and Lipton, 2001).

Cluster Headache

Cluster headache prevalence is lower than that of migraine or TTH, with a rate of 0.01–0.24% in various populations. Prevalence is higher in men (70–90%) than in women and in Caucasians compared with African-Americans. The most common form of cluster headache is episodic (only about 10% of cluster patients have chronic cluster headache) (Table 12). Cluster headache can begin at any age: it most commonly begins in the late 20s, rarely in childhood, and occasionally (10%) in patients in their 60s. The prognosis of cluster headaches is guarded; it is a chronic headache disorder that may last for the patient's entire life (Dodick *et al.*, 2000).

The diagnosis of cluster headaches requires the patient to have at least five attacks. Episodic cluster has bouts lasting one week to a year with remission periods lasting at least one month, whereas chronic cluster has no remission periods or remissions that last less than one month. Untreated, the attacks generally last from 30 to 90 minutes, but they may also last up to 180 minutes. Most patients have one or two cluster periods a year that last two to three months, with one to two attacks per day. Episodic cluster can evolve into

Table 12 Cluster headache

3.1 Cluster
Diagnostic criteria
A. At least 5 attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15 to 180 minutes if untreated
C. Headache is accompanied by at least one of the following:
   1. Ipsilateral conjunctival injection and/or lacrimation
   2. Ipsilateral nasal congestion and/or rhinorrhea
   3. Ipsilateral eyelid edema
   4. Ipsilateral forehead and facial sweating
   5. Ipsilateral miosis and/or ptosis
   6. A sense of restlessness or agitation
D. Attacks have a frequency from one every other day to 8 per day
E. Not attributed to another disorder

3.1.1 Episodic cluster
Diagnostic criteria
A. Attacks fulfilling criteria A–E for 3.1 *Cluster headache*
B. At least two cluster periods lasting 7 to 365 days and separated by pain-free remission periods of ≥1 month

3.1.2 Chronic cluster
Diagnostic criteria
A. Attacks fulfilling criteria A–E for 3.1 *Cluster headache*
B. Attacks recur over >1 year without remission periods or with remission periods lasting <1 month

chronic cluster. Cluster attacks may begin with slight discomfort that rapidly increases (within 15 minutes) to excruciating pain. Patients may say "It's like driving a hot poker into my eye". The attacks often occur at the same time each day and frequently awaken patients from sleep. Lacrimation, the most common associated symptom, is reported by about 83% of patients. Patients with cluster headaches should avoid alcohol and nitroglycerin. Most cluster headache patients require preventive treatment because each attack is too short in duration and too severe in intensity to treat with only abortive medication. In addition, ergotamine, DHE, and sumatriptan are risky in the elderly, and oxygen inhalation, while safe, may just postpone, rather than abort, the attack. Preventive therapy for episodic cluster, in order of preference, includes calcium channel blockers, divalproex, topiramate, lithium, corticosteroids, and melatonin. Long-term corticosteroids are not appropriate for chronic cluster (Dodick *et al.*, 2000).

Hypnic Headache

Hypnic headache (Table 13) is a rare, strictly nocturnal headache that occurs in older persons (mean age 63). The headache typically awakens the patient from sleep and can occur at the same time on one or more occasions per night. The headaches are usually throbbing and bilateral, last approximately 1 hour, and may be associated with nausea. There are usually no associated autonomic features. Lithium carbonate, at a low dose of 300–600 mg at bedtime, is an effective treatment. Other treatments include caffeine and indomethacin (Evers and Goadsby, 2003).

SECONDARY HEADACHE DISORDERS

Headache Associated with Cerebrovascular Disease

Stroke incidence increases with age. In one study, headache was a feature of 17 of 29 (59%) infarcts. It is more common in large artery occlusive disease than cerebral embolism, and less common in lacunar infarction. Headache in carotid artery occlusion is usually located around the eye of the occluded side. Headache location is unreliable to localize a stroke, especially for vertebrobasilar disease. About 50% of headaches are severe enough to be "troubling"; they may last from 8 to 24 hours. Headache is present in 23–68% of patients with intraparenchymal hemorrhage; the highest headache frequency occurs in cerebellar and lobar hemorrhages. It is not clear how often the headache location predicts the site of the hemorrhage.

The frequency of headache in transient ischemic attacks (TIAs) varies from 6 to 44%. Medina noted headache in 15 of 34 TIA patients occurring during, immediately before, or after the neurologic event. Migraine headaches occurred independently of the TIAs in 38% of these patients. It is possible that late-onset migraine may be a marker for cerebrovascular disease.

Table 13 Hypnic headache

4.5 Hypnic headache
Diagnostic criteria
A. Dull headache fulfilling criteria B–D
B. Develops only during sleep, and awakens patient
C. At least two of the following characteristics:
1. Occurs >15 times per month
2. Lasts ≥15 minutes after waking
3. First occurs after age of 50
D. No autonomic symptoms and no more than one of nausea, photophobia or phonophobia
E. Not attributed to another disorder

Giant Cell Arteritis (*see* Chapter 115, Diseases of the Joints)

Giant cell arteritis (GCA) occurs in three to nine per 100 000 patients over the age of 50, with women affected three times as often as men. Headache, the most frequent symptom, is present in 70–90% of patients. Pain can be intermittent or constant. The headache is often located over the temples and associated with scalp tenderness. Symptoms of polymyalgia rheumatica, which include muscle pain and joint stiffness, are present in 25% of patients. Other common symptoms include fever, weight loss, night sweats, masseter claudication, tongue ischemia, amaurosis fugax (which may be bilateral in half), permanent blindness (often without warning), or partial visual loss due to anterior ischemic optic neuropathy. Amaurosis fugax is particularly ominous; if it is not treated, about one-half of patients will become blind.

Induration and tenderness of the temporal or occipital scalp arteries are the most common signs of temporal arteritis. Optic disc edema and visual loss may occur. Altitudinal defects and central scotomas breaking into the periphery are frequently seen. Diplopia is rare and, when present, is due to extraocular muscle ischemia. True cranial nerve palsy is very uncommon. Arterial bruits or diminished pulses are present in one-third of patients. Aortic arch syndrome may occur with rupture.

The most consistent laboratory abnormality is an elevation of the erythrocyte sedimentation rate (measured by the Westergren method). Wall and Corbett (2000) report that 41% of patients had a value greater than 100 mm hour^{-1} and 89% had a value greater than 50 mm hour^{-1}. Elevated C-reactive protein, mild liver function abnormalities, and mild hyperchromic or hypochromic anemia are common. Temporal artery biopsy, the diagnostic gold standard, should be performed within one week of initiating steroid treatment. Color-coded duplex sonography helps identify the most appropriate part of the superficial temporal artery to biopsy. A long piece of artery should be obtained and multiple sections examined to improve yield. If the biopsy is negative and the index of suspicion is high, more sections should be examined and a second temporal artery biopsy done. Corticosteroids, with or without methotrexate, should be started as soon as possible to prevent blindness.

Headache Associated with Mass Lesions

Headache frequently accompanies subdural hematoma; in one series it occurred in 62% of patients. Headache occurs at presentation in up to half of the patients with brain tumors and develops during the course of the disease in 60%. Headache is partly dependent on tumor location: it is a rare initial symptom in patients with pituitary tumors, craniopharyngiomas, or cerebellopontine angle tumors. In older, pre-CT or MRI series of brain tumor patients, headache occurred as often without as it did with elevated intracranial pressure. The headache, while usually generalized, could overlie the tumor.

Postulated mechanisms of headache development include traction on pain-sensitive intracerebral vessels, transient herniation of hippocampal gyri, traction on cranial or cervical nerves, elevation of intracranial pressure, or activation of a quiescent headache disorder. Although increased cerebrospinal fluid (CSF) pressure is not necessary for headache development, it clearly plays a role in a group of patients with central nervous system neoplasms.

One pre-CT/MRI series looked at the characteristic headache features of 221 patients who had brain tumors, only 60% of whom had headache. Tumor location had no significant bearing on the presence or absence of headache. Pain intensity was mild to moderate in 63% of patients and severe in 37%. The headaches were intermittent in 85%, throbbing in 15%, aggravated by changing position in 20% and by coughing or exertion in 25%, and on the side of the tumor in 30%. Five patients had exertional headache. Half of the patients had nausea or vomiting. Twenty-five percent had headache during sleep, upon arising, or both. Increased intracranial pressure was observed in 42% of patients with headache and 6% of patients without headache.

In a survey of 778 patients with cerebral tumor, headache was the earliest or principal symptom in 54%. No difference in headache frequency was noted between rapidly growing and slow-growing tumors. The headache could occur intermittently and mimic migraine.

In a modern series, 111 consecutive patients with primary (34%) or metastatic (66%) brain tumor were diagnosed with neuroimaging. Increased intracranial pressure was defined by the presence of papilledema, obstructive hydrocephalus, communicating hydrocephalus from leptomeningeal metastasis, or a lumbar puncture opening pressure >250 mm of CSF. Headache, present in 48% of both primary and metastatic tumors, was similar to TTH in 77% of patients and to migraine in 9%. Unlike true TTH, brain tumor headaches were worsened by bending in 32%, and nausea or vomiting was present in 40%.

Eight-six percent of patients with increased intracranial pressure had headache that was typically frontal in location and pressure-like or aching in character. Only 1% had a unilateral headache. The headache was constant in 61%. The pain was severe in intensity, associated with nausea and vomiting, and resistant to common analgesics. Ataxia was present in 61%. In contrast, only 36% of patients with a supratentorial tumor without increased intracranial pressure had headache. These headaches were milder and more likely to be intermittent (however, they were constant in 20% of patients). Nausea, vomiting, and ataxia were much less common.

Patients with a history of prior headache were more likely to have brain tumor headache. In many cases this headache was similar in character to the prior headache, but it was more severe or frequent, or associated with neurologic signs or symptoms.

In another prospective study of patients with brain tumor, only 8% had headache as their first and isolated clinical manifestation at the time of diagnosis. Thirty-one percent had headache, but only one of the original patients continued to have headache as an isolated symptom.

There is a significant overlap between brain tumor headache and migraine and TTH. Any neurologic sign or symptom that occurs with a headache and cannot be easily explained by the aura of migraine, a headache of recent onset, or a headache that has changed in character requires a thorough evaluation, particularly if the headache is severe or is accompanied by nausea or vomiting. Increased headache frequency and morning or nocturnal headache associated with vomiting can be seen with both migraine and brain tumor. Brain tumor headache is more common in patients with a history of prior headache, increased intracranial pressure, and large tumors with a midline shift.

In space-occupying lesions other than brain tumors, such as subdural hematomas and brain abscesses, headache is a more frequent and earlier symptom. McKissock (1960) reported that 81% of his 216 patients with chronic subdural hematoma had headache, with a lesser prevalence in acute (11%) and subacute (53%) subdural hematomas. The difference in headache prevalence between tumor and subdural hematoma is believed to be due to the more rapid evolution and greater extent of the hematomas. The lesser occurrence of headache in acute and subacute subdural hematomas compared with chronic subdural hematoma may be due to the underlying traumatic cerebral changes in the former obtunding consciousness early and making it difficult to elicit a history of headache. The headache is often ipsilateral to the subdural hematoma or brain tumor.

Patients with brain abscesses often have a progressively severe, intractable headache. In published clinical series, headache was present in 70–90% of patients. The higher headache prevalence in abscess, compared to tumor, may be due to its faster evolution, the associated meningeal reaction, and the occasional low-grade fever that may accompany abscess.

Parkinson's Disease (*see* Chapter 66, Parkinson's Disease and Parkinsonism in the Elderly)

The association between Parkinson's disease and headache is controversial. In one series, headache occurred in 41% of patients with Parkinson's disease and 13% of controls. Another controlled series found no difference in headache prevalence. Possible headache mechanisms include comorbid

depression and muscle rigidity. In one study of early morning occipital headache in Parkinson's disease, headache failed to improve with treatment directed at muscle spasm, but did improve with levodopa. Headaches may respond to amitriptyline.

Medication-induced Headache

Medications used for the treatment of coexistent disease may trigger headaches. These include nitrates, some calcium channel blockers, estrogens and progestins, histamine receptor blockers, theophylline, and NSAIDs. Overuse of caffeine, analgesics, narcotics, ergotamine, and triptans can lead to CDH.

Posttraumatic Headache

Age is probably neither protective nor conducive to the development of posttraumatic headache (PTH) after mild head injury. The features of PTH are variable, and diagnosis requires the onset of a new kind of headache (substantially different from previous headaches) within 7 days of the head injury or of regaining consciousness from the head trauma. Increasing age is associated with less rapid and less complete recovery.

Headaches Associated with Disorders of the Cervical Spine

The association between disease of the spine and headache is controversial. The IHS has adopted restrictive criteria for these headaches. Generally accepted causes of headache related to cervical spine lesions, as well as currently controversial causes, are listed in Table 14. Many of the noncontroversial causes of cervicogenic headache (such as Paget's disease and tumors) are more common in the elderly. Radiographic spondylosis worsens with age but its relationship to headache is uncertain. If the patient has nonheadache indications for MRI or EMG, such as myelopathy or radiculopathy, these disorders should be diagnosed and treated on their own merit. Tender spots can be treated with an injection of local anesthetic and corticosteroids.

Table 14 Cervicogenic headache

11.2.1 Cervicogenic headache
Diagnostic criteria
A. Pain, referred from a source in the neck and perceived in one or more regions of the head and/or face, fulfilling criteria C and D
B. Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be, or generally accepted as, a valid cause of headache
C. Evidence that the pain can be attributed to the neck disorder or lesion based on at least one of the following:
   1. Demonstration of clinical signs that implicate a source of pain in the neck
   2. Abolition of headache following diagnostic blockade of a cervical structure or its nerve supply using placebo- or other adequate controls
D. Pain resolves within 3 months after successful treatment of the causative disorder or lesion

Glaucoma

Primary open-angle glaucoma, the most common cause of glaucoma, is rarely painful. Miotic eyedrops used in its treatment may produce brow ache. Acute angle closure glaucoma is less common and may produce intense eye pain that radiates widely and may be associated with nausea and sinus area pain; it is often associated with a red eye, corneal cloudiness, and a red sclera. Laser iridotomy is curative. Secondary angle closure glaucoma resulting from diabetes or carotid insufficiency may produce a deep, boring, unrelenting pain associated with a red eye and poor vision. To make the diagnosis of glaucoma-related headache, the pain should develop simultaneously with the glaucoma and be relieved within 72 hours of effective treatment.

Sinusitis

Acute purulent sinusitis produces severe headache associated with purulent nasal discharge. A dangerous exception to this rule is sphenoid sinusitis, which may present as a severe, intractable, progressive headache.

OTHER HEAD AND FACIAL PAIN SYNDROMES AFFECTING THE ELDERLY

Trigeminal Neuralgia

Trigeminal neuralgia is the most common neuralgic syndrome, with a peak incidence in the 6th and 7th decades (Table 15). Secondary trigeminal neuralgia usually presents at a younger age. Trigeminal neuralgia is typically unilateral, but is bilateral in 4% of patients. Symptoms include repetitive jolts of electric-like pain in the distribution of one or more divisions of the trigeminal nerve. The paroxysms of pain are characteristically induced by touching a "trigger zone" in the relevant division of the 5th cranial nerve. Brushing the teeth,

Table 15 Cranial neuralgias

13.1.1 Classical trigeminal neuralgia
Diagnostic criteria
A. Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes, affecting one or more divisions of the trigeminal nerve and fulfilling criteria B and C
B. Pain has at least one of the following characteristics:
   1. Intense, sharp, superficial or stabbing
   2. Precipitated from trigger areas or by trigger factors
C. Attacks are stereotyped in the individual patient
D. There is no clinically evident neurological deficit
E. Not attributed to another disorder

chewing, talking, or even a wisp of air on the face can trigger an attack. Between paroxysms, a sustained, deep, dull ache may be present.

Pretrigeminal neuralgia is a dull, continuous, achy pain in the jaw, which may be provoked by pressure about the face or mouth and may evolve into trigeminal neuralgia. It may account for many of the cases of trigeminal neuralgia diagnosed after multiple dental procedures, since the clinical features are not distinctive.

The diagnosis of trigeminal neuralgia is established by typical clinical features and an examination that is negative except for positive trigger points; diagnostic studies are generally normal. Impaired sensation in the distribution of the fifth nerve suggests a structural, demyelinating, or compressive trigeminal nerve lesion. Aneurysms, GCA, intracranial tumors, dental mandibular malignancy, or cranial malignancy can produce the symptoms of trigeminal neuralgia associated with decreased facial sensation. Multiple sclerosis, dental pathology, or a dental procedure can produce a pattern of pain indistinguishable from trigeminal neuralgia. The natural history of trigeminal neuralgia is variable. Periodic remissions are common, but permanent spontaneous remissions are rare. Over 50% of patients have a remission that lasts 6 months or more.

Trigeminal neuralgia is thought to be due to focal demyelination of the trigeminal nerve. In 80–90% of cases, this is caused by vascular compression from abnormal arterial loops near the root entry zone of the nerve. Aberrant neuronal activity may arise from these injured areas, which could promote changes in the trigeminal nucleus caudalis.

Medical treatment is usually successful (Figure 2, Table 16). Drugs used include gabapentin, carbamazepine, oxcarbazepine, phenytoin, baclofen, valproic acid, clonazepam, and pimozide, alone or in combination. Combination therapy is often effective and necessary. Phenytoin can be given intravenously to control especially painful paroxysms.

If medication fails to adequately control symptoms, ablative procedures should be considered. Alcohol or glycerol injections may be used. More proximal injections produce better long-term results. Gasserian ganglion injections have a five-year recurrence rate of 41–86%. Retrogasserian glycerol injections can produce mild facial numbness, but painful dysesthesias are rare and anesthesia dolorosa is absent. Mean recurrence time varies from 6 to 47 months. Percutaneous

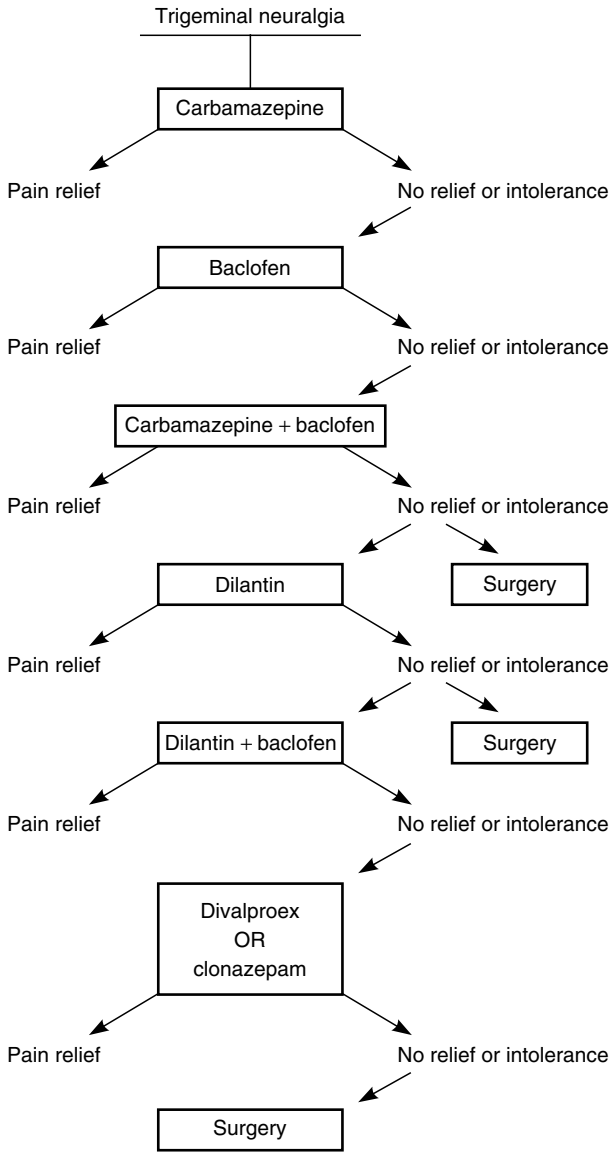

Figure 2 A proposed algorithm for the medical treatment of trigeminal neuralgia. Once the patient has been pain-free for 3–6 months on a medication, the drug should be slowly tapered off to avoid medicating during spontaneous remission. If the pain recurs, the medication is reinstituted. Individual needs may dictate earlier surgery. (Modified from Masdeu (1990))

Table 16 Characteristics of antineuralgic drugs

Drug	Bioavailability (Percentage)	Time to maximum concentration (H)	Half-life (H)	Time to steady state concentration (Days)	Therapeutic 'Target' range (Mmol l^{-1})
Baclofen	–	3–8	3–4	1	–
Carbamazepine	>70	2–8	11–27	5	24–43
Clonazepam	100	1–2	24–48	12	30–270
Gabapentin	60–27[a]	2–3	5–7	2	70–12
Lamotrigine	100	2–3	18–30	8	4–16
Oxcarbazepine	100	1–2	14–26	7	35–110
Phenytoin	98	4–8	15–20	14	20–80
Valproic acid	99	1–4	6–17	5	200–700

Modified from Zakrzewska (1995).
[a]Low dose gabapentin (900 mg day^{-1} divided) is 60% and high dose 3600 mg is 27% bioavailability (Nahlik, 2004).

balloon compression of the trigeminal ganglia may be similarly effective. Radiofrequency gangliolysis provides relief in 82–100% of patients and has a recurrence rate between 9 and 28%. Major complications are rare; loss of corneal reflex occurs in as many as 70% of patients and masseteric weakness occurs in approximately half, but improves over three to six months. Minor paresthesias occur in about 10%, but anesthesia dolorosa is rare.

The Janetta procedure, performed via an occipital craniotomy, removes aberrant blood vessels, if present, from the trigeminal nerve root. Long-term benefit is reported in over 80% of patients, with recurrence rates of 1–6%. Surgical mortality is 1% and serious morbidity 7%. Because of this, other, less invasive surgical procedures, such as percutaneous glycerol injection and radiofrequency rhizotomy, which have less morbidity, should be tried first, even though they may be only temporarily effective. More recently, several radiosurgical techniques aimed at the trigeminal nerve root adjacent to the pons have been successful.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia (GN) (Table 17) is less common than trigeminal neuralgia. The unilateral pain occurs in the distribution of the glossopharyngeal and vagus nerves in and around the ear, jaw, throat, tongue, or larynx. Radiation from the oropharynx to the ear is common. Paroxysms of jabbing or electric pain last for about one minute and may be accompanied by deep, continuous pain between paroxysms. Patients may have as many as 30–40 attacks per day and may be awakened from sleep.

Paroxysms of pain may be triggered by chewing, talking, yawning, coughing, or swallowing cold liquids. Stimulation of the external auditory canal and postauricular area may also provoke pain. In approximately 2% of cases, syncope (secondary to bradycardia or asystole) and seizures (from cerebral ischemia) have occurred. Atropine prevents syncope, which suggests that vagal afferent discharge is its mechanism.

The diagnosis of GN is clinical. Neurologic examination is usually normal. Other disorders are ruled out by history, physical examination, and diagnostic testing. The assumed cause of GN is nerve compression from aberrant blood vessels. Symptomatic causes of a GN-like syndrome include cerebellopontine angle tumor, nasopharyngeal carcinoma, carotid aneurysm, peritonsillar abscess, and compression from an osteophytic stylohyoid ligament lateral to the glossopharyngeal nerve.

The best diagnostic test involves anesthetizing the tonsil and pharynx, which can temporarily terminate a painful paroxysm and confirm the diagnosis. Drug treatment is the same as for trigeminal neuralgia. Surgical treatment involves intracranial sectioning of the glossopharyngeal nerve and the upper rootlets of the vagus at the jugular foramen. A microvascular decompression procedure has recently been described.

Table 17 Glossopharyngeal neuralgia

13.2.1 Classical glossopharyngeal neuralgia
Diagnostic criteria
A. Paroxysmal attacks of facial pain lasting from a fraction of a second to 2 minutes and fulfilling criteria B and C
B. Pain has all of the following characteristics:
1. Unilateral location
2. Distribution within the posterior part of the tongue, tonsillar fossa, pharynx or beneath the angle of the lower jaw and/or in the ear
3. Sharp, stabbing and severe
4. Precipitated by swallowing, chewing, talking, coughing and/or yawning
C. Attacks are stereotyped in the individual patient
D. There is no clinically evident neurological deficit
E. Not attributed to another disorder

Postherpetic Neuralgia (*see* Chapter 148, Infections of the Central Nervous System)

Postherpetic neuralgia (Table 18) follows an attack of acute herpes zoster, evolving as the acute attack subsides. One definition is the presence of pain more than a month after the eruption of zoster. Old age, diabetes mellitus, ophthalmic herpes zoster, and a compromised immunologic system increase the risk for postherpetic neuralgia. Postherpetic neuralgia is a significant cause of head pain in the elderly.

Acute zoster often begins with paresthesias and pain in the affected region, followed four or five days later by a vesicular eruption. Most patients have a deep aching or burning pain, paresthesias, and dysesthesias. Some may have hyperesthesia or electric shock-like pains. Typical involvement in the head occurs unilaterally in the distribution of the ophthalmic or maxillary divisions of the trigeminal nerve, or at the occipitocervical junction. Ophthalmic herpes may be associated with diplopia due to involvement of cranial nerves III, IV, and VI. Geniculate herpes is associated with facial palsy (CN VII). Vesicles are often seen in the external auditory canal.

The incidence of postherpetic neuralgia depends on its definition, which varies from pain persisting for one month to pain persisting for six months. Age, severity, and the presence of uremia correlate with developing postherpetic neuralgia. It is more common in the elderly, occurring in 5% of patients with acute zoster who are below 40 years of age, in 50% of those in the 7th decade, and in 75% of those above 70 years of age. Slow, spontaneous improvement of pain occurs in most patients; in 3 years, 56% of patients are either completely pain-free or have nontroublesome pain.

The pain occurs in areas overlying abnormal hyperesthetic skin and has three components: (1) constant, deep,

Table 18 Chronic postherpetic neuralgia

13.15.2 Postherpetic neuralgia
Diagnostic criteria
A. Head or facial pain in the distribution of a nerve or nerve division
B. Herpetic eruption in the territory of the same nerve
C. Pain preceded herpetic eruption by <7 days
D. Pain persists after 3 months

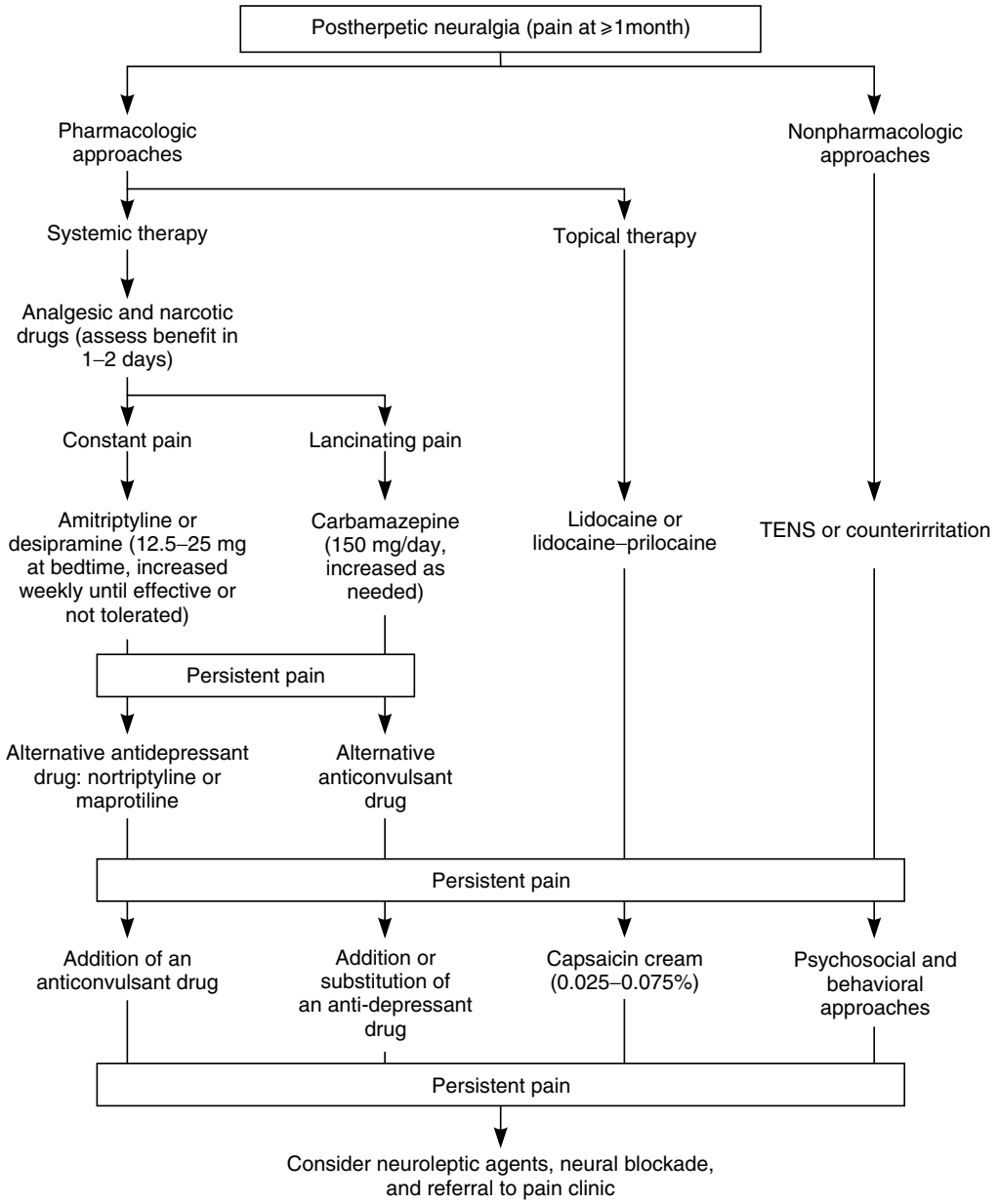

Figure 3 Algorithm for the treatment of persistent postherpetic pain. (Reprinted with permission from *New England Journal of Medicine*, vol 335, Kost and Straus, Drug Therapy: Postherpetic neuralgia – pathogenesis, treatment and prevention, pp 32–42. Copyright 1996 Massachusetts Medical Society)

burning pain; (2) repetitive stabs and needle pricking sensations; and (3) superficial, sharp, radiating or itch sensation provoked by light touch. Sleep is often interrupted. Postherpetic neuralgia may reflect a deafferentation pain syndrome and may be accompanied by increased sympathetic activity.

Topical therapies such as compresses of Burow's solution, colloidal oatmeal, or calamine lotion are used to treat acute zoster. The skin should be protected with sterile dressings. Oral glucocorticoids may lead to faster resolution of acute zoster pain, but it is not clear if they have any value in preventing or attenuating postherpetic neuralgia. Antiviral agents may attenuate acute herpes zoster in immunocompromised patients. Acyclovir used for 21 days may ameliorate pain in the acute phase. Famciclovir, valacyclovir, and brivudin may be superior to acyclovir. Acyclovir and famciclovir have not been proven to reduce the risk of postherpetic neuralgia. Epidural blockade or sympathetic blockade may help pain acutely and may reduce postherpetic neuralgia.

Postherpetic neuralgia should be treated as soon as the diagnosis is made. Amitriptyline is commonly used, but nortriptyline or desipramine may be preferable, since they have fewer anticholinergic side effects. Gabapentin and pregabalin were studied in several double-blind, placebo-controlled trials to control pain (at doses of gabapentin

from 2400 to 3600 mg day^{-1} or pregabalin at 600 mg day^{-1}). Capsaicin, a substance-P depleter, may be of some benefit, but burning may limit its usefulness. Topical nonsteroidal anti-inflammatory agents may be useful. Local anesthetic preparations are also effective. Peripheral and central surgical techniques are of little, if any, value (Figure 3).

KEY POINTS

- The International Headache Society (IHS) divides headaches into two broad categories: primary and secondary headache disorders.
- With aging, not only is there a change in prevalence of the primary headache disorder but also a shift to new or organic causes of headache.
- Headache is common in the elderly.
- The evaluation of the elderly patient with headache must be directed to rule out serious secondary causes of headache such as tumor, subdural hematoma, stroke, transient ischemic attack, and temporal arteritis.
- Medications that are more commonly used by the elderly may exacerbate or trigger migraine.
- In the elderly, migraine aura without headache (acephalic migraine) is also called late-life migraine accompaniments.
- Hypnic headache is a rare, strictly nocturnal headache that occurs in older persons.
- Giant cell arteritis occurs in three to nine per 100 000 patients over the age of 50, with women affected three times as often as men.
- The association between Parkinson's disease and headache is controversial.
- Trigeminal neuralgia is the most common neuralgic syndrome in the elderly, with a peak incidence in the 6th and 7th decades.

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66

Parkinson's Disease and Parkinsonism in the Elderly

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INTRODUCTION

Parkinsonism is a major cause of disability in old age. Parkinson's disease (PD) is almost the perfect example of an age-related disease. In the United Kingdom, the development of multidisciplinary Parkinson's clinics has been led by geriatricians and almost 70% of parkinsonian patients have their care supervised by geriatricians. The disease, a chronic disabling disorder that is progressive, becomes more common with increasing age. Approximately two-thirds of the patients are over the age of 70. Features which make this disease a suitable condition for geriatricians to specialize in are frequent nonspecific presentation, and a wide range of disabling features such as immobility, postural instability, cognitive impairment and psychiatric illnesses, loss of independence in the activities of daily living, and disturbances in autonomic function. Although the disease results from an irreversible degenerative pathology, the skilled use of drugs and rehabilitation can be extremely successful in reducing disability and maintaining independence.

Parkinsonian patients have complex and often unmet needs, which require sophisticated developments in service to provide the necessary support within the community. Multidisciplinary management needs to be the rule with the provision of rehabilitation and social support being central. For many years the diagnosis of Parkinson's disease has been purely clinical and often prone to significant errors. New imaging techniques such as SPECT scanning and clearer criteria for diagnosis are leading to improved differentiation between Parkinson's disease and other parkinsonian syndromes.

There have been major advances in the understanding of the underlying pathophysiology of Parkinson's disease. These insights link it with other neurodegenerative diseases such as Alzheimer's disease. There is a real hope that this increase in understanding will result in treatment that is disease modifying. At the moment there is considerable debate on the correct strategy for managing Parkinson's disease. The age of the patient is certainly a crucial factor in deciding the appropriate therapeutic regimen for the individual patient.

Definition, Classification, and Diagnosis of Parkinsonian Syndrome

Parkinsonism is an umbrella term for any chronic movement disorder, having two or more of the clinical features of rest tremor, rigidity, bradykinesia, and the gait/postural changes associated with Parkinson's disease. The term Parkinson's disease is usually reserved for the clinicopathological condition where the features of Parkinsonian disorder correlate with the pathological changes in the basal ganglia, most notably Lewy body inclusions and the loss of pigmented neurones in the substantia nigra. When the diagnosis is made on purely clinical grounds, precision in the diagnosis of Parkinson's disease is relatively poor. Meara *et al.* (1999) in North Wales showed that there was an error rate of $>50\%$ in general practice diagnoses. Hughes *et al.* (1992) in two studies 10 years apart showed that 25% of patients confidently diagnosed initially by experts on the basis of the strict Brain Bank Criteria did not demonstrate the pathological changes of Parkinson's disease at autopsy. A follow up study 10 years later showed that this error rate had been reduced by 10%, but the increase in specificity was off set by loss of sensitivity with cases of classical Parkinson's disease being missed (Hughes *et al.*, 2002). There has been a growing recognition that Lewy bodies are not confined to the basal ganglia and are represented in the cortex in all cases of Parkinson's disease. Lewy body dementia, in which parkinsonism is associated with visual hallucinations, dementia, and other psychiatric features is an increasingly recognized and defined clinical

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entity (McKeith *et al.*, 2004). Although Lewy bodies are required for the pathological diagnosis of Parkinson's disease they are certainly not specific to it, having been described in a range of other disorders including Alzheimer's disease, Hallervorden-Spatz disease, Down's syndrome, and motor neurone disease. Incidental Lewy bodies not associated with pathology increase with age. In patients dying over the age of 80, Lewy bodies can be demonstrated in approximately 13% of autopsies with no correlation with parkinsonian symptoms.

The United Kingdom Parkinson's Disease Brain Bank Diagnostic Criteria for Parkinson's disease (Table 1) form a useful basis for diagnosing Parkinson's disease. The first step is to accurately recognize the cardinal features of parkinsonism. Bradykinesia is indicated by the presence of a variety of symptoms and signs, of which the most important are, loss of normal spontaneous movement, lack of facial expression, reduced arm swing, difficulty in initiating stopping movements or sequential movements, progressive reduction in the amplitude and speed of repeated movements, and overall slowness in all forms of movement. The akinesia complex is the main source of disability in parkinsonism. Rigidity (increase in muscle tone and response to passive movement) affects all muscle groups, and although usually demonstrated in the upper limb, also affects axial muscles, which may be accentuated by asking the patient to move a contralateral limb. Classically, extrapyramidal rigidity remains constant throughout the range of movement (lead pipe rigidity); however; in practice it is usually jerky as a result of a combination with tremor (cogwheel rigidity). In the older patient often the tremor is not overtly expressed, but its presence is actually determined by the demonstration of cogwheel rigidity. The distribution of increased tone in axial muscles is slightly biased to flexor muscles resulting in a characteristically stooped posture. Although tremor is the commonest presenting feature in 70% of patients with Parkinson's disease, it is not unusual for a tremor to be absent, particularly in late onset disease. Parkinsonian tremor is very distinctive; a coarse peripheral tremor most often affecting upper limbs, in the form of the classical pill-rolling tremor between the thumb and index finger, which is present even at rest. The resting frequency is 4–6 Hz but there is quite often a more rapid postural element. However, the tremor is usually abolished by purposeful movement of the hand. In some patients, there is an intentional element, which can often confuse the diagnosis.

Table 1 United Kingdom Parkinson's Disease Society brain bank diagnostic criteria for PD

STEP 1 Diagnosis of parkinsonian syndrome

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following:

- Muscular rigidity
- 4–6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebella, or proprioceptive dysfunction

STEP 2 Exclusion criteria for PD

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- >1 affected relative
- Sustained remission
- Strictly unilateral features after three years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinsk's sign
- Presence of a cerebral tumor or communicating hydrocephalus on computed tomography scan
- Negative response to large doses of levodopa (if malabsorption excluded) *MPTP* exposure*

STEP 3 Supportive prospective positive criteria for PD: three or more required for diagnosis of definite PD

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side of onset most
- Excellent (70–100%) response to levodopa
- Severe levodopa-induced chorea
- Levodopa response for >5 years
- Clinical course of >10 years

Differential Diagnosis of Parkinsonism

Some aspects of "normal aging" can superficially mimic parkinsonian features (see Table 2) – stooped posture, generalized slowing of movement, intellectual change, absence of emotional expression, reduced amplitude to stride, increased sway, stiffness of joints and muscles, and poor exercise tolerance. Confounding disease processes are almost universal over the age of 75 – degenerative osteoporosis, dementia, and depression are sufficiently common that one or more of these may be expected in over 50% of patients. Several conditions give rise to disproportionate diagnostic difficulties: essential tremor, Alzheimer's disease with extrapyramidal features (especially gait disorder), and pseudoarteriosclerotic parkinsonism (Rodnitzky and Uc, 1997).

Table 2 Differential diagnosis of Parkinson's

Parkinson's plus syndromes
Progressive supranuclear palsy (PSP)
Multisystem atrophy (MSA)
  Shy-Drager syndrome (SDS)
  Olivoponto Cerebella Atrophy
  Striator Nigral Degeneration

Drug-induced parkinsonism

Toxin-induced parkinsonism
MPTP
Carbonmonoxide, manganese, copper

Others
Trauma – pugilistic encephalopathy
Multi-infarct state
Parkinsonism associated with dementia

Essential tremor is very common in the elderly, affecting approximately 3% of patients over the age of 75. Many of the cases have a clear family history with some families showing a clear autosomal dominance. The tremor is coarser and more rapid than parkinsonian tremor; it becomes accentuated with purposeful movement and lessens at rest. It may often affect the head and neck and is the commonest cause of titubation. Intentional element is usual and it may be confused with a cerebellar tremor. Foot tremor can occur and this is unusual in Parkinson's disease. Diagnostic difficulty occurs when associated aging features such as stooped posture and slowness of movement occur at the same time as essential tremor. Levodopa has no effect on the tremor. Alcohol will improve tremor in 50% of the cases. Propranolol and primadone have been used to control symptoms although there is a poor evidence base for their use. Isolated dystonic tremors occur occasionally and can confuse diagnosis, particularly as they will respond to levodopa.

A bewildering variety of neurological signs have been described in dementia and specifically Alzheimer's disease, these include rigid akinetic states and gait disturbances. The signs of predominantly axial rigidity often associate with frontal and parietal signs; such as gegenhalten. Levodopa has no benefit and can induce psychotic side effects.

Periventricular white matter changes are frequently seen on computed tomography (CT) scans in the elderly and can be associated with the condition of pseudoarteriosclerotic parkinsonism. It was first described by MacDonald Critchley in 1929. Unusually, he was able to reassess his findings over 50 years later in 1981 (Critchley, 1981). He correctly deduced from clinical findings that multiple small infarcts, close to the internal capsule could be responsible for the very characteristic clinical picture of "bottom half" parkinsonism. These patients are usually the elderly with cognitive impairment. Hypertension and diabetes are more common than in idiopathic Parkinson's disease; facial expression and arm swing are preserved; tremor is absent; gait is highly abnormal and characterized by a "marche a petit pas" – short stuttering steps where the feet appear to stick on the ground – "magnetic gait". The condition is easily distinguished from Parkinson's disease by the presence of upper motor neurone features, such as jaw jerk, extensor plantars, and hyperreflexia. The use of levodopa in these cases is unlikely to provide benefit and may increase confusional states and falls.

In the process of establishing the diagnosis of Parkinson's disease, once the cardinal features have been confirmed, step two is to look for exclusion criteria for Parkinson's disease. A history of exposure to neuroleptic drugs or neurotoxins, severe head trauma or multiple strokes would question the diagnosis. Signs of features of Parkinson's plus syndrome such as ophthalmaplegia, pyramidal or cerebellar signs, or marked autonomic dysfunction all point to alternative diagnoses. Patients, who have a poor response to levodopa, have symmetrical signs of onset, have rapid and unusual progression of symptoms, or who have a complete absence of rest tremor, raise questions about the validity of the diagnosis.

There are now established diagnostic criteria for the diagnosis of multisystem atrophy (MSA). This group of disorders is characterized by cytoplasmic inclusions in oligodendrocytes, which stains positively for α-synuclein. Clinical syndromes are determined by the pattern of neuronal loss and gliosis. The overlap with Parkinson's disease occurs because of the pathology in the striatum and substantia nigra but in addition, the lower brain stem is involved in inferior olives, pons, cerebellum and the intermedial lateral cell columns, and Onufs nucleus in the spinal cord. Patients who present with predominantly parkinsonism are characterized as striato nigral degeneration (SND), those with predominantly cerebellar signs are labelled as sporadic olivopontocerebellar atrophy (SOPCA). Where predominantly autonomic features, particularly postural hypotension, are present, this is labeled Shy-Drager syndrome (SDS). Quinn and Gillman have established diagnostic criteria based on the consensus criteria for these conditions (Quinn, 1989). Cases can present with Parkinson's, which does not respond to anti-Parkinson medication or where the initial response is not sustained. The presence of postural hypotension, bladder dysfunction, and cerebellar or pyramidal signs make the diagnosis likely. The tremor is often atypical of Parkinson's disease, being jerky with marked postural and intentional elements. The disease is often characterized by falling at an early stage and a more rapid progression of signs. Sleep disorders are common and patients often have the characteristic disorder of speech – reduced volume and loss of rhythm. Emotional lability is common. Since the weight of pathology falls on the putamen, magnetic resonance imaging (MRI) scanning in skilled hands can be helpful in making the differential diagnosis.

Progressive supranuclear palsy (PSP) or Steele Richardson Olszewski syndrome is probably the most distinctive of the Parkinson's plus syndrome. The underlying pathology is a tauopathy. It is to be suspected when patients present with marked postural instability early in the disease process. They have the distinctive features of vertical gaze palsy, resulting from a supranuclear ophthalmaplegia. Patients often have a fixed staring expression and blink infrequently. The head is often retracted (retrocolis) and the voice has a distinctive growling quality. Falling is exacerbated by the tendency to rush movement and general clumsiness, resulting in the "rocket sign" as they jet out of a chair and the "messy tie sign" as they tend to have difficulty swallowing and spill food liberally. There is often a major cognitive component to this illness and notable slowing of cognitive processing.

Major advances and better knowledge of this condition have led to robust diagnostic criteria and increasing understanding of underlying pathological processes (Litvan, 1997). MRI in experienced hands can be helpful as there are characteristic changes in midbrain diameter, changes in signal intensity from the red nucleus, and the globus pallidus. There is little evidence to support any specific drug therapy in this condition, but increased understanding of the pathophysiological basis leads to the hope that future treatments will be developed.

Drug-induced Parkinsonism

Drug-induced parkinsonism has been ranked in several studies as the second most frequent cause of parkinsonism (Hubble, 1997). Many drugs interfere with the action of dopamine in the brain, either by causing dopamine depletion or by blockade of the dopamine receptors. Neuroleptics that are specific for D2 receptor antagonists are particularly liable to give Parkinsonian signs. With the recognition of the risks of antipsychotic drugs, there is increased use of atypical neuroleptics. Calcium antagonists such as cinnarizine and flunarizine, antiemetic preparations such as metochlopramide and prochloperazine, are an increasing cause of this problem. Once the causative drugs are removed, recovery from the syndrome is slow and in many cases incomplete. Stephen and Williamson, 1984 showed that 50% of patients with drug-induced parkinsonism failed to recover completely on withdrawing the drug. The suggestion is that dopamine-blocking drugs and calcium antagonist, which affect the dopaminergic transmission, may pick out vulnerable dopaminergic systems in patients who, given time, might develop idiopathic Parkinson's disease.

Epidemiology

The cumulative lifetime risk of developing Parkinson's disease has been estimated to be 1 : 40. The disease is certainly age related. Two-thirds of the patients treated for the disease are over the age of 70. After stroke and Alzheimer's, Parkinson's is the third commonest neurological disease in old age. The age of the patient is the strongest predictor of the likelihood of having Parkinson's disease. Population studies consistently show that prevalence rate increases exponentially with age. Earlier studies showed a fall in the very oldest age-groups. This is probably explained by the lack of ascertainment or precision of diagnosis of cases in extreme old age. Males have a slightly increased risk of developing the disease. The male/female standardized ratio being 1.35 for prevalence and 1.31 for incidence as obtained from studies. There is wide variation between different studies however. Socioeconomic status and race appear only to effect frequency of the disease where there is differential access to health care.

The incidence of Parkinson's disease (the number of new cases/year) averages 18 : 100 000 in the United Kingdom, amounting to about 10 000 new cases each year. The prevalence (number of cases in a population at a particular time) suggests an average prevalence of around 120 : 100 000 population in the United Kingdom with a variation in studies of 108 and 160. The comparisons made between studies, particularly between different geographical studies, produce considerable difficulties in interpretation and comparability of the information available. The central problems of such studies are the lack of uniform diagnostic criteria. Diagnosis of Parkinson's disease is unusual in being entirely clinical with no gold standard investigation to confirm the clinical label. Methodological differences in studies give rise to variation, as do the failure to adjust data to a single standard population. The difficulty in ensuring complete case ascertainment is common in all studies. Zhang, in a detailed analysis in all world literature, concluded that although the disease appeared commoner in Caucasians in Europe and North America, and lowest in African races, data was not robust enough to make firm conclusions (Zhang and Roman, 1993). They also felt that based on the data available, there is no evidence of significant temporal change in the incidence of the disease, but the prevalence is increasing as a function of the aging population.

A study of Parkinson's disease in a Scottish city by Mutch *et al.* (1986) still forms a reliable basis for our knowledge of the disease in the United Kingdom. The results of this study are consistent with international studies. This study confirms that the disease is largely confined to people over the age of 55, with its prevalence rising steeply with increasing age.

Knowledge of the natural history of Parkinson's disease is hampered by the lack of good quality and comparable longitudinal data. The data is difficult to interpret because of variations in the accuracy of death certification. Clarke (1995) have carried out a detailed analysis of mortality data for England and Wales. It is possible to tie some of the rises in deaths from Parkinson's disease to a greater awareness and increased probability of the diagnosis being made. Parkinson's disease reduces life expectation, particularly in older patients. The most recent data shows that the standardized mortality ratio for patients with Parkinson's disease is 2.4 with 95% confidence limits of 1.6 to 3.4. These figures overlap with a pre-levodopa standardized mortality ratio of 2.9 with confidence limits of 2.4 to 3.6. In the period immediately following the introduction of levodopa, standardized mortality ratio dipped to about 1.3. Analysis of the data in case-control studies have shown that the early gains of levodopa have gradually been lost over a period of time, because the benefit of levodopa was to shift the age of the specific mortality curve. Recent studies show that younger patients have a longer survival rate than older patients. However, given their longer life expectancy they will lose more of their life than older patients, and the relative mortality of younger patients is greater compared to the general population than the relative mortality of older patients. Patients with the onset of tremor have a better prognosis than those with falls or gait disturbance, perhaps suggesting misdiagnosis of Parkinson's plus syndrome in the data (Diederich *et al.*, 2003).

Analytical epidemiology has yet to change the status of Parkinson's disease as an idiopathic disorder; nevertheless, it has outlined some important risk factors. There is a well-known inverse relationship between smoking and Parkinson's disease. This finding has been robust over different populations and cultures. There is no universally agreed explanation for this finding. Biologically, stimulation of nicotine receptors could possibly be neuroprotective. There is little biological evidence to support this, however. Smokers and nonsmokers are differentiated on personality. Smokers being greater risk takers. It has been suggested that there is a pre-Parkinson personality with a more rigid and less risk

taking personality. The habit of smoking therefore could be a method of selecting patients who are less likely to develop Parkinson's disease in the longer term.

Since the epidemic of postencephalitic parkinsonism following the outbreak of Von Economo's encephalitis, there have been repeated studies to try and link the development of parkinsonism with exposure to viral infections. Intrauterine influenza, measles, and whooping cough infection have been suggested to have links with parkinsonism. To date, there is no strong empirical support either by the identification of viral genomes in patients with Parkinson's disease or serological data of previous infection being more common.

The occurrence of MPTP-induced Parkinson's disease in the 1970s raised the possibility of the disease being due to exposure to an environmental toxin. MPTP has a similar structure to paraquat and other herbicides. Parkinson's disease was shown to be common in agricultural areas where pesticide use was high. This finding has been consistently confirmed by more detailed case-control studies. Other putative toxins are solvents, wood preservatives, mercury, or any other metals. Further work needs to be done to clarify these risks.

Attention has been drawn to a positive association between head injury and occupations such as football or boxing. Such studies are difficult because of recall bias. Pugilistic encephalopathy may give rise to parkinsonian features, but has a distinct pathology.

Rural residence and exposure to well water showed an increased risk to parkinsonism in Canadian studies, and this has been subsequently confirmed over a series of studies. There has been an increasing interest in the relationship of diet, and whether diet can be protective of Parkinson's disease by mediating antioxidant effects. To date the results of the various studies are confusing, even though a number of studies have been based on very large populations. Vitamin E has shown to have no protective effects although there have been claims that vitamin C is protective, while vitamin A is associated with increased risk. None of these studies warrant unequivocal advice to patients on dietary supplements that may be protective.

Pathology and Pathogenesis

Dopaminergic neurones are lost in the normal process of aging. However, in Parkinson's disease the rate of loss is many times greater and the distribution is more selective, affecting the ventrolateral and ventromedial nuclei of the substantia nigra, in contradistinction to the more general pigmentative loss associated with aging (Gibb and Lees, 1994). The role of accumulation and loss of neuromelanin in the pathology of Parkinson's disease is poorly understood. Neuromelanin is a polymer, which is thought to be a waste product of bioamine metabolism and which normally accumulates through life. There is no evidence that neuromelanin itself is toxic, in fact it is probably formed as a protection against the auto-oxidation of dopamine, which would otherwise produce toxin-free radicals.

There is increasing understanding of the Lewy body (Spillantini *et al.*, 1997). These inclusion bodies contain a complex mix of cytoskeletal elements including phosphorylated microfilaments, tubulin, and microtubin-associated proteins. They stain heavily for ubiquitin. Ubiquitin is present in all eukaryotic cells. It is a 76 amino acid peptide that is a necessary ligand for the disassembly of proteins within the proteosome of the cell. A further important peptide is α-synuclein. The importance of this protein for Parkinson's disease is based on mutations found in familial cases of the disease. α-Synuclein has a variety of tertiary structures and is represented in the Lewy body as a β-pleted sheet. The aggregation of the α-synuclein is also associated with MSA and Lewy body dementia. It is speculated that oxidative stress alters the structure of normal α-synuclein preventing its ubiquination and hence it accumulates in the cell. Lewy bodies may be a cytoprotective response to limit cell disruption.

Parkinson's disease does not develop until 60% of the cells are lost, with a reduction of striatal dopamine by 80%. It seems highly unlikely that there is a long presymptomatic phase of the illness, as suggested by the finding of incidental Lewy bodies.

Brains that contain pathological hallmarks of Parkinson's disease have a greater risk of exhibiting other neurodegenerative pathology including Alzheimer's disease. There is a debate whether Lewy bodies dementia is a distinct pathological entity with a predominance of Lewy bodies in the cortex or part of a spectrum of disease, with Parkinson's disease at one end and dementia at the other and both associated with similar pathogenic processes.

In addition to the loss of dopaminergic neurones resulting in a depletion of dopamine in the brain, there is also a depletion of brain stem neurones, which produce both noradrenaline and 5-HT (5-hydroxytriptamine). Cholinergic neurones in the nucleus basalis are lost with reductions in cotransmitter substances P-met-encephalin, cholecystokinin, and somatostatin (Crossman, 1987).

In spite of increasing knowledge, Parkinson's disease can still be truly classified as idiopathic. As seen earlier, analytical epidemiology has drawn a list of risk factors and protective factors. Parkinson's disorder produced by MPTP has encouraged the developing of primate models of the disease and has led to the strong belief that environmental factors are very important in the development of the disease. One explanation of the age distribution of the disease is the accumulation of toxic damage throughout life, resulting eventually in overt dysfunction. Environmental factors were seen as a cause of oxidative stress resulting in an excess production of free radicals, which cause a variety of cellular damage. The mitochondria are particularly vulnerable, being the site that generates free radicals in the cells. Studies have consistently shown abnormalities in complex one of mitochondria in patients with Parkinson's disease (Schapira, 1997). Neuromelanin-containing cells have hallmarks of free radical damage with increased iron content, lipid peroxidation, and glutathione depletion (Jenner and Olanow, 1998). The evidence for and against oxidated stress as a cause of Parkinson's disease is complex with many anomalies in the

data. Antioxidants seem to have little effect on the evolution of the disease.

The genetics of Parkinson's disease has been perhaps the greatest area of research growth over the last 10 years. The younger the age of the patient with Parkinson's disease, the more likely that genetic factors are important. Overall, there is a 17% increased risk of first-degree relatives developing Parkinson's disease. In 1949, Mjones, 1949 conducted a large family study in Sweden and inferred an autosomal dominant inheritance with incomplete penetrance. Subsequent analysis of some of his data led to a suggestion of polygenic inheritance (Marras and Tanner, 2004). The genetics of PD has been advanced by the description of a number of kindreds with familial Parkinson's disease, which has resulted in the identification, at the time of writing, of 11 mutations that result in the phenotype of Parkinson's disease. Initial twin studies found that there was little difference in concordance rates between monozygotic and dyzygotic twins for Parkinson's disease. However, this data was reanalyzed using modern imaging techniques and now suggests that Parkinson's disease starting below the age of 50 has an important genetic component. Mutations are now named *PARK* followed by a number in order of their discovery. Park 1 was an important breakthrough and consisted of over fifty members of four generations of a family that originated in Contursi, Italy (Golbe *et al.*, 1996). Polymeropoulos identified a mutation for chromosome 4Q. Although these types of mutations are rare, this discovery focused attention on α-synucleinopathy. Park 2 is also a very significant mutation. It is found as an autosomal recessive form of juvenile Parkinson's disease, first described in Japanese families. It is located on chromosome 6. Patients with this variant of Parkinson's do not produce Lewy bodies but produce the Parkin protein which results from the mutation of an ubiquitin ligase, which is again linked with the cellular process of the production of unwanted protein. Each new discovery of a *PARK* gene is developing a clearer picture of the process of the pathogenesis of Parkinson's disease and possible future targets for drug action.

The increased understanding of the molecular basis of Parkinson's disease has also led to increased insights into the functional anatomy of the basal ganglia, and this has led to increased possibilities of surgical intervention and a better understanding of the action of drugs (Brotchie, 1999). Basal ganglia consists of the striatum (caudate nucleus and putamen) globus pallidus (medial and lateral segments), the subthalamic nucleus, and the substantia nigra. The striatum is the input portion of the basal ganglia and it receives input from the cerebral cortex, thalamus, and substantia nigra (pars compacta). The medial globus pallidus and the substantia nigra pars reticulata are the output region of the basal ganglia with a projection predominantly to the thalamus. There are two pathways – direct and indirect pathways that control the output of the basal ganglia (see Figure 1). The indirect path controls the subthalamic nucleus. The activation of the direct pathway inhibits the basal ganglia output, whereas the activation of the indirect pathway causing excitation, so that with normal function, there is

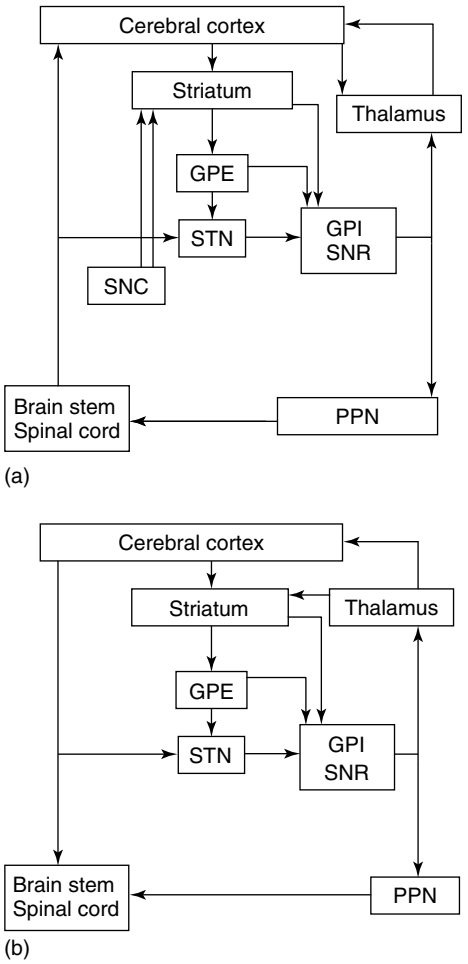

Figure 1 Direct and Indirect pathways

a balance between the two pathways. The direct pathway is dependent on D1 dopamine receptor activation and the indirect pathway is inhibited by D2 dopamine receptor activation.

The heterogeneity of dopamine receptors in the Striatum has important implications for drug therapy. Although five drug receptors have been described, they consist of two families – D1-like and D2-like receptors. Each receptor type has a differential distribution in the brain. One explanation for an increased likelihood of hallucinations with dopamine agonist compared with levodopa is that dopamine agonists often have an affinity for D3 and D4 receptors, which are represented in the frontal lobes of the brain. Dyskinesias result from complex adaptation of the receptors involving calcium channels produced by long-term levodopa therapy in Parkinson's disease.

Management of Parkinson's Disease

The management of Parkinson's disease needs to vary through the course of the illness, the primary-care pathway

Table 3 Management of Parkinson's disease

Clinical Pathway of Parkinson's Disease
Diagnosis
Maintenance
Complex
Palliative

Source: Reprinted from Journal of Neurology, V245, McMahon DG *et al.*, Clinical Pathways of Parkinson's Disease, S19–22, Copyright 1998 with permission from Springer.

developed by MacMahon and Thomas (1998) is a useful schema (see Table 3).

The ideal treatment would be recognition of the presymptomatic stage of the disease followed by preventative therapy. This remains a distant prospect rather than an actuality. There is much research activity to try and introduce therapy, which slows down progression of the disease once diagnosed, either by neuroprotection or even more ambitiously by neurorestoration. Techniques such as PET and SPECT scanning hold the promise of being able to measure neuronal loss (Piccini *et al.*, 1997; Benamer *et al.*, 2000) and there are already promising reports of beneficial effects of dopamine agonist on neuronal loss.

At present we only have strong evidence for symptomatic therapy. The best way of deploying the available drugs is still contentious in spite of a number of authoritative guidelines for the management of Parkinson's disease formulated in the United Kingdom and United States (Bhatia *et al.*, 2001; Olanow and Koller, 1998). At the time of writing, NICE guidelines on Parkinson's disease are awaited. So far, none of the guideline groups have used rigorous methods of analysis or meta-analysis. All the guidelines have been supported by commercial interests. The individual clinician needs to exercise clinical judgment in initiating drug therapy. The age of the patient at onset is an important consideration.

The goals of treatment are the same for all individuals regardless of age: good symptomatic control and minimizing possible adverse effects of medication. In the younger patient or a patient with long life expectation, the need to reduce the risk of motor complications of therapy is paramount. In older patients and patients with psychiatric illness, cognitive impairment, or multiple comorbidity, the risks of psychiatric side effects of drug therapy are more important. It is vitally important that drug therapy is seen as one component of the support for a chronic illness. The overall framework of the management is based on the principles of rehabilitation and require a multidisciplinary approach. Drug therapy should be seen as an aid to achieving rehabilitation goals and symptom control. Patients frequently require a combination of different drugs throughout the course of their illness. The older patient is more susceptible to side effects than younger patients and this effect is accentuated by the presence of comorbidity and increased number of other prescribed drugs.

There are only few clinical trials representative of the older population for whom drugs are prescribed. Populations on whom clinical trials are conducted tend to be younger and exclude frailer patients with comorbidity and cognitive impairment. In applying the evidence base, the individual clinician needs to make a judgment about how relevant the evidence is to the particular characteristics of the individual patient for whom they are prescribing. Such an approach leads to a cautious prescribing with an emphasis on levodopa rather than dopamine agonists.

Levodopa is the gold standard for treatment of Parkinson's disease, and after 40 years of use, it is still the most effective drug for relieving parkinsonian symptoms. Levodopa is combined with the peripheral dopa-decarboxylase inhibitor, either benserazide (madopar) or carbidopa (sinemet). These limit the peripheral effects of the drug and reduces the side effects of nausea and postural hypotension. In the patient with true idiopathic Parkinson's disease, introduction of levodopa is in almost all cases followed by a sustained and positive response. Complications of therapy are listed in Table 4. In studies of older patients, it was estimated that 50% of patients on L-dopa had motor complications after 5 years of treatment; with lower doses and more cautious prescribing this figure is an overestimate, particularly in older patients who are less liable than younger patients to develop motor complications. The range of doses and different formulations of levodopa that is available allow very flexible titration of dose in individual cases. The central problem of levodopa is its short half-life, which results in pulsatile delivery of dopamine to the striatum. Adjunct therapy with COMT inhibitors (catechol-*O*-methyltransferase), dopamine agonists, or monoaminoxidase inhibitors is required in the majority of patients on longer-term use. COMT inhibitors inhibit the methylation of dopa. At the time of writing, entacapone is the only licensed COMT inhibitor. It may be either given as a separate 200 mg tablet (Comtess) or combined with levodopa and carbidopa (Stalevo) and has been shown to be effective at relieving wearing-off effects and increasing on time (Brooks *et al.*, 2000). Theoretically, early use of this drug could achieve continuous dopamine stimulation and reduce motor complications of levodopa therapy. The outcome of ongoing studies is awaited. Entacapone is

Table 4 Complications of levodopa therapy

Immediate
• Gastrointestinal upset
• Postural hypotension
Motor complications
• Wearing off and end of dose deterioration
• On/Off syndrome
• Dose failure (delayed on and drug resistant off)
• Freezing
Dyskinesias
• Peak dose
• Biphasic
Non-motor symptoms
• Muscle pain
• Excess sweating
• Excess sleeping
Neuropsychiatric complications
• Hallucinations
• Psychosis
• Hypersexuality

well tolerated in the older patient and, in particular, does not increase psychiatric side effects unlike other adjunct therapy. Nonadjustment of levodopa dosage may increase involuntary movements. Its use is associated with discolored urine.

Selegiline, at the time of writing, is the only licensed monoaminoxidase B (MAOB) inhibitor. There are other agents with reversible inhibition of MAOB, which are still on trials. Selegiline is available in two forms, the conventional tablet of 5 or 10 mg daily, or a 1.25 mg buccal preparation; it produces less amphetamine like metabolites in the hope that it reduces psychiatric complications of the drug. Selegiline came to prominence following the DATATOP trial and for some time was thought to be neuroprotective (Parkinson Study Group, 1989). This claim has not been sustained, and the Parkinson's disease research group UK study indicated that selegiline increased both the motor and nonmotor complications of levodopa, and only this study associated this drug with increased mortality (Lees, 1995). The risks for patients with dementia or falls are increased and this has led to its limited use in the older patient.

Dopamine agonists have an increasing role in the management of Parkinson's disease, fueled by a number of excellently designed studies on monotherapy, which clearly indicate that this class of drugs reduce the rate of motor complications (Parkinson Study Group, 2000; Rascol *et al.*, 2000; Rinne, 1999). They may be used as either monotherapy or as an adjunct to levodopa. The monotherapy trials show that dopamine agonists are less effective at relieving symptoms than levodopa but marginally so in the earlier stages. Ergot derivatives have been associated with complications of fibrosis, increased neuropsychiatric side effects, and restrictive valvular heart disease. This has meant a decline in the use of these agents, especially in the older patients who appear to be more susceptible to these side effects. Nonergot dopamine agonists are increasingly used as monotherapy; they are associated with somnolence and neuropsychiatric effects. The average age of patients in monotherapy trials was 61 and patients with cognitive impairment were excluded. These agents are therefore better suited for the younger more robust patient with good life expectation, low comorbidity, and no cognitive impairment.

Apomorphine is one of the most potent anti-Parkinson drugs known (Stocchi *et al.*, 2001). It is delivered subcutaneously and therefore requires organized support with the supervision of a specialist nurse in Parkinson's disease. It can either be administered by a penject injection to rescue the patient from off periods or by continuous subcutaneous infusion. This therapy is useful in patients with severe motor fluctuations and an on-off syndrome where other methods of therapy have failed. This therapy can be well tolerated by the older patient. The main problem is nausea, which requires prophylactic treatment with domperidone; skin nodules and postural hypotension are further problems.

Anticholinergic agents are still licensed for use in Parkinson's disease, but great caution has to be applied. The drugs were originally introduced before the more stringent need of evidence of efficacy from random control trials. They are poorly tolerated in older patients and significantly increase the rate of psychiatric complications of therapy. Amantadine has a long history in Parkinson's disease, having been used since the early 1970s. The mechanism of its action is complex and uncertain, but it certainly modifies both dopaminergic and cholinergic pathways, by virtue of its glutamate antagonist action. Recent small studies have shown it to be effective in reducing dyskinesias (Luginger *et al.*, 2000). In higher doses, it can cause increased psychiatric complications as well as ankle edema and livedo reticularis.

Neurosurgery

There is an increased interest in neurosurgical approaches to the treatment of Parkinson's disease; particularly when dealing with the late complications of the failure of medical therapy (Varma, 2001). Surgical approaches are listed in Table 5. Surgery often seems an attractive option to patients because of the publicity it attracts; however, it remains an option of therapy that can only be extended to a few patients and is associated with significant comorbidity, with 2% of patients developing hemiparesis and a 0.5% mortality. The surgery is often prolonged, with the patients remaining conscious throughout. Option of surgical therapy tends to be selective to younger and more generally fit patients. Although surgery appears to be good at relieving motor complications it is associated with a higher risk of psychiatric complications. Intracerebral grafting has been banned in the United States owing to the complication of severe abnormal involuntary movements associated with the procedure.

Nondrug Interventions

Parkinson's disease gives rise to a complex range of disabilities. Accurate assessment of the patient's problems and planning of future management requires sophisticated service development to enable full range of multidisciplinary skills to be employed for the benefit of the patient. Rehabilitation is central to the management of Parkinson's disease, aiming at optimizing physical, psychological, and social function. The input of physiotherapists, occupational therapists, and speech and language therapists in the assessment process,

Table 5 Neurosurgery in Parkinson's disease

Destructive surgery
Pallidatomy
Thalamotomy
Subthalamotomy
Deep brain stimulation
Thalamic
Subthalamic
Intracerebral grafting
Fetal cells
Stem cells
Infusion of growth factors
Glial derived nerve growth factor (GDNF)

the planning of therapeutic goals and nonpharmacological interventions, and the evaluation of patients, both in hospital and their own environment are essential. Individual professional's inputs are complimentary and when good multidisciplinary working is in place, there are great gains for the patient even though it is very difficult to test these objectively. Most present practice is based on consensus, but there has been a growing recognition that harder evidence-based practice is needed. There are over 25 randomized controlled trials examining paramedical and complimentary therapies involving nearly a thousand patients. Unfortunately, published literature is often beset with methodological problems. Current evidence base for nonpharmacological therapies was recently comprehensively reviewed by Deane and Playford (2003). It is clear that large pragmatic randomized control trials are required and a significant amount of work in both physiotherapy and occupational therapy is being done by means of Delphi surveys of best practices. Once established, it can then be tested by randomized trials.

Physiotherapy maximizes mobility, exercise tolerance, posture, and improved gait patterns. Research confirms that they can reduce the risk of falls and educate the patients on how to maintain fitness; axial movements, ankle and rotational movements, which are particularly difficult for patients with Parkinson's disease. Patients lose the normal heel strike on walking. As the heel is used as a brake and the toes are used as an accelerator in walking, the reverse pattern leads to postural instability. Indeed patients with long standing Parkinson's disease have a shortening Achilles' tendon leading to an inefficient gait. Early intervention by physiotherapy goes some way to preventing these problems.

Occupational therapy analyses functional disabilities and aims to maintain independence, safety, and confidence, and allow patients to undertake rewarding activity. There is an increasing emphasis not only in the physical but also in the psychological and social aspects of problems. Patients with Parkinson's disease need aids and appliances that are appropriate to their condition, a prime example being that of the zimmer aid which is counterproductive as it interrupts the flow of movement while walking and patients would require a wheeled aid. Major impacts can be made on the disability by adapting to the home environment. Occupational therapy can significantly improve the quality of life by analyzing the issues affecting activities of daily living.

Speech therapists have a dual role of improving speech, communication and swallowing difficulties. There is a significant evidence base for their work (Robertson and Thomson, 1984).

Parkinson's disease specialist nurses have a rapidly developed and an essential role in the chronic disease management of Parkinson's disease, providing a continuity of care and coordinating different elements of care. Specialist nurses have developed effective protocols of care and educational programs for the patients. A randomized control trial of intervention by a primary-care–based Parkinson's disease specialist nurse appeared to underestimate the benefit because of methodological failings (Jarman *et al.*, 2002). Many Parkinson's disease specialist nurses are partly hospital based, outreaching to the community, and this model was not tested.

A whole range of other individuals can have an impact on the disability, including dietitians, clinical psychologists, carers, and support groups – particularly the Parkinson's Disease Society. Private practitioners in podiatry, massage, and Alexander technique, all have endeavored to create knowledge and evaluate their services for Parkinson's disease patients. Parkinson's disease has a significant economic impact (Findley *et al.*, 2003) and there is also an undue burden on carers (Cousins *et al.*, 2001).

Psychology and Psychiatry in Parkinson's Disease

In addition to affecting movement, Parkinson's disease affects cognition and mood (Hindle, 2001). Patients who have poor mental states suffer its effect on their quality of life more than those with only physical disability. Acute psychosis is probably the most serious side effect of drugs in Parkinson's disease. Table 6 shows the most significant associated psychiatric symptoms of Parkinson's disease. Older patients show great variation in the psychiatric manifestations, with aging and comorbidity determining how psychological and psychiatric features present themselves. The basal ganglia have important functions in cognitive processing, with a series of parallel circuits. In many areas it is difficult to separate motor and psychological functions of the brain. In the older patient Parkinson's disease is a psychomotor disorder rather than a pure movement disorder. Even early in the disease, executive functions of abstract reasoning, planning, set shifting, working memory, semantic memory, and temporal sequencing can be demonstrated to be abnormal. The frequency of dementia in Parkinson's disease patients is significantly higher than age- and sex-matched controls. Figures of incidence and prevalence vary markedly among different studies; between 30 and 40% of patients with Parkinson's disease will eventually develop dementia. The age at onset is the most powerful predictor of development of dementia. Dementia in PD is characterized by dysexecutive function with impaired and fluctuating attention, reduced speed of mental processing and apathy. Visiospatial perception and cueing are also disrupted. Memory impairment is characterized by reduced free recall, unlike

Table 6 Neuropsychiatric features of Parkinson's disease

Cognitive impairment
Dementia
Depression
Drug induced phenomena
• Anxiety
• Sexual dysfunction
• Psychosis
Sleep disorders
Hallucinations

Alzheimer's dementia where encoding of memory is disrupted. Core language function tends to be preserved but there is reduced fluency. Personality change with anxiety and rigidity of thought are described. Illusions and visual hallucinations are common.

In ordinary clinical practice it is often difficult to distinguish between PD dementia, Lewy body dementia, and associated Alzheimer's disease. Patients often have a combination of pathology. In Parkinson's disease, there is a loss of cholinergic neurones in the basal nucleus of Meynert. In Alzheimer pathology, Lewy bodies in the cerebral cortex and limbic areas are more common. Alzheimer pathology is more frequent than would be predicted by chance.

The management of dementia in Parkinson's disease is complex. It depends on accurate assessment of cognition, capacity, mood, psychosis, motor features, activities of daily living, and social function. On the basis of such an assessment, providing a supportive environment and carer support are crucial. Specialist Parkinson's disease nurses or psychogeriatric nurses provide support as the key workers. Cognitive strategies for management of the environment can be helpful with the input of specialist occupational therapy being valuable.

Medical care is based largely on the avoidance of precipitative factors of psychosis, particularly avoiding drugs, which may exacerbate the situation, especially neuroleptics. Acetyl cholinesterase inhibitors have been shown in a number of trials to be helpful, but at the time of writing are not licensed for this indication in Europe.

Mood change and depression are extremely common in older patients with Parkinson's disease (MacCarthy and Brown, 1989). It has been estimated that nearly two-thirds of patients will have depressive episodes at some time in the course of their illness. Diagnosis is difficult, as psychomotor retardation appears to be uncannily similar to bradykinesia. At present there is no disease specific tool for making the diagnosis of depression in Parkinson's disease. Depression has the greatest effect on quality of life. The pathophysiology of depression in Parkinson's disease is complex. Depletion of dopamine by itself can cause mood disturbance, but it is likely that a decrease in noradrenaline and 5- HT may play an important part in the biological genesis of depression. Psychosocial factors may also play a significant role, as may the associated comorbidity.

The presentation of depression in Parkinson's disease is variable. Ahedonia is very common in Parkinson's disease, and there is a spectrum from a mild mood disturbance to depression. Cognition is often disrupted, depression giving rise to pseudodementia is important in the differential diagnosis of cognitive impairment. Apathy and lack of drive is also a common feature in Parkinson's disease and probably represents frontal lobe disorder.

Treatment depends on the severity. It is of value to optimize anti-Parkinson's treatment before introducing antidepressants. Recent systematic reviews of the literature on depression in Parkinson's have shown that the evidence base in this area is very weak, comprising largely small-scale studies with poor methodology. Currently the selective serotonin reuptake inhibitors (SSRIs), sertraline, and citalopram are the drugs of choice. There are case reports of worsening of Parkinson's symptoms on SSRIs, but it is difficult at the moment to quantify how serious a problem this is. There is evidence that ECT may be effective not only in the treatment of depression but also in improving the motor aspects of Parkinson's disease.

Hallucinations are common in Parkinson's disease. Studies vary from between 30 and 80% of patients developing hallucinations. They tend to be nonthreatening visual hallucinations, varying from illusions of presence to fully formed images of people and animals, sometimes reduced in size (Lilliputian hallucinations). Many patients show a remarkable tolerance and often do not bring hallucinations to the attention of the medical practitioners. They are frequently associated with sleep disturbance. It has been suggested that the visual hallucinations and illusions arise as a form of visual confabulation, compensating from deficits in visuospatial processing in Parkinson's disease. Hallucinations occur in toxic confusional states and psychotic episodes are more threatening and often associated with paranoid ideation.

Management of psychotic features of Parkinson's disease depend on its severity. Acute episodes of delirium caused by intercurrent illness need to be ruled out. The patient with Parkinson's disease, particularly if they have a chest infection or urinary tract infection have a low threshold of developing delirium. A rigorous review of medication is needed. Drugs with a particularly high risk of causing psychotic features such as anticholinergics, tricyclics, selegiline, and amantadine should be stopped first. It should be recognized that dopamine agonists are more likely to cause hallucinations and conversion to levodopa may be necessary. Patients on a higher dose need their dose to be reduced even at the risk of motor deterioration. Psychotic features often cause a great deal of distress in carers, and careful explanation needs to be given. Management of the environment, providing adequate lighting, best conditions for undisturbed sleep, and so on, may be helpful. The evidence base for treatment of hallucinations is poor. This is largely based on consensus. The strongest evidence is for clozapine, an atypical neuroleptic, but this is not licensed for use because of its increased risk of causing agranulocytosis. Quetiapine is the current drug of choice; titration of dose is difficult and varies between individual patients.

Common Management Problems in Parkinson's Disease

Falls

Falls are common in the elderly patient with Parkinson's disease and are often associated with other phenomena as gait disorder and postural instability. Postural instability is a late feature of Parkinson's disease and there is little evidence that drug therapy helps in these problems. Rehabilitation techniques can be helpful; education is required to prevent the risk of falls. Patients who regularly fall need to be

assessed to exclude orthostatic hypotension, or falls at the time of motor dyskinesias. The patients who exhibit freezing are particularly liable to fall. Comorbidity can add to the risk of falling. Falling is a mark of general biological frailty in these patients and carry a bad overall prognosis.

Autonomic Dysfunction

Constipation, bladder dysfunction, orthostatic hypotension, swallowing disorder, excess sweating, and sexual problems all have a complex etiology, which includes in part autonomic dysfunction.

Patients with Parkinson's disease have been shown to have Lewy bodies in degenerating colonic mesenteric plexus. This may be part of the reason that colonic transit time is reduced. Constipation is virtually universal in Parkinson's patients. There has been demonstration of incoordination of pelvic muscular activity resulting in problems with defecation. This problem has been helped by the use of apomorphine. The more usual causes of constipation are, however, commonplace in all geriatric patients; inadequate fluid input, a diet that does not contain enough roughage, and lack of physical activity. Many drugs exacerbate the problem, particularly anticholinergics. Early uses of stool softeners, such as docusate or osmotic agents such as movicol are recommended in Parkinson's patients. Cognitive impairment may be exacerbated when the colon is loaded. Although lower urinary tract symptoms are frequently seen in Parkinson's disease, Grey *et al.* 1995 have suggested that these problems are no commoner than in age- and sex-matched controls. Urodynamic studies have shown no specific abnormality in Parkinson's disease. Prostatic abnormalities and hyperactive bladder are very common in the age-group affected by Parkinson's disease and are the commonest cause of problems.

Orthostatic hypotension is dealt with in detail elsewhere in this text. When it is severe in patients of Parkinson's disease, it raises the possibility of MSA as a diagnosis. However, rapid resting pulse rate and fall in blood pressure have been demonstrated in true idiopathic Parkinson's disease. Use of support stockings and withdrawal of exacerbating drugs are usually sufficient to control the problem. Use of fludrocortisone is often hazardous due to coexisting cardiovascular morbidity.

Dysphagia is a very significant problem in Parkinson's disease, with an estimated 40% of the patients having an abnormality of esophageal immobility. Silent aspiration resulting in aspiration pneumonias is a significant cause of mortality in Parkinson's disease. In patients with recurrent aspiration pneumonias, management can be helped by percutaneous endoscopic gastroscopy (PEG feeding). Referral to a speech therapist is essential. This group is developing a strong evidence base for the management of these problems, including assessment with video fluoroscopy or nuclear medical techniques. Swallowing is related to the common problem of drooling, which is due to failure of clearing saliva from the oral cavity. Traditional methods of giving anticholinergics or even radiotherapy to the parotid glands to reduce the production of saliva, often lead to secondary increase in the swallowing problems.

KEY POINTS

- Parkinson's disease is predominantly a condition that affects the elderly.
- Age and frailty of patients are important in determining management decisions regarding drug therapy and rehabilitation.
- Clinical trials in drug treatment for Parkinson's disease are not representative of the age distribution of the condition and exclude comorbidity.
- Parkinson's disease give rise to a very complex range of disabilities, which require multidisciplinary management.
- The molecular basis of the pathophysiology of Parkinson's disease is increasingly understood and has links with other neurodegenerative conditions.
- Parkinson's disease, although classified as a movement disorder, has significant nonmotor aspects, of which cognitive impairment and mood disturbance are of fundamental importance.

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Non Parkinsonian Movement Disorders in the Elderly

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INTRODUCTION

Non-parkinsonian movement disorders that tend to primarily affect the elderly include chorea, restless legs, and periodic leg movements during sleep and while awake, dystonia and tremor (Table 1).

CHOREA

Chorea, derived from the Greek word for "dance", is a continuous, random sequence of irregular, unpredictable movements that flit from one body part to another. A variety of choreatic disorders begin during childhood or early adulthood. Those that are important in the elderly include Huntington's disease (HD), senile chorea, and tardive dyskinesia.

Huntington's Disease

HD is an autosomal dominant neurodegenerative disorder characterized by abnormal involuntary movements, progressive dementia, and psychiatric manifestations. In 1993, the specific mutation in HD was identified as an expansion of the unstable CAG trinucleotide repeat in the IT15 gene in chromosome 4p (Kremer *et al.*, 1994; Hersch *et al.*, 1994). Individuals with HD have more than 40 CAG repeats. There is an association of age of onset and number of repeats only in the very early and very late-onset HD (Andrew *et al.*, 1993). Juvenile onset cases are associated with repeat lengths greater than 52 and paternal transmission. This preponderance of paternal transmission has been reported for cases with onset before age 21 and is due to CAG repeat length expansion during spermatogenesis (Hersch *et al.*, 1994). Early onset is associated with the rigid type or Westphal variant of HD. In contrast, late-onset HD, defined as onset at age 50 or later, is associated with less than 42 repeats. Although it is believed that individuals with repeat lengths of 40 and 41 may not exhibit symptoms in their lifetime, it is unclear whether this is due to decreased penetrance among carriers with such lower repeat sizes or the mere fact that they did not live long enough. Approximately 1 to 2% of at-risk individuals screened for HD will have repeat lengths between 36 and 39. It is difficult to predict which of these individuals will develop symptoms of HD within a normal life span (Myers *et al.*, 1998).

HD has a subtle, insidious onset in the third and fourth decade of life and gradually worsens over a course of 10 to 20 years until death. Clinically, the disease usually presents with an involuntary movement disorder characterized by chorea, dystonia, bradykinesia, incoordination, and impaired postural reflexes. Oculomotor dysfunction is a frequent early sign and is characterized by slowed, delayed, or inaccurate saccades. As HD advances, swallowing and speech may become impaired, eventually disrupting communication and leading to aspiration pneumonias. Intellectual decline or dementia is a uniform feature, although the severity of cognitive impairment varies among patients. Psychiatric features are also common and disabling, appearing as the presenting manifestation in up to a third of HD patients (Biglan and Shoulson, 2002).

Approximately 25% of persons affected by the disease exhibit initial signs of chorea at age 50 or later, and half of these will not come to medical attention until after age 60. The clinical features of late-onset HD resemble those of midlife onset but the illness is more slowly progressive and less functionally debilitating. In late-onset disease, symptoms may appear to plateau or progress very slowly over several years. The most common symptoms in a series of 25 late-onset cases were mild to moderate chorea and

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Table 1 Definition of movement disorders

Disorder	Definition
Tremor	Rhythmic oscillation typically about a joint, alternating or simultaneous co-contraction of agonist and antagonist muscle groups.
Chorea	Irregular, nonstereotypical quick jerks, randomly distributed.
Dystonia	Sustained abnormal postures, often with a twisting character, sometimes overlying repetitive jerks.

cognitive impairment (100% of cases), dysarthria (88%), and gait disturbance (72%) (Myers *et al.*, 1985). The chorea in late-onset HD often allows the patient to stay at home, with minimal nursing support, to remain ambulatory, and to maintain activities of daily living for many years.

Pathology and Pharmacology

Histological studies of HD have demonstrated diffuse brain atrophy with severe neuronal loss and gliosis occurring selectively in the caudate nucleus and putamen. This neuronal loss in the striatum is largely confined to the GABAergic medium-sized spiny neurons that project to the globus pallidus, and which receive glutamergic input from the cortex and dopaminergic input from the substantia nigra. The severity of neuropathological changes was found to be closely related to the age at onset of the illness. An earlier clinical onset is associated with more severe neuropathologic involvement, while older onset cases show a slower rate of progression of neuropathological changes (Myers *et al.*, 1988).

The exact mechanisms that lead to the selective neuronal loss in HD are poorly understood. Hypotheses include glutamergic excitotoxicity, mitochondrial bioenergetic dysfunction, apoptosis, and transcriptional dysregulation (Biglan and Shoulson, 2002). Huntingtin, the mutant protein product of CAG expansion, undergoes abnormal cleavage in the cytoplasm, resulting in the translocation of the N-terminal fragment in the nucleus and the formation of aggregates in the nucleus. It has been hypothesized that this altered cleavage and subsequent nuclear translocation represent key steps in the pathogenic cascade leading to neuronal dysfunction and cell death (Saudou *et al.*, 1998).

Treatment

Currently, there is no effective treatment to slow or reverse the inexorable progression of HD. Neuroprotective strategies have been explored, including coenzyme Q10, remacemide, minocycline, creatine, and Huntington's disease advocacy center (HDAC), but none of these agents has been proven to alter the natural history of the disease, under the specific experimental conditions studied (Biglan and Shoulson, 2002). There are, however, several approaches to control the symptoms. Unfortunately, HD research has had a tendency to concentrate on the motor aspects of the disorder, whereas the major problems are behavioral (e.g. dementia, depression, psychosis) and the chorea is often the least relevant in terms of management. Chorea improves with the use of dopamine receptor-blocking agents (e.g. neuroleptics) or dopamine-depleting agents (e.g. reserpine or tetrabenazine). The newer, atypical neuroleptics, especially olanzapine, have become the drugs of choice, when treatment of chorea is needed (Bonelli *et al.*, 2002; Jimenez-Jimenez *et al.*, 2002; Paleacu *et al.*, 2002). More recently, amantadine, an *N*-Methyl D-Aspartate (NMDA) antagonist has been found to be effective in treating chorea in patients with HD (Verhagen Metman *et al.*, 2002). Management of the associated psychiatric disorders with the appropriate administration of psychotropic drugs should also be considered. Depression is managed with selective serotonin reuptake inhibitors (SSRIs) and mirtazapine, and psychosis and behavioral issues are addressed with atypical antipsychotics (Bonelli *et al.*, 2004). Dementia is unfortunately the most disabling facet of this disorder and is untreatable. In fact, the most effective approach to HD available today is genetic counseling.

Spontaneous Oral Dyskinesia and Senile Chorea

Clinical Features

Gowers, in the end of the nineteenth century, described an isolated form of chorea of late life as an entity separate from HD and neuroleptic use (Critchley, 1931). Isolated spontaneous oral dyskinesia (SOD) in the elderly is a clearly defined and fairly common syndrome but is more often recognized as part of other neurologic syndromes such as tardive dyskinesia, Huntington's chorea, acquired hepatocerebral degeneration, complication of prolonged levodopa therapy in Parkinson's disease (PD). In some patients, the occurrence of SOD is associated with the edentulous state and the improvement with appropriate dental appliances suggests that the absence of teeth in some individuals causes or makes the clinical syndrome worse (Sutcher *et al.*, 1971). In a recent study, observation was carried out on 1018 non-institutionalized, frail elderly subjects attending day care centers to document the prevalence of SODs. A total of 38 subjects were suspected to have SODs for a prevalence rate of 3.7% and 31 had probable tardive dyskinesia, for a prevalence rate of 3.0%. In a survey covering medical and dental issues in the same population, subjects with suspected SOD reported more frequent ill-fitting dental devices, oral pain, and a lower rate of perception of good oral health compared to non-dyskinetics. Individuals with suspected SOD typically presented with mild stereotyped masticatory or labial movements compared to the more complex phenomenology of probable TD (tardive dyskinesia) cases (Blanchet *et al.*, 2004, *see* **Chapter 22, Oral Health**).

Pathology and Pathophysiology

Recent developments in molecular genetics have provided a reliable test for confirmation of the diagnosis of HD that is highly sensitive and specific. Shinotoh *et al.* (1994) measured

CAG trinucleotide repeat expansion in the Huntington's gene in four cases of senile chorea, and found that CAG repetition lengths were normal. They considered this evidence that senile chorea exists as a distinct clinical entity that is nosologically separate from HD.

There is a paucity of pathological reports of senile chorea in the literature. Neuropathological cases of senile chorea reported in the past were before the advent of genetic testing for HD and it is possible that many of them represented mild cases of HD and no cognitive changes.

Treatment

Chorea can be ameliorated with neuroleptic agents. Neuroleptic agents should be initiated at low doses and slowly titrated upward to optimal symptom control. Neuroleptic use in this age group is associated with a higher incidence of TD and drug-induced parkinsonism (*see* **Chapter 66, Parkinson's Disease and Parkinsonism in the Elderly**). Thus, the use of newer atypical neuroleptics is preferable. Although the atypical neuroleptics have been advocated to carry a much smaller risk of drug-induced parkinsonism or TD, this has not been the case with some of them. Therefore, physicians should be vigilant for the development of these complications. Amantadine is useful in ameliorating chorea, but it is excreted unchanged in the urine and it can become toxic in elderly people with decreased renal function. Anticholinergic agents and dopamine agonists tend to worsen these movements and should be avoided. Treatment of either senile chorea or SODs is indicated only if the movements are severe enough to cause functional impairment. In edentulous patients, well-fitting dentures may improve the symptoms.

Tardive Dyskinesia

TD is defined as abnormal involuntary movements associated with chronic treatment with dopamine receptor-blocking agents. Neuroleptics are the most frequently implicated drugs, although other agents, for example, metoclopramide, have also been associated with the development of TD (Khot *et al.*, 1992). The diagnosis of TD requires (1) history of at least 3 months total cumulative (continuous or discontinuous) neuroleptic exposure; (2) the presence of at least "moderate" abnormal involuntary movements in one or more body areas or at least "mild" movements in two or more body areas; (3) absence of other causes for the movements (Task Force on late Neurological effects of antipsychotic drugs, 1980). Since the earlier reports of TD, a variety of involuntary movements, in addition to the well known oral-buccal-lingual masticatory movements, have been described, including dystonia, akathisia, tics, and myoclonus (Burke, 1992). It has been suggested that the newer, atypical neuroleptics (risperidone, olanzapine, quetiapine, ziprasodone, clozapine) are less likely to cause TD (Jeste, 2004; Dolder and Jeste, 2003). Clozapine and quetiapine are the ones associated with the lowest risk (Tarsy *et al.*, 2002).

The typical movements of TD are choreic in speed and amplitude, but usually tend to be more stereotypic and repetitive and less random or unpredictable than chorea of other etiologies. The orofacial and lingual muscles tend to be involved earlier and more frequently in TD. The disorder is usually only slowly progressive after initial development, and in many patients, especially the elderly, it does not appear to progress at all and may actually gradually improve with age.

Possible risk factors for TD include advanced age, female gender, affective disorder, mental retardation, brain damage, length of neuroleptic exposure, use of anticholinergic drugs, history of acute extrapyramidal side effects, antidepressant drugs, depot neuroleptics, history of drug interruptions or holidays, elevated serum neuroleptic concentrations, and late-onset psychosis (Lohr and Bracha, 1988).

Studies evaluating the prevalence and risk factors for TD have been largely confounded by vague diagnostic criteria, biased study samples, lack of matched control populations, and concurrent neuroleptic use, which can mask TD. Overall, most studies suggest that the average prevalence of TD is estimated as 15 to 20% (Khot *et al.*, 1992). In one series, 45% of patients had relatively persistent symptoms over the course of 5 years, while 24% had a fluctuating course. Only 11% improved, while 7% got worse. Remissions usually appear within 1 to 2 years after discontinuation of medication, although they may not occur until 5 years after discontinuation of medication (Bergen *et al.*, 1989).

Pathology and Pathophysiology

No characteristic pathological abnormalities have been found in TD. The pathophysiology is not clearly understood. The development of dopamine receptor supersensitivity following chronic dopamine receptor blockade is hypothesized to be the mechanism underlying TD. This would explain why, as the neuroleptic agents are withdrawn and receptor blockade reduced, TD may appear for the first time, or preexisting TD may worsen. Furthermore, exacerbation of the movements by dopaminergic agonists and improvement with increased dopamine receptor blockade or dopamine depletion support the notion that alterations in dopamine receptors are likely to be involved. As a result of the deficiencies in the dopamine supersensitivity hypothesis, attention has also been focused on other neurotransmitters, such as GABA, norepinephrine, acetylcholine, and serotonin (Khot *et al.*, 1992).

Treatment

Once it occurs, TD is frequently difficult to treat. Therefore, only individuals with defined indications for the use of these agents should be treated, especially among the elderly, who appear to be at a higher risk for developing TD. Although it is not proven, the neuroleptic dose should be maintained the lowest possible and the drug should be used for the shortest period of time allowed by the patient's psychiatric disease. If the patient's psychiatric disorder is sufficiently severe to require long-term neuroleptic use, an atypical neuroleptic should be considered.

Several medications have been used in the treatment of persistent TD with variable response. These include dopamine depleters reserpine or tetrabenazine, noradrenergic antagonists (propranolol, clonidine), γ-aminobutyric acid (GABA) agonists (clonazepam, diazepam, valproate, baclofen), botulinum toxin injections, and, to a lesser degree, vitamin E, buspirone, and calcium channel blockers, which have been used with variable results (Miyasaki and Lang, 1995). When the predominant movement is chorea, anticholinergic agents may worsen the movements; if, on the other hand, dystonia is the primary characteristic, these agents can be beneficial.

RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENTS DURING SLEEP AND WHILE AWAKE

Restless legs syndrome (RLS) is a sensorimotor disorder characterized primarily by motor restlessness, which is brought on by rest and accentuated later in the day and during the early night in those with normal circadian rhythms. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching. The prevalence of RLS is estimated to be 10 to 15% in the general population. Symptoms often begin before age 20, but usually become severe enough to seek medical attention in the fourth decade (Walters *et al.*, 1996). Periodic limb movement disorder (PLMD) is frequently associated with RLS but may occur independently, especially in the elderly. The prevalence of PLMD increases with advancing age. RLS and PLMD, taken together, are the primary diagnosis in 13.3% of patients complaining of insomnia (*see* **Chapter 63, Sleep Disorders in Elderly People**) and in 6.9% of patients complaining of excessive daytime sleepiness (Montplaisir and Godbout, 1989).

RLS and PLMD have been related to several other medical conditions, including peripheral neuropathy, iron deficiency anemia, and end-stage renal disease (Garcia-Borreguero *et al.*, 2004). Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and monoamine oxidase inhibitors can induce or aggravate PLMD as does withdrawal from anticonvulsants, benzodiazepines, and barbiturates. Exacerbations of RLS can occur during pregnancy or with iron deficiency anemia. Finally, PLMD may accompany other sleep disorders, in particular, sleep apnea or narcolepsy (Montplaisir and Godbout, 1989).

RLS can be diagnosed by the following four clinical criteria: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; (3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching; (4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (Hening *et al.*, 2004). Supportive clinical features include a positive family history, positive response to dopaminergic therapy, and the presence of periodic limb movements (during wakefulness or sleep) (Hening *et al.*, 2004). Family history of RLS can be found in 40 to 90% of patients with RLS (Montplaisir *et al.*, 1997; Winkelmann *et al.*, 2000). PLMD occurs in 80% of patients with RLS. The severity of RLS can vary greatly throughout a patient's lifetime but the disease is typically chronic and the course progressive. The sudden remissions, lasting for months or even years, are as difficult to explain as are the relapses, which appear without any apparent reason.

Periodic limb movements of sleep (PLMS), originally called *nocturnal myoclonus,* are best described as rhythmic extensions of the big toe and dorsiflexions of the ankle, sometimes with flexions of the knee and hip, each movement lasting 0.5 to 5.0 seconds and occurring every 20 to 40 seconds. Standard criteria for PLMS include their occurrence in a series of four or more movements spaced by intervals of 5 to 90 seconds (onset to onset) with electromyogram (EMG) burst durations of 0.5 to 5 seconds that rise to 1/4 of the EMG biocalibration amplitude (Hening *et al.*, 2004). Intense movements may cause numerous arousals, leading to nonrestorative sleep. PLMS may be asymptomatic, diagnosed through a bed partner's report or polysomnogram. PLMS occur primarily in stage 2, non-REM (rapid eye movement) sleep, less often in stages 3 and 4, and infrequently during REM sleep.

Fifty percent of patients with RLS have abnormal involuntary movements while awake, called *periodic leg movements during wake* (PLMW), formerly called *dyskinesias while awake*. Like the PLMS, PLMW are discrete, repetitive, stereotyped movements that recur at intervals of seconds, tend to involve primarily the legs, and occur almost exclusively at rest and disappear with action. PLMW are longer compared to the leg movements during sleep (shorter than 10 seconds during wakefulness vs 5 seconds during sleep).

Differential diagnosis of RLS and PLMS should include hypnic myoclonus, fragmentary myoclonus, painful legs and moving toes syndrome, nocturnal cramps, body jerks induced by long-term administration of levodopa, or akathisia. The symptoms of akathisia are prominent throughout the waking hours of the day or night, whereas the symptoms of RLS are more prominent at night. Akathisia patients manifest the external signs of an inner urge to move, whereas patients with RLS move about to relieve the dysesthetic sensations they have in their legs.

Although our understanding of the pathophysiology and genetics of RLS has advanced considerably, there is currently no recognized objective test for the disorder. Standard sleep measures remain useful in terms of sleep initiation, continuity, and sufficiency. These are often combined with measures of PLMS. Recently, the suggested immobilization test (SIT) has been proposed as a possible auxiliary measure, examining the ability of a period of imposed rest to induce subjective and motoric features of RLS. A combination of the SIT conducted in the evening with measurement of sensory discomfort and the presence of frequent PLM during awake epochs of the standard polysomnography (PSG) can provide

a high degree of diagnostic accuracy (sensitivity of 82% and specificity of 100%) (Hening *et al.*, 2004).

Pathophysiology and Pharmacology

Several lines of evidence suggest that RLS results from dysfunction of the central rather than the peripheral nervous system. RLS improves with centrally acting dopamine agonists, and this effect can be antagonized only by centrally acting and not peripherally acting dopamine antagonists (Garcia-Borreguero *et al.*, 2004). Nevertheless, the spinal cord may also be involved in the generation of PLM as they have been observed in patients with spinal cord lesions. However, treatment with dopamine agonists produces only mild improvement in the symptoms of these patients, compared to the marked response in patients with RLS (de Mello *et al.*, 1996).

Neurophysiological studies, including reflex studies and studies on cortical activity, have failed to elucidate the etiology of this syndrome. There is evidence though, obtained from functional magnetic resonance imaging (MRI), pointing toward a subcortical site as a location for the dysfunction (Bucher *et al.*, 1997). It is possible that the disease arises as a result of subcortical dysfunction with state-dependent reduced spinal and cortical inhibition. In addition, the periodic nature of the PLMS reflects the disinhibition of intrinsic spinal periodic generators (Garcia-Borreguero *et al.*, 2004). Functional imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT) have only found modest decrease for the dopamine D2 receptor. Iron deficiency may be associated with RLS, particularly for patients with onset at a later age and family history. Decreased midbrain iron despite normal serum iron has also been demonstrated in RLS. RLS severity correlates with serum ferritin levels and oral administration of iron seems to improve RLS symptoms, especially if pretreatment ferritin levels are lower than 45 mcg l^{-1} (O'Keeffe *et al.*, 1993; Sun *et al.*, 1998). Several steps in dopaminergic pathways require normal iron levels; therefore iron deficiency would be expected to result in dopaminergic dysfunction.

Treatment

At present, dopamine receptor agonists are the treatment of choice for RLS, particularly if daily treatment is needed or the condition is severe. This is mainly due to their longer elimination half-life, which results in less long-term complications. Several dopamine agonists have been studied under controlled conditions, showing efficacy for the treatment of the symptoms of RLS. Interestingly, cabergoline, the dopamine agonist with the longest half-life, is the only one to which no cases of augmentation have been linked so far (Garcia-Borreguero *et al.*, 2004).

L-Dopa at a daily dose of 50 to 250 mg, in conjunction with a decarboxylase inhibitor, given as a single dose before bedtime, has been proven to be effective in producing subjective improvement of symptoms and sleep quality, shortening of sleep latency and a reduction in PLMS (Collado-Seidel *et al.*, 1999). Yet, in the course of long-term treatment with L-Dopa, rebound and augmentation appear. Rebound refers to the reappearance of symptoms at a time coinciding with the end of the half-life period of the drug, usually early in the morning. Augmentation reflects the occurrence of RLS symptoms earlier in the day, an overall increase in symptom severity as a result of long-term dopaminergic treatment. Augmentation frequently represents a serious problem in treating patients with RLS.

Opioids have been found to be effective in treating RLS/PLMS in a subgroup of patients and they are considered second choice options. The required doses found to be effective are relatively high, often in the higher end of the analgesic range. Although opioids can be useful in a subpopulation of patients, the risk for abuse and the addictive potential of these compounds limit their clinical use.

Anticonvulsants such as gabapentin have been found to exert therapeutic effects. Gabapentin is particularly effective for cases associated with pain or dysesthesias (Happe *et al.*, 2001). Benzodiazepines, like clonazepam, can be useful in ameliorating some of the symptoms of RLS, but their effects might be mediated by sleep induction rather than direct suppression of RLS symptoms.

In addition to symptomatic medication, it is important to ascertain that the body iron stores are adequate. Oral administration of iron is recommended if serum ferritin levels are lower than 45 to 50 mcg l^{-1} (O'Keeffe *et al.*, 1993).

DYSTONIA

Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures (Fahn, 1990). Dystonia is classified in three ways: by body distribution of the abnormal movements, by etiology, and by age at onset (Table 2). Focal dystonia refers to the involvement of a single body

Table 2 Classification of dystonia

By age at onset
Childhood onset, 0–12 years
Adolescent onset, 13–20 years
Adult onset, >20 years
By cause
Idiopathic
Sporadic
Familial
Symptomatic
By distribution
Focal
Segmental
Multifocal
Generalized
Hemidystonia

Table 3 Classification of dystonia according to distribution

Focal Dystonia: single body part
Blepharospasm: eyelids
Oromandibular dystonia: mouth
Spasmodic dysphonia: larynx
Torticollis: neck
Writer's cramp: arm
Segmental Dystonia: two or more contiguous body parts
Meige syndrome: eyes and mouth
Generalized Dystonia: one leg and trunk or both legs and another body part
Childhood-onset hereditary torsion dystonia
Multifocal Dystonia: two or more noncontiguous body parts
Hemidystonia: ipsilateral arm and leg

area, segmental to the involvement of contiguous body areas, multifocal to the involvement of noncontiguous body areas, hemidystonia to the involvement of one arm and one leg on the same side, and generalized to the involvement of one leg and trunk or two legs and an additional body area (Table 3). The etiologic classification divides the causes of dystonia into two major categories: idiopathic (or primary) and symptomatic (or secondary). The idiopathic group is further subdivided into familial and nonfamilial (sporadic) patterns.

Dystonia beginning in childhood usually starts in the legs and progresses to become generalized or multifocal. Early onset primary torsion dystonia usually starts around age nine and has a genetic background in the great majority of cases. Approximately 80 to 90% of Ashkenazi Jewish children and 50% of non-Jewish children test positive for the DYT1 defect. The remaining cases are either nongenetic or belong to less common (e.g. DYT6, DYT13) or still unknown genetic causes of dystonia (Ozelius *et al.*, 1997). In contrast, adult-onset dystonia is usually sporadic. The onset of dystonic symptoms is usually gradual, with slow progression over the first 5 to 10 years. Although the dystonia may slowly worsen or spread to an adjacent body area, it seldom generalizes in the adult. Up to 33% of dystonic patients may experience a partial or complete remission, but this is rarely permanent (Greene *et al.*, 1995).

The most frequent primary focal dystonia seen in a movement disorder clinic is spasmodic torticollis or cervical dystonia (CD). CD is a focal dystonia affecting the muscles of the neck and upper torso. Depending on the specific pattern of muscles involved, it can produce turning of the head (torticollis), tilting of the head toward the shoulder (laterocollis), and flexion (antecollis) or extension (retrocollis) of the head (Bressman and Greene, 2000).

The second most frequent dystonic syndrome seen in the adult is blepharospasm. Blepharospasm is manifested by increased blinking, clonic eye closure or sustained, tonic eye closure. In some patients, reading, driving, or watching a movie may be impossible. The severity of the spasms can be such that can render the patient functionally blind. The association of blepharospasm with lower facial or oromandibular dystonia is referred to as Meige or Bruegel's syndrome. Oromandibular dystonia involves the muscles of facial expression or the masticatory and other oral muscles. Clinically, patients have involuntary grimacing, puckering, frowning, jaw opening or closing, tongue protrusions, and a variety of other movements that may be exacerbated by the use of the muscles. In addition to social embarrassment, it may impair speaking, eating, and drinking.

Spasmodic dysphonia is a focal dystonia of the laryngeal muscles resulting in either a strained and choked or quiet and breathy voice, depending on the dystonic position of the vocal cords (adductor or abductor, respectively). Limb dystonia can affect either the upper or lower extremity, and is usually task-specific. The most common form is writer's cramp.

Pathology and Pathophysiology

Pathological studies have been carried out on patients with primary torsion dystonia and there are no consistent pathological abnormalities identified by light microscopy (Gibb *et al.*, 1988). Studies in symptomatic hemidystonia show lesions of the putamen, the thalamus, and the connections of the basal ganglia with the thalamus and the cortex (Marsden *et al.*, 1985). Although autopsy studies have shown variable changes in norepinephrine, there have been no consistent neurochemical changes described in idiopathic dystonia. The lack of sufficient brain specimens has hindered further pathologic studies.

PET using fluoro-deoxyglucose (FDG) in 11 patients with unilateral dystonia compared to 11, age-matched controls showed a relative metabolic overactivity of the lentiform nucleus and premotor cortices (Eidelberg *et al.*, 1995). Pathophysiologic mechanisms have been suggested by electrophysiologic studies. Electomyography shows prolonged co-contracting bursts of activity in agonist and antagonist muscles and frequent spread of activity to distal muscles not normally used in a particular movement. These abnormalities can be explained by a loss of inhibitory control at the segmental (spinal cord, brainstem) or cortical level (Berardelli *et al.*, 1998).

The DYT1 gene encodes for a protein, torsin A. In normal adult brain, torsin A is widely distributed, with intense expression in the substantia nigra compacta, cerebellar dentate nucleus, Purkinje cells, basis pontis, locus ceruleus, numerous thalamic nuclei, the pedunculopontine nucleus, the oculomotor nuclei, the hippocampal formation, and the frontal cortex. Although the exact function of torsin A remains elusive, speculation on the mechanism the mutant torsin A compromises cellular function includes disrupted processing of normal torsin A or other proteins, interference with membrane trafficking and formation of cytoplasmic inclusions (Walker *et al.*, 2002).

Treatment

Treatment of dystonia has had limited success. Pharmacologic treatment of dystonia is largely based on empirical,

rather than scientific rationale. Anticholinergic medications, such as trihexyphenidyl, have been found to be of benefit in 67% of patients with idiopathic dystonia studied, mean age 18.6 years (Greene *et al.*, 1988). In the elderly, the side effects from anticholinergics are frequent and often dose-limiting. These include sedation, mental clouding, dry eyes and mouth, blurred vision, urinary retention, and constipation. Other agents reported anecdotally to be of benefit include baclofen, tizanidine, clonazepam, tetrabenazine, reserpine, tegretol, lithium, and bromocriptine. Although dopamine receptor-blocking agents have been used, the risk of TD has traditionally precluded routine administration of these agents. The newer, atypical neuroleptics, which carry less of a risk for tardive syndromes, can be an alternative approach. Patients with dopa-responsive dystonia manifested as childhood-onset dystonia with diurnal fluctuations and associated parkinsonism may respond dramatically to low doses of levodopa (Nutt and Nygaard, 2001).

The introduction of botulinum toxin into clinical practice in the late 1980s has revolutionized treatment of focal dystonia. Botulinum toxin, when injected locally, blocks acetylcholine release at the neuromuscular junction and, therefore, weakens the muscle. It has been successfully used in the treatment of most forms of focal or segmental dystonia (Comella and Pullman, 2004; Goldman and Comella, 2003), although it does not provide any permanent benefit or change in prognosis.

When drugs are ineffective or have shortcomings, surgical approaches can be considered. The procedure of choice currently is deep brain stimulation (DBS) of the internal segment of the globus pallidum (GPi). Bilateral pallidal lesions can be associated with significant adverse effects including speech difficulties and cognitive disturbances. It is for this reason that neurosurgeons have sought to develop surgical procedures that offer the efficacy of selective pallidal lesions but have a better index of safety. With the introduction of DBS to treat first chronic pain and then PD, it became logical to apply DBS to treat dystonia. There is now increasing experience in the use of DBS to treat various forms of dystonia. The initial results suggest that certain primary dystonias can show a strong improvement with GPi DBS (Lozano and Abosch, 2004).

TREMOR

Tremor is a rhythmic, oscillatory movement produced by alternating or synchronous contractions of antagonistic muscles. Tremor is considered the most common movement disorder. Tremors can be classified according to their phenomenology, distribution, frequency or etiology. Phenomenologically, tremors are categorized as rest, postural, and kinetic tremors (Lang *et al.*, 1992) (Table 4). Rest tremor is defined as tremor occurring when the affected body part is in complete repose. The classic example of a rest tremor is found in PD. Postural tremor is defined as tremor occurring during maintenance of an antigravity posture. Essential tremor (ET) is the prototype. ET is primarily a postural tremor, although it may be present to a lesser degree during movement, particularly when the movement involves postural adjustments. ET is familial in approximately half of the patients, with an autosomal dominant inheritance pattern. Some studies have suggested that there is an association between ET and dystonia, and between ET and parkinsonism. On the basis of an analysis of 678 patients diagnosed as ET, 6.1% were found to have concomitant PD and 6.9% had coexisting dystonia (Koller *et al.*, 1994).

Table 4 Tremor classification

Tremor type	Description	Associated disorder
Rest tremor	Large amplitude; 4 to 6 Hz	Parkinsonism rubral tremor
Postural tremor	Amplitude varies; 6 to 12 Hz	Essential tremor
Kinetic tremor	Large amplitude; 3 to 4 Hz	Cerebellar tremor

ET is more common in the upper extremities, although legs, head, trunk, face, and vocal cords may be affected. Although sometimes referred to as benign, the symptoms result in major disability in up to 15% of those afflicted, with 3% of patients being completely disabled. Over time, it tends to slowly progress with long periods of stable symptoms intervening. Alcohol suppresses the tremor for a few hours in 30% to 60% of patients (Boecker *et al.*, 1996).

Kinetic tremor is seen with voluntary movement, during the initiation (initial tremor), the course of the movement (dynamic tremor), and as the affected part approaches a target. Clinical–anatomical correlations indicate that kinetic tremor is usually associated with lesions of the cerebellum or the cerebellar outflow pathways. Lesions of the cerebellar hemispheres or upper brainstem may cause kinetic tremors with a frequency ranging from 5 to 7 Hz. Caudal brainstem lesions may cause faster tremors, ranging from 8 to 12 Hz (Cole *et al.*, 1988).

Task- or position-specific tremors occur either during a specific task, for example, writer's tremor, or while maintaining a position, for example, orthostatic tremor. In 1984, Heilman described a tremor occurring after few seconds of standing, which would progressively increase unless the patient began to walk, at which time the tremor ceased and the gait was normal (Heilman, 1984). Usually, patients with orthostatic tremor have normal clinical examination except for wide base standing and unsteadiness, which disappear when walking. Arm tremor resembling ET is found present in one-third of cases. Electrophysiological exploration is necessary for diagnosis and shows a regular rapid tremor (frequency around 16 Hz) in the weight-bearing muscles (Sander *et al.*, 1998; Mastain *et al.*, 1998). Orthostatic tremor cannot be considered as a clinical variant of postural essential tremor. Its pathophysiology is unknown, but the efficacy of clonazepam, primidone, or barbiturates suggests the impairment of the gabaergic system.

Tremor is widely experienced in neurologically intact individuals undergoing intense anxiety or stress, with the use

Table 5 Non-parkinsonian movement disorders associated with selected drugs

Disorder	Drug
Tremor	Amphetamines
	Bronchodilators
	Sympathomimetics
	Lithium
	Tricyclic antidepressants
	Selective Serotonin Reuptake Inhibitors
	Valproic acid
	Corticosteroids
Chorea	Levodopa
	Dopamine agonists
	Anticholinergics
	Neuroleptics (tardive)
	Metoclopramide (tardive)
	Estrogens
	Amphetamines
	Anticonvulsants
Dystonia	Neuroleptics (acute and tardive)
	Metoclopramide (aute and tardive)
	Levodopa
	Dopamine agonists
	Chloroquine
Tics	Neuroleptics (tardive)
	Metoclopramide (tardive)
	Cocaine
	Amphetamines
	Lamotrigine

of drugs (Table 5), and with other metabolic derangements. Nonpathological tremor has a low amplitude and a high frequency (Marsden, 1984).

Pathophysiology and Pharmacology

The mechanism underlying ET is not known. It has been hypothesized that the tremor arises from abnormal spontaneous firing of the inferior olivary nucleus, which drives the cerebellum and its outflow pathways via thalamus to the cerebral cortex and then to the spinal cord. The involvement of the olivo-cerebellar-thalamo-cortical circuitry in ET is supported by changes in the cerebellar blood flow as measured by PET. Using a higher-resolution camera, the investigators were additionally able to demonstrate bilateral midbrain activation in the region of the red nuclei during tremor, without change in the activity of the inferior olive (Wills *et al.*, 1995).

The neurochemical abnormality underlying ET may relate to the adrenergic system. This is based on clinical observations of improvement in tremor using β-adrenergic antagonists and tremor induction when using β-adrenergic antagonists (Koller *et al.*, 2000a).

Treatment

Treatment of ET is indicated if the symptoms are sufficiently severe to interfere with daily activities or threaten job security. Propanolol is considered the treatment of choice. It is started at a low dose and is gradually increased until clinical benefit, side effects, or a maximal dose of 320 mg is reached. β-blockers are contraindicated in patients with broncho-constrictive disorders, peripheral vascular disease, congestive heart failure, and relatively contraindicated in diabetes mellitus. If propanolol is ineffective or contraindicated, primidone may provide symptomatic relief. The starting dose is 25 to 50 mg once daily with a slowly increasing dose schedule until clinical benefit or side effects occur. The major drawback of primidone is the occurrence of sedation, although small increments in the dose may avoid this side effect. Other drug alternatives include: clonazepam, methazolamide, flunarizine, nimodipine, gabapentin. All these have been tried in small numbers of patients with variable results.

Surgical treatment for ET has been used since the early 1950s. The optimal target has been determined to be the ventralis intermedius (VIM) nucleus of the thalamus. Thalamotomy improves contralateral tremor in more than 90% of patients. Long-term studies of thalamotomy indicate that the benefits continue in most patients. Persistent morbidity associated with thalamotomy, which occurs in less than 10% of patients, includes dysarthria, dysequilibrium, weakness, and cognitive impairment. Bilateral thalamotomy is associated with substantial morbidity and is usually avoided. Chronic stimulation of the VIM is a safe and effective alternative to thalamotomy. Adverse effects of chronic stimulation include paresthesia, dysarthria, dysequilibrium, and localized pain. DBS of the VIM nucleus of the thalamus appears to be safer than thalamotomy and is now the recommended procedure of choice (Koller *et al.*, 2000b; Koller *et al.*, 2001; Pahwa *et al.*, 2000).

KEY POINTS

- Chorea in the elderly is a clearly defined and fairly common syndrome but is more often recognized as part of other neurologic syndromes such as tardive dyskinesia, Huntington's chorea, acquired hepatocerebral degeneration, complication of prolonged levodopa therapy in PD.
- The clinical features of late-onset HD resemble those of midlife onset, but the illness is more slowly progressive and less functionally debilitating.
- TD is frequently difficult to treat, therefore only individuals with defined indications for the use of these agents should be treated, especially among the elderly, who appear to be at a higher risk for developing TD, and atypical neuroleptics should be the agents of choice.
- RLS is a sensorimotor disorder characterized primarily by motor restlessness, which is brought on by rest and relieved by movement, such as walking or stretching. PLMD is frequently associated with RLS but may occur independently, especially in the elderly. Both RLS and PLMD are treated with dopaminergic agents.

- Dystonia in the elderly appears mostly as focal or segmental dystonia and not generalized. It can be treated with botulinum toxin injections or medications.
- Tremor is a frequent occurrence in the elderly and can be seen as rest tremor, in PD, postural and kinetic tremor, in ET and as a side effect of medications, intention tremor in situations associated with cerebellar lesions, and task or position-specific tremor, in dystonia.

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Normal Pressure Hydrocephalus

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INTRODUCTION

Hydrocephalus is a condition with an excess amount of cerebrospinal fluid (CSF) in the ventricles; this leads to ventriculomegaly and subsequent neurological signs and symptoms. The accumulation of CSF can result from a block in the ventricular system (e.g. aqueductal stenosis), or a decrease in CSF resorption (e.g. scarring after subarachnoid hemorrhage). It is virtually never a result of CSF overproduction in the realm of geriatrics, and it is most relevant as it relates to the condition called *normal pressure hydrocephalus* (*NPH*). A recent estimate on its annual incidence is 1.8 cases/100 000 (Krauss and Halve, 2004).

First identified in 1965, NPH is classically described as a syndrome of unsteady gait, urinary incontinence and mental deterioration without papilledema and with normal CSF pressure on lumbar puncture (Adams *et al.*, 1965). It is important to note that it is fundamentally a clinical diagnosis. It should be noted that while the term "normal pressure hydrocephalus" is widely used, changing ideas and new concepts have given rise to questions on the validity of this nomenclature. Some authors have suggested, for example, that CSF pressure in NPH is not exactly "normal" as some show abnormalities in CSF dynamics (Bret *et al.*, 2002). This condition is not exclusive to the geriatric population and can be seen in children as well. Terms such as "chronic hydrocephalus" have been proposed, but thus far, none have been convincingly better than "NPH" (Dunn, 2002).

ETIOLOGY AND PATHOPHYSIOLOGY

NPH can be secondary to conditions that cause a decrease in resorptive capacity at the level of the arachnoid granulations along the skull base and over the hemispheres (Gleason *et al.*, 1993). Some authors feel that resorption also occurs in the brain parenchyma through capillaries and venules (Penar *et al.*, 1995; Castro *et al.*, 1991) and resorptive problems can be at this level as well. Among the known causes of NPH are subarachnoid hemorrhage, trauma and meningitis, all of which can lead to scarring of the arachnoid granulations and subarachnoid space. Such conditions are commonly referred to as *secondary NPH*. In over half of NPH patients, however, there is no identifiable cause. The development of idiopathic NPH remains unclear, but it appears to involve the interplay of several factors such as cerebral ischemia, decreased vascular compliance, decreased cerebral blood flow to periventricular regions, and brain atrophy. MR flow quantification studies showed lower venous compliance in NPH patients, which could lead to increased resistance to CSF outflow and cerebral ischemia in the concerned areas (Bateman, 2000). Cerebral blood flow has been shown to be decreased in patients with idiopathic NPH, particularly in periventricular regions (Momjian *et al.*, 2004) and the basal ganglia and thalamus (Owler *et al.*, 2004a). Idiopathic NPH patients have also been found to have brain atrophy in addition to hydrocephalic features (Tsunoda *et al.*, 2002), a finding that further shows why the total understanding of the pathophysiology and clinical picture of this condition is quite complicated.

CLINICAL PRESENTATION

NPH usually presents as a clinical triad of gait disturbance, urinary incontinence and mental deterioration. Other less consistent clinical findings include signs of hyperreflexia and positive palmomental reflex. One study showed that patients with NPH (as a group) have significantly larger head sizes than normal controls (Krefft *et al.*, 2004), although this finding is rarely apparent when one sees an individual patient. Progressive difficulty in ambulation is usually the most prominent symptom, and it is described as wide-based

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gait, slow and unsteady. The patient walks in small steps and he does this with his feet clearing the floor at a low height. He or she feels that the feet are glued to the floor. The degree of gait disturbance depends on the severity of the NPH, and patients who are in the early stages of the disease can walk almost normally except for some unsteadiness. Conversely, patients with severe NPH can be so debilitated that the patient is unable to stand without support. Mental decline is usually in the form of problems with memory, particularly short-term memory. It may also involve a decrease in mental alertness and an overall slowing of thought processes. Urinary incontinence may start as progressive urgency but many will have frank incontinence by the time of consult. It is a symptom that the examiner needs to specifically ask about because it may not be recognized by the elderly patient or family members as significant. It may be considered as a symptom of late-stage NPH (Meier *et al.*, 1999).

It is readily apparent that the above symptomatology in an elderly patient can be easily mistaken for and brushed aside as part of the aging process. Awareness of this condition is not as prevalent as it should be, and many patients do not come to medical attention. Indeed, one can only wonder how many patients have gone undiagnosed and have potentially missed out on a better quality of life had they been shunted.

NPH can be difficult to differentiate from Parkinson's and Alzheimer's disease. Gait similarities in NPH and Parkinson's include short steps and leg rigidity (Curran and Lang, 1994). The typical tremor of Parkinson's may help make this diagnosis, but sometimes patients with NPH can also have confusing tremors. In general, it is possible to differentiate between the two by the gait patterns. NPH is characterized by reduced stride length, reduced step height and balance difficulty. Parkinson's patients have a shuffling gait with impaired arm swing and walk with their hips and knees slightly flexed and trunk bent forward (Stolze *et al.*, 2001).

In comparing Alzheimer's and NPH, the dementia is not as pronounced as in Alzheimer's. It is not uncommon to find NPH patients with concurrent Alzheimer's disease (Jeong *et al.*, 2004). It is important to identify patients with both Alzheimer's and NPH, because this particular subset responds poorly to shunting (Savolainen *et al.*, 2002).

DIAGNOSTIC MODALITIES

A host of diagnostic tests have been developed to study NPH. The evolution of these tests reflects the dynamic ideas that have been put forth on its pathophysiology over the past four decades. Often times, recognition of NPH can be made with a good history and physical examination, together with a CT or MRI and a lumbar CSF pressure determination. However, the diagnostic work-up for NPH is as much about diagnosis as it is about determining whether a patient will respond well to surgery. For this reason, a number of other diagnostic modalities have been developed to predict shunt-responsiveness. However, consensus over their use remains far from being reached and there are wide variations in the diagnostic management of these patients.

CT/MRI

The main diagnostic tool in NPH is computed tomography (CT) or magnetic resonance imaging (MRI). Ventriculomegaly is revealed by a CT scan (Figure 1), and it is adequate in detecting complications such as subdural collections. MRI allows visualization of additional information that may contribute to the evaluation of a patient. White matter changes in the subcortical and periventricular areas have been associated with NPH and these appear on MRI as T2 hyperintensities (Figure 2). MRI may also provide details that may be helpful in excluding other disease entities. When evaluating MRIs of patients with NPH, it is common to see flattened gyri and obliterated sulci that indicate a "tight" intracranial compartment. However, it is important to remember that even if the arachnoid space looks "spacious", it does not necessarily mean that there is nothing to treat.

Lumbar Puncture

A lumbar puncture is a simple and widely used test in the evaluation for NPH. It is helpful not only in determining CSF pressure but also in boosting the diagnosis of NPH and indicating its shunt-responsiveness if there is subsequent improvement in gait. The amount of CSF that is removed varies, but is usually between 40 and 50 ml to induce improvement of symptoms. Several studies highlight the high predictive value of a positive lumbar puncture test (Ahlberg *et al.*, 1988; Sand *et al.*, 1994; Walchenbach *et al.*, 2002). There are doubts, however, about how well this test identifies

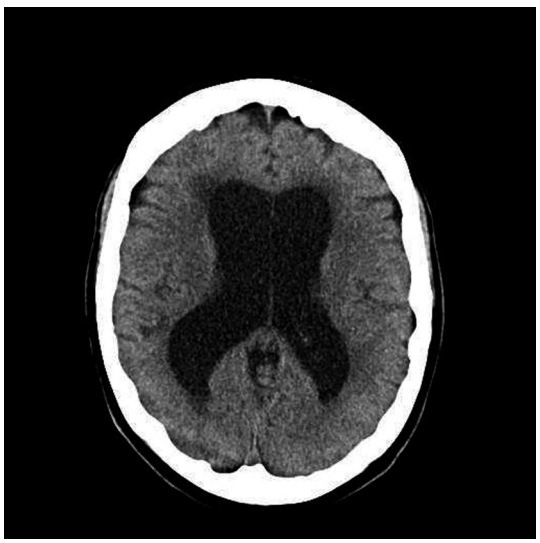


Figure 1 CT scan showing typical features of NPH, with ventricular enlargement out of proportion to atrophy

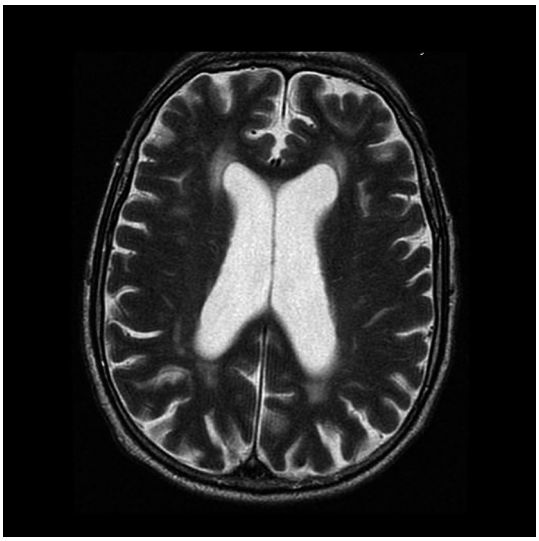


Figure 2 MRI showing white matter changes that commonly accompany NPH

patients who can benefit from surgery, because the amount of CSF removed in this one-time process can be inadequate in producing neurologic improvement in many patients, and it does not mimic the continuous drainage of shunting.

Lumbar Drain

A lumbar drain trial involves doing a lumbar puncture with a large bore needle and inserting a small caliber catheter that is left to drain CSF from the thecal sac for approximately 4 days. The catheter is connected to an external bag within a closed system that on average drains about 100–150 ml of CSF a day. The patient stays in the hospital and is checked daily for improvement in gait and cognitive function. In our institution, this test is the only one that we consistently use, aside from clinical and CT/MRI findings, in determining which patients to shunt. It has been shown to predict the surgical outcome in up to 100% of cases (Haan and Thomeer, 1988; Chen *et al.*, 1994); our overall experience appears to be closer to 80%. A prospective multicenter study found that a positive lumbar drain test predicted good shunt response in 87% of cases, but cautions that a negative result on the test is unreliable as the false negative rate was 64% (Walchenbach *et al.*, 2002). We suggest that patients who have a negative lumbar drain test should still be considered for shunting, and one should look toward the overall clinical picture and the patient's wishes as guides in the decision-making process.

Lumbar or CSF Infusion Test

A diagnostic test for NPH advocated by Danish investigators is the lumbar infusion. This is a hydrodynamic test that is performed by inserting two cannulas into the lumbar thecal sac, with one cannula attached to an infusion pump and the other to a closed-system pressure monitor. A similar maneuver can be done intraventricularly through a surgically placed ventricular access device but this is less popular as it is more invasive. The test assesses CSF absorption on the premise that the pathology lies in increased resistance to CSF outflow. Normal saline is infused at a constant rate until a steady state intracranial pressure (ICP) plateau is reached. A value for resistance to CSF outflow, commonly noted as R_{CSF}, is then calculated by dividing the increase in pressure during infusion by the infusion rate (Czosnyka and Pickard, 2004). R_{CSF} values below 13 mmHg/ml/minute are regarded as normal (Borgesen and Gjerris, 1982), while values above 18 mmHg/ml/minute are abnormal (Boon *et al.*, 1997). The positive predictive value has been estimated to be 80% and its false negative prediction is about 16% (Kahlon *et al.*, 2002). There has been some argument on the details of the formula used to calculate R_{CSF} (Czosnyka *et al.*, 2003), as well as on what absolute value predicts good response to shunting. There are some who feel that the infusion test is of no value in diagnosing NPH (Savolainen *et al.*, 2002). Our general impression is that it is useful but cumbersome and that equivalent data can be obtained with the lumbar drain.

Flow within the Aqueduct

CSF flow characteristics in the Aqueduct of Sylvius can be studied using MRI. Bradley *et al.* (1991) found that increased flow void in the aqueduct, as seen on proton density-weighted conventional spin-echo images, was associated with better shunt outcome. Phase-contrast MRI is able to demonstrate CSF movement within the Aqueduct during the cardiac cycle. This has been *termed* aqueductal CSF stroke volume and a finding of hyperdynamic flow correlates well with good response to surgery (Bradley *et al.*, 1996; Mase *et al.*, 1998). Although high Aqueductal CSF flow is a good predictor of a favorable outcome, a finding of normal velocity should not be interpreted as ruling out NPH (Poca *et al.*, 2002). In such instances, further evaluation with other tests need to be done. It should be mentioned that there have been dissenting opinions on the usefulness of CSF flow rate analysis. One such study showed that measurement of Aqueductal CSF flow was not reliable in predicting postshunt improvement (Dixon *et al.*, 2002).

Neuropsychological Testing

The cognitive dimension of NPH is probably the most challenging to study and manage. Neuropsychological testing is gaining popularity as a tool in outcome assessment for patients with NPH. It has been shown that visual attention, verbal recall and motor precision were the most representative tests, and measuring these would be a good way of following up patients through surgery and beyond (Klinge *et al.*, 2002). Its role in predicting dementia reversal after

shunting has also been described (Goodman and Meyer, 2001). Although there have been doubts about the value of neuropsychological testing in diagnosing NPH and in outcome prediction (Savolainen *et al.*, 2002), it is nonetheless an important tool in detailing the profile of cognitive impairment in NPH patients, and may even differentiate between signs of NPH and mild Alzheimer's Disease (Iddon *et al.*, 1999).

Other Tests

ICP monitoring has been described to have some use in NPH. The presence of B waves, which indicate normal mean baseline ICP with transient elevations of mean and pulse pressure, in more than half the monitoring points to a better outcome with shunting (DiRocco, 1984; Vanneste, 2000). Radionuclide cisternography is another study that has been used to diagnose NPH, but its results have been found to be poor predictors of response to shunting (Hebb and Cusimano, 2001). The same is true for positron emission tomography (PET) that showed decreased regional glucose metabolism in patients with idiopathic NPH as a group, but there was no significant correlation with shunt outcome (Tedeschi *et al.*, 1995). PET has focused some attention on the thalamus and basal ganglia (Jeong *et al.*, 2004) where mean cerebral blood flow was found to be decreased in NPH patients (Owler *et al.*, 2004b). Single-photon emission computed tomography (SPECT) has also been used in the study of NPH and it appears that the finding of an enlarged subcortical low-flow area corresponds to a better clinical response upon shunting (Waldemar *et al.*, 1993).

TREATMENT

Ventriculoperitoneal Shunting

The mainstay of treatment of NPH is CSF diversion in the form of ventriculoperitoneal shunting. Basically, the procedure involves inserting a catheter into the lateral ventricle and connecting it to a distal catheter that goes to the peritoneal cavity. There is an intervening flow-regulating device between the two catheters, as well as a reservoir that can be tapped with a small-gauge needle in cases where CSF samples are needed or the patency of the shunt system needs to be tested. The ventricular catheter is placed through an occipital or frontal burr hole, and the rest of the shunt system is introduced down the side of the neck and anterior chest wall in the subgaleal-subcutaneous layer with the aid of a tunneling device. The patient is left with two small incisions, one in the scalp and another in the abdominal wall. Alternatively, the placement of the distal catheter may be to the pleural cavity or the atrium of the heart. The operation is done under general anesthesia and usually lasts about an hour or two. It commonly entails an overnight or a two-day stay in the hospital.

There is considerable variation in the type of flow-regulating device that is used. Conventionally, shunt systems employ valves that come with preset opening pressure levels – low, medium, and high. NPH patients usually do best with the low-pressure valve, as it allows CSF drainage even when intraventricular pressure is not high, although one report indicated that medium-pressure valves give equivalent clinical outcome (McQuarrie *et al.*, 1984). A problem that arises not infrequently is overdrainage that leads to the formation of subdural effusions. It is apparent that finding the right balance between CSF diversion and overdrainage is not something that is best addressed by preset valves. For this reason, programmable shunts were developed and are becoming widely used in the treatment of NPH. The device that we use in our institution is the Codman-Hakim programmable valve. The procedure is the same as in conventional shunts. Postoperatively, and in subsequent clinic visits, the valve setting can be adjusted, according to the patient's progress, from anywhere between 30 and 200 mmH20 by holding up a programmer over the shunt device (Figure 3). It, therefore, eliminates the need for a reoperation in cases of overdrainage or underdrainage, and allows us to find the right pressure setting for a particular patient. Elderly patients can be ambulated within a day of their procedure with the high-pressure setting and the pressure can be gradually diminished, a tactic that avoids the prolonged bed rest that used to be part of the adjustment to a shunt. In one study, about half of shunted patients required adjustments, downward in 52% for underdrainage (Figure 4) and upward in 46% for overdrainage and subdural hematoma formation (Zemack and Romner, 2002). The ability to program and reprogram the shunt valve is an extremely useful advantage, not only in the immediate postoperative period but also in later years, as a particular patient who does well at a certain pressure level may later require a different setting as his or her intracranial dynamics change.

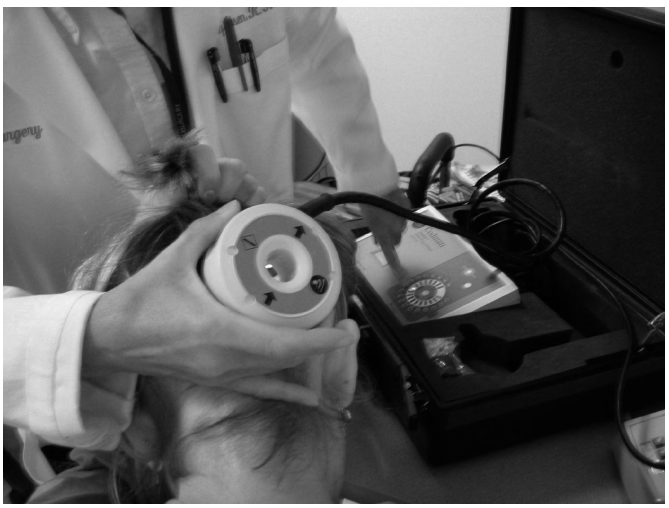
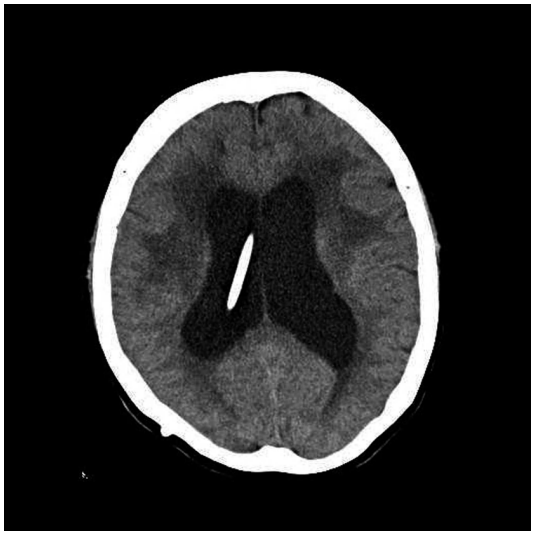
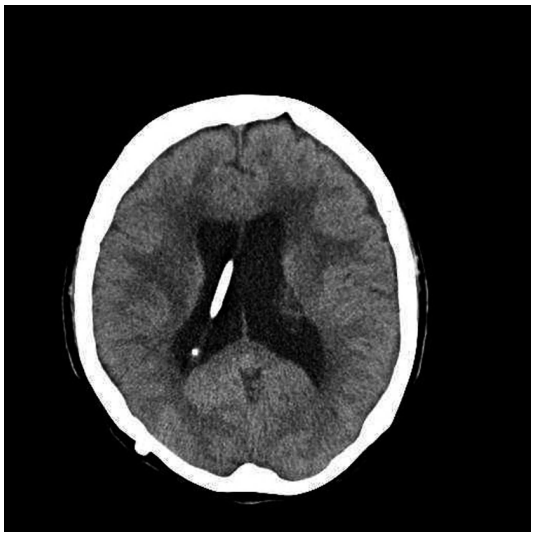


Figure 3 Valve pressure adjustment with a programmer for the Codman-Hakim valve, one form of programmable valve, in the clinic



(a)



(b)

Figure 4 Decrease in ventricular size/hydrocephalus and in overall brain "tightness" after lowering the pressure setting of a programmable valve

Endoscopic Third Ventriculostomy

It should be noted that ventriculoperitoneal (VP) shunting is not the only way of diverting CSF from the ventricles. Endoscopic third ventriculostomy (ETV), a well-established procedure for hydrocephalus in children, has been reported to be useful in NPH if aqueductal stenosis is the cause. Essentially, ETV involves creating a hole in the thin, membranous floor of the third ventricle with the use of a neuroendoscope, which is introduced through a frontal burrhole in order to let intraventricular CSF out into the basal subarachnoid space. It does away with having to leave any hardware in the body, and with it, complications such as shunt infection are avoided. It is a safe procedure and is as quick as a standard shunt operation. The hole in the third ventricular floor can spontaneously close at a later time, and there are questions as to how effective ETV can be when it does not bypass the level of CSF impedance that is further downstream from the arachnoid villi. Some reports suggest that ETV is promising and it is postulated that the effect is relief of periventricular tissue stress and improved local blood flow (Mitchell and Mathew, 1999). At the moment, the strongest indication for ETV in NPH is in patients whose outflow resistance is increased in the ventricular infusion test but not in the lumbar infusion test, a finding that suggests functional aqueductal stenosis (Meier *et al.*, 2000). Imaging that demonstrates aqueductal stenosis may also be useful in defining this situation.

Patient Selection

There are differences among institutions in the criteria for determining which patients to shunt. In general, patients whose clinical picture is that of NPH with consistent CT or MRI findings are candidates for shunting. At our institution, we employ the lumbar drain test to further select who will most likely benefit from a shunt, and this increases the shunt response rate by about 20%, that is, from 60% to 80%. In the CSF infusion test, experts recommend a cutoff value of 18mmHg/ml/minute on outflow resistance, while those with values below 18mmHg/ml/minute may also be shunted if their CT shows typical findings of NPH and limited white matter lesions and no significant cerebrovascular disease on history (Tans and Boos, 2002). There are a number of other ancillary tests that may be useful, but these are either not widely accepted or not easily available. The value of the CSF tap test has not been lost, though as many continue to use it for its simplicity and reliability.

Complications

A shunt operation is generally safe, but systemic complications in the elderly and subdural effusions may be problematic. There is a 1–2% risk of perioperative bleeding or infection. However, late shunt complications are among the most persistent and frustrating problems in neurosurgery. A recent systematic review of studies on NPH spanning the period of 1977–2000 reveals an overall complication rate of 38% and reoperation rate of 22% (Hebb and Cusimano, 2001). More recent data, though, show lower complication rates at 14–20% (Poca *et al.*, 2004, Zemack and Romner, 2002), reflecting advances in techniques and materials. Furthermore, the advent of programmable valves has made many of these cases readily solvable.

Shunt infection is another complication that may occur, although the rate is notably lower than in the pediatric shunt population. It is usually due to proteinaceous debris or blood products clogging up the ventricular catheter, valve chamber, or distal catheter. This may be checked by doing a shunt tap, as previously mentioned, which allows the measurement of intraventricular pressure and the evaluation

of shunt patency. Any part of the catheter may also fracture or become disconnected for reasons such as trauma. This can be revealed by X rays that show the entire shunt system, commonly referred to as a *shunt series*. The appropriate malfunctioning component should be diagnosed and replaced at surgery.

Shunt infection is manifested as fever or erythema along the shunt tract, and is verified by CSF cell counts and positive cultures obtained through a shunt tap. The optimum treatment for shunt infection is externalization of the system for at least a week; if the patient is not too shunt dependent it can simply be removed. Intravenous antibiotics directed against the specific bacteria should be used. Subdural effusions, low signal collections over the hemisphere, can sometimes be watched, as they are less than a centimeter in thickness. If the shunt is a programmable one, the pressure setting can be raised to obliterate the subdural collection (Figure 5). While not all subdural collections have to be addressed, and may actually coexist with improved CSF dynamics and good clinical response (Fisher, 2002; Nakamizo *et al.*, 2002), those that are persistent and symptomatic have to be surgically drained. If there is bleeding within the subdural collections, they particularly require surgery.

An intriguing complication that has been recognized only recently is hearing loss. Subjective note of postshunt hearing loss is not common but a study actually showed that two-thirds of ears tested showed a loss of more than 10 decibels after shunting (van Veelen-Vincent *et al.*, 2001). Most of it was temporary, however, and recovery was seen within a few months. The cause is unknown.

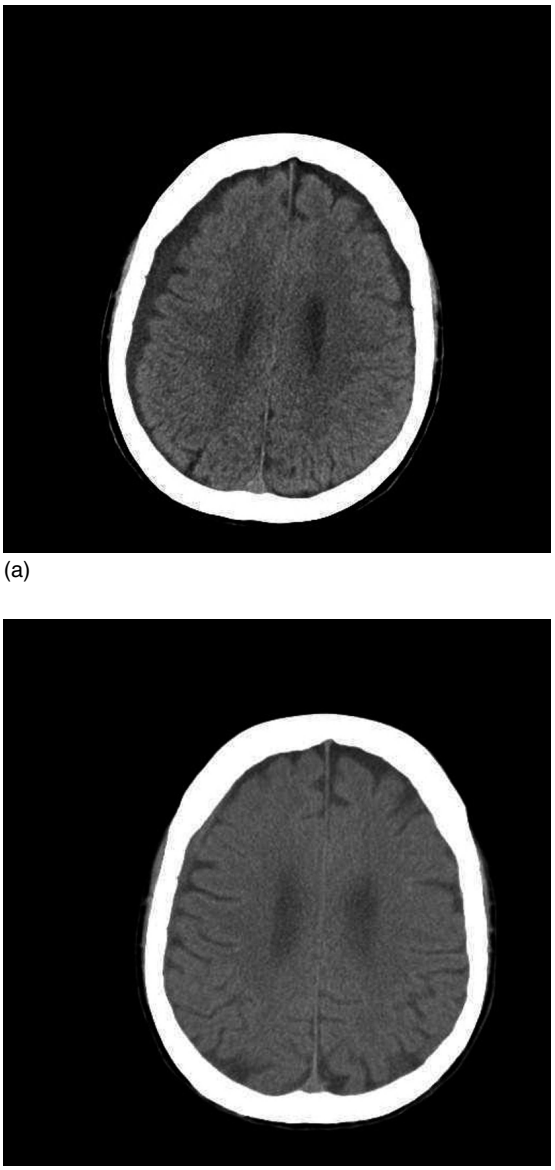


Figure 5 Subdural effusion before and after increasing the pressure setting of a programmable valve

OUTCOME AND PROGNOSIS

Several factors have been identified as predictors of good outcome to shunting. These include the presence of the classical clinical features of NPH, a positive result on the lumbar drain test, and the presence of pressure signs on CT or MRI such as periventricular transependymal effusion. CSF outflow resistance values of more than 20 mmHg/ml/minute and the absence of dementia have also been correlated with good outcome in patients with late-stage NPH (Meier *et al.*, 2004). For patients undergoing continuous ICP monitoring, the presence of B waves in more than 50% of the recording time predict good outcome (Vanneste, 2000). Factors that do not appear to affect outcome were patient's age, duration of symptoms, extent of ventricular dilatation and degree of dementia (Poca *et al.*, 2004).

Overall, as many as 80% of NPH patients who undergo shunting may experience some clinical improvement. In terms of symptoms, improvement is commonly seen in gait and urinary incontinence, but not as consistently in cognitive impairment particularly short-term memory. Studies estimate that 81–86% improve in gait, 70% in bladder control, and 40–44% in cognitive function (Dixon *et al.*, 2002; Poca *et al.*, 2004). Sustained long-term improvement is more difficult to predict, as some patients who initially do well after shunting may experience deterioration in later months or years. However, this problem has been greatly reduced with the use of programmable valves. As the mechanical characteristics and CSF flow dynamics of a patient's brain change over time, reprogramming the valve setting can help in establishing a favorable flow soon after or long after surgery without the need for a reoperation. Shunt devices are designed to last long and they usually last a lifetime. Replacement is only necessary when it is clogged, fractured or infected. The survival rate of shunt devices in general is 50% in 5 years while for programmable valves it has been estimated to be around 80% in 5 years (Zemack and Romner, 2002).

LONG-TERM CARE AND FOLLOW-UP

Many patients readily recover their functions after surgery. For some, however, rehabilitation is an essential component of the recovery process. Physical therapy can be done in a rehabilitation center or at home depending on how well the patient does after surgery and how much social support is available. After optimal improvement at the right valve setting has been achieved during the postoperative period, the patient is usually followed up once a year with a CT scan. Naturally, patients are advised to seek immediate attention if any problem occurs in the interim.

KEY POINTS

- Most prominent symptom is wide-based gait, with short steps and low floor clearance.
- Other symptoms include urinary incontinence, poor short-term memory and slow mentation.
- CT scan or MRI of the brain shows ventriculomegaly.
- Lumbar drain trial helps with patient selection for surgery.
- Mainstay of treatment is surgery in the form of ventriculoperitoneal shunting.

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69

Epidemiology of Stroke

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INTRODUCTION

Cerebrovascular disease (CVD) or "stroke" is the third leading cause of death and an important cause of long-term disability in most industrialized nations. The World Health Organization (WHO) defines stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin". An estimated 700 000 persons in the United States (US) will have a stroke in 2004 of whom 160 000 (23%) will die (American Heart Association, 2003). Almost half of stroke deaths will occur before patients are transported to hospitals, and 15–30% of stroke survivors will be permanently disabled. With the general population aging in the United States, one can expect an increase in both the incidence and prevalence of stroke.

Despite its significance, the epidemiology of stroke has been relatively ignored, but over the last 20 years, a number of studies have been published defining the natural history and risk factors for stroke. While many questions have been clarified by epidemiologic studies, others have been made more complex.

This chapter is organized to introduce the reader to general epidemiologic concepts and then focus on the major epidemiologic trends in stroke. It is by no means an exhaustive review, but an attempt to highlight the predominant issues in the field.

While important in its own right, subarachnoid hemorrhage will not be formally covered in this review. Its pathophysiology, age distribution, and prognosis are different from other types of stroke (*see* **Chapter 87, Subarachnoid Hemorrhage**). Where it is relevant to a particular topic, it will be discussed.

EPIDEMIOLOGY

Epidemiology is that field of medical science that deals with the patterns of disease as they occur within populations. The subject matter consists of the frequency of a given disorder and its distribution by sex, age, race, geography, and other demographic characteristics, and the presence of predisposing, precipitating or protective factors in its appearance, severity, course, or duration. Thus, epidemiology comprises *descriptive* aspects, on which may be based *analytic* studies leading to specific hypotheses as to cause, treatment, or prevention; these hypotheses in turn are occasionally amenable to an *experimental* test by epidemiologic methods.

Socioeconomic planners for a community should have knowledge of the burden of illness expected in order to allocate the required facilities (hospitals, clinics, offices) and personnel (physicians, nurses, and ancillary health staff). The costs of these services, as well as the economic burdens of illness on the patient and his or her family, must be measured. The closer one approaches an accurate estimate of needs, the more likely there is to be an appropriate allocation of available resources.

The public health worker requires epidemiologic data to determine the baseline experience of a community in order to evaluate any changes over time, whether increases (including epidemics) or decreases. Projection of these trends is used to estimate future needs. The identification of major and especially increasing health problems signals areas of concern and investigation.

Clinicians use epidemiologic methods and information in a search for factors associated with a disorder and for modifications of its course. For example, hypertension has been shown to be a strong independent risk factor for CVD in a number of epidemiologic studies. This information has fueled the effort to treat individuals with hypertension, which has likely had a major impact on the decline in stroke mortality found over the last 30 years. Furthermore, the differential diagnosis of any disease may be refined by knowledge of local disease frequency and predilections by age, sex, and other characteristics. Such factors serve to direct an efficient work-up of patients.

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Rates in Epidemiology

The primary measures of epidemiology are those of the frequency of the disease within specific populations or subgroups of populations. The critical difference between clinical case series and epidemiologic series is the reference of the cases in the latter to a specific denominator, which is the "population at risk", that is, that group or subgroup of the defined population under study that is subject to the disorder in question. This population may comprise the entirety of a community or country or may be delimited according to age, sex, occupation, or any other definable characteristic. But it is essential that the numerator (cases) and the denominator (population) refer to the same subset. Thus, epidemiologic measures of frequency are proportions or ratios (cases/population), which are generally transposed to convenient unit denominators, such as cases per 1000 or 100 000 population. When time is added as a factor, these ratios are referred to as *rates*. Three measures in common usage are the incidence rate, the mortality rate and the prevalence "rate".

The *incidence* or *attack rate* of a disease is the number of new cases of a disease over a given period per population at risk for the disease in the period. It is a measure of the appearance of disease. The period most often employed is the year, so that one speaks of an annual incidence rate per unit of population. The age-specific incidence rate is that referable to a given age-group, for example age 15–19, or age 85+.

The *mortality* or *death rate* has the same characteristics as the incidence rate, except that deaths caused by the disease comprise the numerator.

The (*point*) *prevalence "rate"* is more properly called a *prevalence ratio*. It refers to the total number of cases of a disease at a given time, expressed per unit of population. There is also a *period prevalence rate*, seldom used, wherein all cases present at any time during the entire interval in question comprise the numerator. Prevalence reflects the existence of disease, and includes both old and new cases. Assuming no change in incidence or duration, and no migration, the average annual incidence rate times the average duration of illness in years equals the point prevalence rate.

When applied to the study population itself, such rates are called *crude rates.* When dealing with a disorder that is limited by age, sex, race, the age-specific (or sex-specific or race-specific) rates would be the appropriate ones to use in comparisons. On the other hand, it is frequently desirable to have a single figure that can be used to compare results of different studies; this leads to the use of age-adjusted rates. One method of calculating an age-adjusted rate is to take each observed age-specific rate and multiply this rate by that proportion of a "standard" population that is represented by the same age-group. The sum of such figures for all age-groups will be the "age-adjusted" rate. One common standard is the US population distribution for a census year. For disorders such as stroke that are strongly age-related (and reasonably common), age adjustment is of major importance.

CVD Classification

Standardized classification schemes are essential in epidemiologic studies. The need to classify stroke is much more than of just prognostic or pathophysiological interest. Currently, treatment trials for acute stroke and for secondary prevention of stroke involve the use of procedures and medications that could potentially benefit individuals with infarction but worsen those with intracerebral hemorrhage. To be useful, a classification scheme should accommodate a wide variety of clinical practices, taking into account variability in age, the type of hospital setting and resource limitations.

The National Institute for Neurological Disorders and Stroke (NINDS) divides ischemic stroke according to the pathological mechanism, the clinical category, and the arterial distribution (Table 1). Making a proper diagnosis (e.g. cardioembolic stroke) in this system requires ancillary investigations; yet even after such information is obtained, the diagnosis is not necessarily definitive (*potential* source of cardiogenic embolism). Using only clinical assessment to arrive at a diagnosis with this system would at best be tentative. The Stroke Data Bank classification system is another system developed by academic hospitals in the United States, but shares similar problems with the NINDS classification system. The Oxfordshire Community Stroke Project (Bamford *et al.*, 1988) has developed an efficient classification system that allows for distinction of stroke subtypes based upon clinical signs at presentation. It also suffers from classification inaccuracies when compared to imaging with a recent study finding a 20% misclassification rate (Aerden *et al.*, 2004).

Uniformly used in mortality studies and less often in morbidity surveys is the categorization of stroke from the International Statistical Classification of Disease, Injuries, and Causes of Death (ICD), as published and revised periodically by the World Health Organization. In the United States, a slight modification was previously used for hospital purposes: the International Classification of Disease, Adapted for use in the United States (ICDA). The hospital variant is now called *ICD-9-CM* (Clinical Modification).

Before the sixth revision (1948) of the ICD, only the generic term CVD as a whole was obligatory for deaths from stroke. The sixth and seventh revisions (1948–68) of the

Table 1 Pathophysiological classification of ischemic stroke

NINDS classification
Mechanism: thrombotic; embolic; hemodynamic
Clinical: atherothrombotic; cardioembolic; lacunar
Arterial site: internal carotid; middle cerebral; anterior cerebral; vertebral; basilar; posterior cerebral
Stroke data bank classification
Large-artery atherosclerosis
Lacunar
Cardiac embolism
Tandem arterial pathology
Infarct of unknown origin
Other (e.g. arteritis)

Source: Reproduced from Bamford J., 1992. Copyright Elsevier.

Table 2 Cerebrovascular disease codes according to 8th (1968–78), 9th (1979–1994) and 10th (1995–) revisions of ICD

8th revision		9th revision		10th revision	
Code	Title	Code	Title	Code	Title
430	Subarachnoid hemorrhage	430	Subarachnoid hemorrhage	I60	Subarachnoid hemorrhage
431	Cerebral hemorrhage	431	Intracerebral hemorrhage	I61	Intracerebral hemorrhage
–	–	432	Other/unspecified intracranial hemorrhage	I62	Other nontraumatic intracranial hemorrhage
432	Occlusion of precerebral arteries	433	Occlusion/stenosis of precerebral arteries	I63	Cerebral infarction
433	Cerebral thrombosis	434	Occlusion of cerebral arteries	–	–
434	Cerebral embolism	–	–	–	–
435	Transient cerebral ischemia	435	Transient cerebral ischemia	G45	Transient cerebral ischemic attacks and related syndromes
436	Acute but ill-defined CVD	436	Acute but ill-defined CVD	I64	Stroke, not specified as hemorrhage or infarction
437	Generalized ischemic CVD	–	–	–	–
438	Other and ill-defined CVD	437	Other ill-defined CVD	I67	Other CVDs
–	–	438	Late effects of CVD	I69	Sequelae of CVD
–	–	–	–	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
–	–	–	–	I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
–	–	–	–	I68	Cerebrovascular disorders in diseases classified elsewhere
–	–	–	–	G46	Vascular syndromes of brain in CVDs

Source: Modified and adapted with permission from Kurtzke J.F. (1994) Epidemiology of stroke: methods and trends. *Health Rep*, **6**, 13–21.

ICD divided CVD into five categories. The eighth revision of the ICD for 1968–78 took CVD out of the neurologic disease group and placed it under vascular disease, where it remained in the ninth revision (Table 2). The tenth revision was published in 1992 with the innovation of an alphanumeric coding scheme of one letter followed by three numbers (i.e. I63.1: "cerebral infarction due to thrombosis of precerebral arteries"). Stroke continues largely to be categorized under "Diseases of the circulatory system" (I00–I99). Transient ischemic attacks (TIAs) and some stroke syndromes, however, have been classified under "Diseases of the nervous system" (G45–G46). The dual classification scheme for etiology and manifestation introduced in the ninth revision has been retained in the tenth revision, allowing retrieval according to either axis. In the United States, ICD 10 came into use in 1999, though many countries have used it since 1995.

Diagnostic Accuracy

Much of the information on the morbidity of stroke in the United States is based on hospital discharge abstracts with stroke listed as a diagnosis. These abstracts often fail to reflect reality, as it is difficult to validate the diagnosis and specific stroke subtype. Furthermore, a stroke diagnosis may not be recorded in the hospital, not all persons with stroke are hospitalized, and it is difficult to separate hospitalizations for new strokes from recurrent admissions for the same or a prior event. Other sources include clinical studies that offer subtype analysis capabilities, but with limited relevance to the general population. Finally, there are population-based studies which are expensive and time intensive, but give the most reliable and representative data on stroke. Many population surveys have been well detailed in terms of the composition of the denominator and considerations of potential biases, but the numerator in some cases suffered from insufficient evidence to make an accurate diagnosis of stroke. One of the problems in validating the diagnostic accuracy of studies in the United States is the shortage of community-based stroke registries that could serve as a gold standard.

The interrater reliability of an etiologic classification of ischemic stroke was evaluated by the Baltimore-Washington Cooperative Young Stroke Study (Johnson *et al.*, 1995). Cases were reviewed by paired neurologists, and agreement was assessed by means of the kappa statistic (κ). For standard pairs (two neurologists remained in a pair throughout the study), kappa was fair to good (k range $= 0.42–0.67$) for all cases except lacunar stroke ($k = 0.31$). This study showed that reasonable reliability for an etiologic classification of stroke can be obtained when criteria are explicit. A consensus approach to classification may help minimize error of fact or interpretation in future epidemiologic studies.

More recently, Allder *et al.* (2003) examined the correlation between magnetic resonance imaging defined stroke subtype and clinical classification systems. Eighty-four patients were classified clinically into total or partial anterior circulation syndromes using the Oxford classification, and the nontraumatic intracranial hemorrhage (NIH) stroke scale. Patients with total anterior circulation syndromes or severe stroke were more likely to have actually suffered a stroke,

to have a correctly classified stroke, to have persisting occlusion, and to have a large diffusion weighted imaging–perfusion weighted imaging mismatch. Patients with partial anterior circulation syndromes or mild to moderate anterior strokes were more likely to be misclassified.

CVD MORTALITY DATA

Stroke mortality in the Unites States has declined steadily from 1900 through the mid-1970s, with possibly a more rapid acceleration through the 1980s. The decline seems to have lessened into the 1990s. Figure 1 illustrates this trend. Stroke data were collected from the US National Vital Statistics System (Thom *et al.*, 1992). Since the 1950s, the age-adjusted (to the 1940 US population) death rate from CVD has declined by more than two-thirds, twice the rate of decline of other causes of mortality. The decline is seen for both sex and race categories.

The treatment of hypertension is often given as the primary explanation for the accelerated decline in stroke mortality since 1973 in the United States. According to the results of the National Health and Nutrition Examination Survey (NHANES) conducted in 1971–74 (NHANES I) and 1976–80 (NHANES II), the proportion of the population taking antihypertensive medication has increased for all age, sex, and race categories except for black men aged 45–54 years. Some would argue that despite this trend, the treatment of hypertension has contributed little to the rapid decline in stroke mortality since the 1970s. Epidemiological observations indicate that 16–25% of the overall decline in stroke mortality can be attributed to the treatment of elevated blood pressure.

Figure 2 shows the average annual death rates for CVD for ages 45–64 years by sex and country. Eight 5-year time periods have been included within the years 1950–87. Men have, in general, higher stroke mortality rates compared to women. Except for the eastern European countries listed

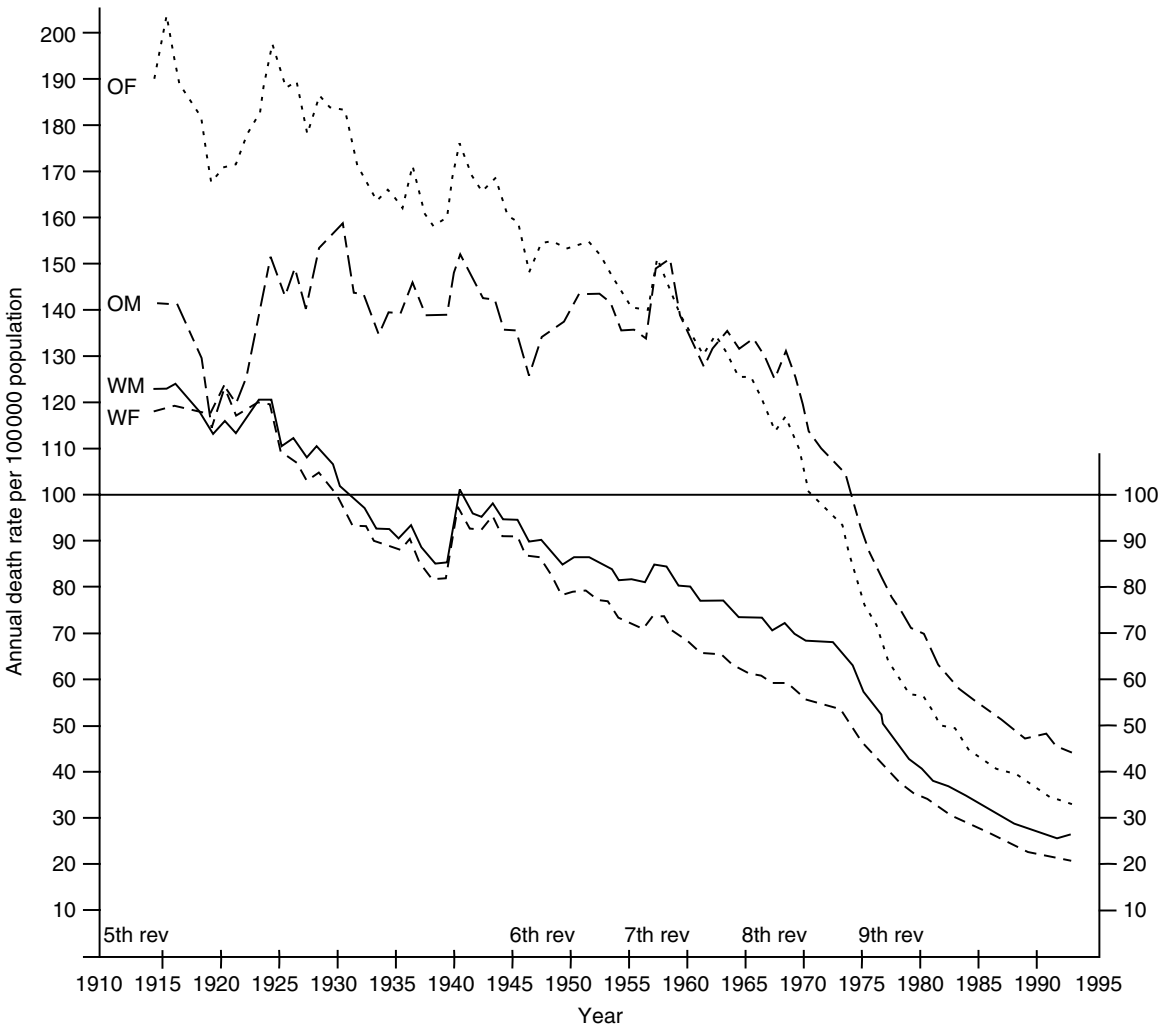

Figure 1 Cerebrovascular disease. Annual age-adjusted (USA 1940) death rates per 100 000 population by sex and race, USA, 1915–1993 White male (WM), white female (WF), other male (OM), other female (OF) (Modified and adapted with permission from Kurtzke J.F. (1994) Epidemiology of stroke: methods and trends. *Health Rep*, **6**, 13–21)

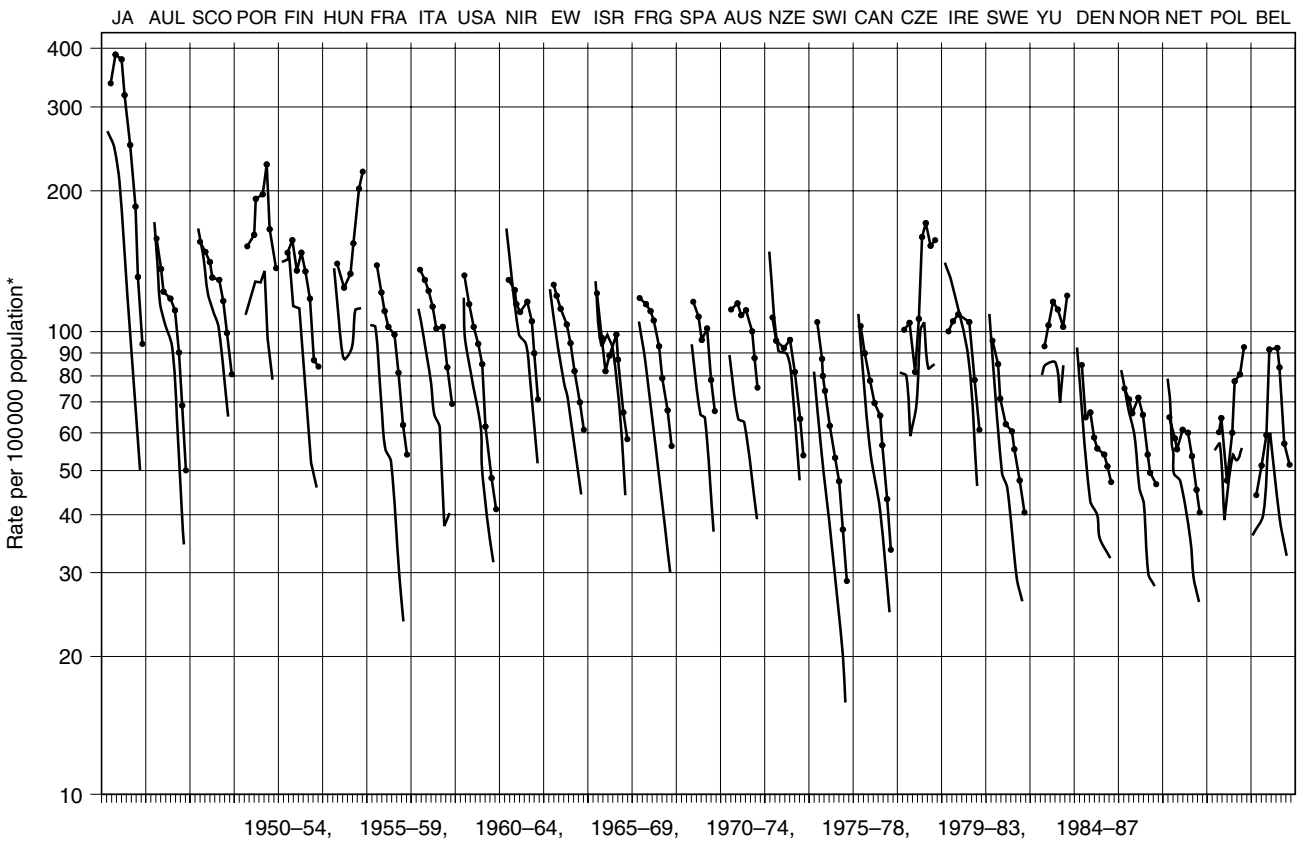

Figure 2 Average annual death rates for cerebrovascular disease by sex and country, ages 45–64 years; eight time periods, 1950–87 (Reproduced with permission from Thom T.J., Epstein F.J., and Feldman J.J. (1992) *Total Mortality from Heart Disease, Cancer, and Stroke from 1950–1987 in 27 Countries*. NIH Publication No. 92-3088)

(Hungary, Czechoslovakia, Yugoslavia, and Poland), death rates have declined dramatically. Moreover, most countries have reported more than a 50% decline since 1970. Japan has had the most precipitous fall in stroke mortality. Any factor(s) that account for this decline must also explain the discrepancy in mortality between eastern European countries and the other nations listed.

Despite advances in prevention and care of the stroke patient, case fatality rates after stroke have remained fairly stable over the past 20 years. Vernino *et al.* (2003) studied cause-specific fatality ratios after first cerebral infarction in a population-based cohort in Rochester, MN. The most frequent causes of death were cardiovascular events (22%), respiratory infection (21%), and initial stroke complications (14%). In the first month after a stroke, mortality was largely from neurologic complications. Thereafter, respiratory and cardiovascular causes were major culprits. To improve stroke survival, prevention efforts would best be aimed at aggressively managing pulmonary and cardiac disease.

Risk factors for death after stroke were recently examined in a population-based study in Connecticut (Bravata *et al.*, 2003). Of the 5123 patients followed, 4781 survived their hospitalization, 670 (14%) died within 6 months of discharge, and 2517 (53%) died within 5 years. Risk factors for 6-month mortality included older age, male sex, increasing comorbidity, discharge to a location other than home, and prior admission within a year of the index hospitalization.

INCIDENCE AND PREVALENCE DATA

Stroke incidence in a particular population traditionally refers to a first-ever stroke event. Figure 3 shows four representative incidence studies from different countries (adjusted to the standard European population); all display an exponential rise in stroke rates with increasing age. Rates in the 85+ group vary between 184 per 10 000 in Rochester, Minnesota, and 397 in Soderhamn, Sweden.

While community-based stroke studies have contributed to our understanding of stroke incidence, differences in study design often limit comparisons across populations. The WHO MONICA project, initiated in the early 1980s, has used uniform procedures and methods to collect and analyze stroke data in unique populations over time. It serves as a model international stroke registry. Stroke events were registered between 1985 and 1987 for people aged 35 to 64 years (Thorvaldsen *et al.*, 1995). Stroke incidence rates were higher for men than for women in all regions with age-standardized incidence rates of men: women varying between

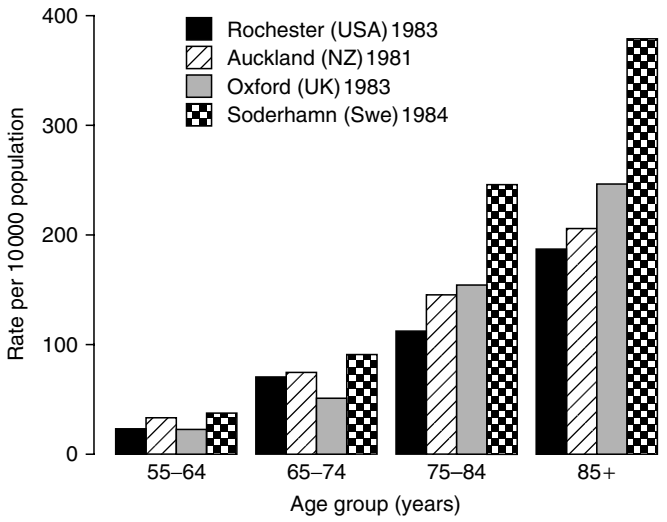

Figure 3 Average annual age-specific incidence (adjusted to the standard European population) of stroke in selected studies (Reproduced from Bonita R., 1992. Copyright Elsevier.)

1.2 and 2.4. Attack rates for first ever and recurrent stroke were similar to incidence rates. For men, the highest stroke attack rate was 361 per 100 000 in Kuopio, Finland, and lowest for Friuli, Italy, at 125 per 100 000 population. In women, the highest rate occurred in Novosibirsk, Russian Federation, at 294 per 100 000 and the lowest in the Rhein-Neckar region of Germany at 61 per 100 000. In recent years, the annual stroke incidence rate in Europe and North America has been between 100 and 300 per 100 000 population.

Like mortality rates, stroke incidence has declined rapidly over the past 50 years. Secular trends in stroke incidence over the past two decades were evaluated by the Oxfordshire Community Stroke Project (Rothwell *et al.*, 2004) Age-specific incidence of major stroke had fallen by 40% between 1981 and 2004. More specifically, the adjusted incidence rates of first-ever stroke fell by 29%, incidence rates for primary intracerebral hemorrhage declined by more than 50%, but subarachnoid hemorrhage rates remained stable. During the study period, the authors found an increased use of preventive treatments and major reductions in premorbid risk factors.

Prevalence studies give a good estimate of the stroke burden in a population after the acute attack. Unfortunately, reliable studies of stroke prevalence are difficult to find. Prevalence rates are based on survivors of the ictus, whose proportions vary markedly depending on the variety of stroke. In general, survival proportions for embolic and thrombotic stroke are better than for subarachnoid hemorrhage, which in turn is better than cerebral hemorrhagic stroke.

Prevalence rates in the early 1980s were around 600 per 100 000 in the West and 900 per 100 000 in Asia. In the United States, age-, race-, and sex-adjusted (1973 US population) stroke prevalence rates in the age-group of 25–74 increased from 1.41% in 1971–1975 to 1.87% in 1988–1994 (Muntner *et al.*, 2002). This corresponded to an increase of 930 000 noninstitutionalized stroke survivors with higher rates observed in all age, race, and gender groups. With decreasing mortality trends and relatively stable stroke incidence rates during the 1980s, these data point to a decreasing stroke case fatality rate as a driver of this prevalence trend. Better estimates of stroke prevalence will be a critical part in planning for future medical and community needs in the prevention and treatment of stroke.

CVD RISK FACTORS

Modification of stroke risk factors may have influenced the declines in stroke incidence and mortality over the last century. Cohort studies and case–control studies are powerful methods to ascertain such risk factors. Trends in the nonmodifiable risk factors, age, and sex, have been discussed above. Selected stroke risk factors will be reviewed in this section. Environmental factors are important in the pathogenesis and prevention of stroke. International epidemiologic data have suggested that immigrants take on the stroke incidence rates of their adopted country.

A recent report from the Center for Disease Control indicated that the prevalence of none of the major risk factors for stroke is decreasing among men and women throughout the United States (CDC, 2004). Table 3 shows that between 1991 and 2001, the prevalence of high blood pressure, high cholesterol, diabetes, and obesity among US adults increased, whereas the prevalence of smoking remained about the same. Specifically, the age-standardized prevalence of having none of these specific risk factors decreased from 42% in 1991 to 36% in 2001. Unfortunately, as a result of these risk factor trends, the burden of stroke is expected to increase.

Hypertension (*see* Chapter 48, Hypertension)

Hypertension is the most important modifiable risk factor for stroke. People with hypertension (Blood pressure >140/90 mmHg) have a relative risk (RR) of stroke two to four times greater than that of normotensive individuals. The risk for stroke mortality increases with increasing diastolic and systolic blood pressure.

In analyzing stroke subtypes, data from the Framingham Study showed that with increasing severity of hypertension, the proportion of strokes due to brain infarction increased (56–70%) at the expense of subarachnoid hemorrhage and embolic stroke (Wolf, 1993). The proportion of strokes due to intracerebral hemorrhage, however, did not significantly change with increased blood pressure.

A meta-analysis of cohort studies and randomized trials of blood pressure–lowering drugs and their effects on stroke was recently published by Lawes *et al.* (2004). Cohort studies in a variety of regions throughout the world show for each 10 mmHg decline in systolic BP, a decrease in stroke risk of

Table 3 Number and percentage[a] of US adults with major risk factors for heart disease and stroke by risk factor – Behavioral Risk Factor Surveillance System, United States, 1991 and 2001

	1991 ($N = 55\,815$)		2001 ($N = 140\,305$)				
Risk factor	Number	%	Number	%	% difference 1991–2001	95% CI[b]	% relative change[c]
High blood pressure	14 824	(23.9)	42 742	(26.7)	2.8	(2.2–3.5)	11.9
High cholesterol level	15 035	(24.9)	43 625	(28.5)	3.5	(2.9–4.2)	14.2
Diabetes	3626	(5.6)	12 628	(8.1)	2.6	(2.2–3.0)	46.5
Smoking	11 741	(21.4)	29 570	(21.3)	−0.1	(−0.8–0.6)	−0.5
Obesity	7628	(13.5)	31 369	(22.3)	8.8	(8.2–9.3)	64.7
One or more risk factors	32 507	(58.2)	89 739	(64.0)	5.7	(4.9–6.5)	9.8
No risk factors	23 308	(41.8)	50 566	(36.0)	−5.7	(−6.5–4.9)	−13.7

[a]Percentages are weighted to state population estimates and age adjusted to the 2000 US standard population. [b]Confidence interval. [c]Calculated by dividing the percentage difference between 1991 and 2001 by the percentage in 1991.
Source: CDC (2004) Declining prevalence of no known major risk factors for heart disease and stroke among adults – United States, 1991–2001. *MMWR Morb Mortal Wkly Rep*, 4–7.

approximately one-third is seen for subjects 60 to 79 years of age. This association is continuous down to levels of about 115/75 mmHg and is consistent across sexes, geography, and stroke subtypes. Similarly, data from randomized control trials indicate that a 10 mmHg reduction in systolic blood pressure is associated with a 30% reduction in stroke risk. This risk reduction appears to be similar between agents, by baseline blood pressure levels, and by whether an individual has a past history of cardiovascular disease.

Cardiovascular Disease

Improved survival of patients with cardiovascular disease over the last 30 years has resulted in a large elderly patient population who are likely at greater risk for developing CVD for this very reason (*see* **Chapter 43, Epidemiology of Heart Disease**).

Well-established cardiovascular-related risk factors for stroke include atrial fibrillation and carotid artery stenosis. In the Framingham Study, chronic atrial fibrillation in the absence of rheumatic heart disease was associated with a fivefold increase in stroke incidence, while atrial fibrillation with rheumatic heart disease showed a 17-fold increase. Carotid artery stenosis is responsible for approximately 30% of all ischemic strokes. Those with the most severe carotid stenosis (60–99%) have a 3% annual risk for stroke (Goldstein *et al.*, 2001).

Left ventricular hypertrophy (LVH) has been shown to increase one's risk for stroke in several studies. Investigators from the Northern Manhattan stroke study presented data on LVH and stroke risk in a multiethnic cohort (Di Tullio *et al.*, 2003). Their results showed LVH was associated with a 2.5-fold increase in stroke risk after adjustment for other variables. Regarding specific geometric patterns of LVH, concentric hypertrophy carried the highest stroke risk (adjusted odds ratio: 3.5) followed by eccentric hypertrophy (adjusted odds ratio: 2.4). LVH was independently associated with stroke risk across all race and ethnic groups suggesting a consistent effect of this structural change.

Diabetes Mellitus (*see* Chapter 122, Type 2 Diabetes Mellitus in Senior Citizens)

Individuals with diabetes are at higher risk for stroke than their nondiabetic counterparts at all ages. A large Danish-population-based study prospectively followed a group of 13 105 patients for 20 years assessing the impact of diabetes mellitus on stroke risk (Almdal *et al.*, 2004). The group showed the adjusted relative risk of first, incident, and admission for stroke was increased 2–6.5-fold for women and 1.5–2-fold for men, with a significant sex difference.

Few studies have clarified the risk for different stroke subclassifications for persons with glucose intolerance and diabetes mellitus. One such study was reported from the Honolulu Heart Program, which followed a cohort of Japanese-American men aged 45–68 years for over 22 years (Burchfiel *et al.*, 1994). After adjusting for other factors, the relative risks for thromboembolic stroke remained significantly elevated for "asymptomatic high" (glucose $>225\,\mathrm{mg\,dl^{-1}}$, relative risk (RR), 1.43; 95% confidence interval(CI), 1.00–2.04) and "known diabetes" groups (RR, 2.45; 95% CI, 1.73–3.47) as compared with the "low-normal group" (glucose $<151\,\mathrm{mg\,dl^{-1}}$). Associations were the same in hypertensive and nonhypertensive patients. There was no significant association between glucose intolerance or diabetes mellitus and hemorrhagic stroke.

Smoking (*see* Chapter 14, Smoking in the Elderly)

There is strong evidence to support a relationship between smoking and stroke. Shinton and Beevers (1989) performed a meta-analysis of 32 separate studies and showed that the overall relative risk of stroke was 1.5. A dose response was found in addition to an age effect with individuals less than 55 years having a relative risk of 2.9; and individuals aged 55–74 years a relative risk of 1.8. Relative risk estimates for stroke among current male smokers in cohort studies have ranged from 0.90 to 4.2. Many studies that have not shown an association between smoking and stroke have suffered from methodological problems.

Passive smoking, generally defined as living with someone who smokes, has been an increasingly important health and policy issue in recent years. Studies have shown it increases one's risk of coronary artery disease by 25–30%. Passive smoking may also increase the risk for stroke but data is limited (Whincup *et al.*, 2004).

Cholesterol (*see* Chapter 48, Hypertension)

Although the relationship between plasma cholesterol and coronary artery disease has been well established, studies evaluating the role of plasma cholesterol in stroke have been mixed. Some studies have shown a positive relationship between total cholesterol or fractions and stroke (Iso *et al.*, 1989) and others have shown no relationship (Bowman *et al.*, 2003; Koren-Morag *et al.*, 2002). Data from the HMG-CoA reductase inhibitor trials have shown that patients in the treatment groups have a decreased ischemic stroke risk, thereby implicating a lipid mechanism (NCEP, 2001).

There appears to be some consensus on the role of high-density lipoprotein (HDL) and stroke. Data from the Northern Manhattan Stroke study has shown that HDL has a protective effect against stroke with a $5\,\mathrm{mg\,dl^{-1}}$ increase in HDL resulting in a 24% reduction in stroke risk (Sacco, 2001). The inverse association between HDL and stroke has also been corroborated by two other groups (Koren-Morag *et al.*, 2002).

Preexisting Cerebrovascular Disease

The Oxfordshire Community Stroke Project is one of a handful of community-based studies detailing prognosis after an acute stroke (Burn *et al.*, 1994). The actuarial risk of suffering a recurrence was 30% by 5 years, roughly nine times the risk for stroke in the general population. The risk was highest in the first year (13%) and tapered off to about 4% in subsequent years. Risk for recurrent stroke did not appear to be related to age or the pathologic type of stroke.

Transient ischemic attacks have been shown to be associated with an annual stroke risk between 1 and 15% (Sacco, 2004). Unlike more chronic risk factors such as hypertension, transient ischemic attacks are linked to a dramatic increase in stroke much sooner after the event. The 90-day risk for stroke after TIA is about 10%. A prior stroke is also a powerful risk factor for subsequent stroke. If the two risk factors are evaluated separately, stroke is associated with a 2.7 higher risk for subsequent stroke and death compared to TIA.

Abnormalities of Hemostasis

It is estimated that hematologic abnormalities account for only 4% of all strokes. This figure is likely an underestimate as a definitive stroke mechanism cannot be determined in a large proportion of brain infarctions. Coagulopathies causing ischemic stroke include deficiencies of protein C, protein S, antithrombin III, plasminogen, and activated protein C/factor V Leiden mutation. These disorders tend to be more common in younger persons and have rather low pretest probabilities (Bushnell and Goldstein, 2000). Older adults are more likely to have coagulation defect states due to an underlying malignancy, medications, or an elevated homocysteine.

Epidemiologic studies emphasize the importance of elevated serum homocysteine as an independent risk factor for stroke. Despite differences in study definitions, generally a homocysteine level $>15\,\mathrm{umol\,l^{-1}}$ is considered high (Malinow *et al.*, 1999). Challenges in screening patients include determining the optimal timing for testing, and evaluating metabolic changes and medications that may alter levels (Bushnell and Goldstein, 2002).

Diet and Obesity (*see* Chapter 30, Obesity in the Elderly)

Over the last 10 years, there have been several reports examining the effect of diet on stroke risk. Long chain omega-3 polyunsaturated fatty acids found in fish are felt to alter platelet aggregation and thereby reduce the risk of ischemic stroke. The association between intake of fish and reduced risk of ischemic stroke has been supported most recently by the results of the Health Professionals Follow-up Study (He *et al.*, 2002).

Studies using body mass index (BMI) as a measure of obesity have produced inconsistent results on the effect of this variable on stroke risk. However, variables that reflect abdominal obesity seem to be providing more clear correlations with stroke risk. Suk *et al.* (2003) used the waist: hip circumference ratio in a large multiethnic cohort of stroke patients in Northern Manhattan. The investigators found that patients with a waist to hip ratio equal to or greater than the median had an overall odds ratio (OR) of 3.0 for ischemic stroke even after adjustment for other risk factors and BMI. Interestingly, BMI was not a significant factor in predicting ischemic stroke in this study. The association between BMI and stroke may be confounded by smoking, alcohol use and age, all of which can reduce this measure. The waist to hip ratio appears to be a more useful method of assessing abdominal fat and a better predictor of stroke than BMI and waist circumference.

Alcohol (*see* Chapter 15, Alcohol Use and Abuse)

The association with alcohol consumption and stroke can be described as complex at best. A correlation between recent alcohol use and stroke has consistently been reported (Mazzaglia *et al.*, 2001). There is also evidence for a linear relationship between hemorrhagic stroke and alcohol consumption. Moreover, the pattern of drinking appears to be important with a higher stroke risk for irregular drinkers. A study evaluating mild to moderate drinking ($<$ or $= 2$ drinks per day) in a large Japanese cohort of middle-aged men found no excess risk of total stroke (Iso *et al.*, 2004).

Differential effects were found on stroke subtypes, however, with mild to moderate drinking associated with a lower risk for ischemic strokes and a higher risk for hemorrhagic strokes.

Race

While not a modifiable risk factor, race is an important independent predictor of stroke incidence and mortality. Blacks have a higher incidence and case fatality rate from stroke than whites. The greater incidence is at least in part due to a higher prevalence of hypertension and lower prevalence of antihypertensive treatment. Kittner showed that blacks had a higher incidence of stroke than whites even after adjustment for age, hypertension and diabetes mellitus (RR, 1.4 for females and 1.1 for males; Kittner *et al.*, 1990). The Greater Cincinnati and Northern Kentucky Stroke Study was the first large metropolitan-based study of stroke trends among blacks (Broderick *et al.*, 1998). The incidence for first-ever stroke among blacks in the region was 288 per 100 000 (age- and sex-adjusted to the 1990 US population). The rate was approximately 1.6 times greater than the overall age- and sex-adjusted incidence rate of stroke among the white population of Rochester, MN.

Mexican Americans have also been shown to have an excess stroke burden compared to non-Hispanic whites. Morgenstern reported data from a community stroke sample in Texas where Mexican Americans had consistently higher cumulative incidence for stroke compared with non-Hispanic whites (Morgenstern *et al.*, 2004). Risk ratios for ischemic stroke ranged between 1.1–2.7 with younger age-groups having the highest risk. The age-adjusted risk ratio was 1.6 for both intracerebral hemorrhage and subarachnoid hemorrhage.

Genetics/Family History

The genetics of CVD continues to be an area of growth in understanding the etiology of stroke. A long-term Dutch twin study found that 10% of monozygotic twins were concordant for stroke death compared with 5% of dizogotic twins (Bak *et al.*, 2002). These results indicate at least a partial genetic role in stroke etiology. Using a well-studied group of families in Iceland, the deCode group conducted a genome-wide screen on 179 pedigrees with at least 2 family members having predominantly ischemic stroke (Gretarsdottir *et al.*, 2002). Evidence for linkage was found on a region of chromosome 5 (5q12) with a logarithm of odds (LOD) score of 4.4 at marker D5S280. More specific information as to the role and function of the gene in this region are eagerly anticipated.

COMMENTS

The explosive increase in epidemiologic studies of stroke has led to notably more data even over the past decade. Much attention has been given to delineating stroke risk factors and "stroke-protective" factors. While the picture may be more complete, it is also considerably more complex. Meaningful differences in time trends, geography, race, sex and various risk factors have been discussed. Newer stroke risk factors continue to emerge including HIV infection, periodontal disease, and sleep disordered-breathing (Diaz and Sempere, 2004).

The most startling revelation is the dramatic fall in stroke mortality over the past century. While much of this decline relates to decreased stroke incidence and possibly improved risk factor modification, the accelerated phase of decreasing mortality experienced since the early 1970s needs further explanation. How long this decrease in mortality can continue is unclear. Pressures of an aging population and increased survival from cardiac and other chronic diseases will undoubtedly contribute to a rise in stroke incidence rates. The near future will give neurologists and other health-care professionals involved in the management of stroke new challenges and opportunities to intervene with primary, secondary, and tertiary prevention strategies.

Application of risk factor modification techniques to the population is an important step in preventive medicine, but one that is often neglected. This process can take place at both the individual patient level and at the population level. As risk factors and trends for various types of stroke become more clearly defined, physicians and public health professionals will be better prepared to elucidate possible pathophysiologic mechanisms. How specific risk factors affect the blood vessels supplying the central nervous system remains to be seen. Confirming epidemiologic data for stroke will allow us to be better prepared to target susceptible groups, educate others, and ultimately lower the burden of stroke in the population.

KEY POINTS

- Stroke is the third leading cause of death and an important cause of disability in most industrialized nations.
- Epidemiologic methods are important for determining the burden of disease and identifying risk factors that influence its development and course.
- Most countries have reported more than a 50% decline in stroke mortality rates since 1970.
- Cohort studies in a variety of regions throughout the world show for each 10 mmHg decline in systolic BP, a decrease in stroke risk of approximately one-third is seen for subjects 60–79 years of age.
- Between 1991 and 2001, an increased prevalence in high blood pressure, high cholesterol, diabetes mellitus, and obesity has been documented for US adults. As a result of these trends, the burden of stroke is expected to increase.

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Management of Carotid Artery Stenosis

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INTRODUCTION

Stroke is the second commonest cause of death in the United Kingdom and in the United States and is the leading cause of long-term acquired adult disability in most countries (Hacke *et al.*, 2003). The majority of strokes are caused by ischemic infarction, which occurs when an artery supplying blood to the brain becomes narrowed or blocked (*see* **Chapter 71, Acute Stroke**). This may be a local process (thrombosis) or may occur when a proximal thrombosis embolizes to the brain. Most infarcts occur in the territory of the carotid arteries (anterior circulation), and significant atherosclerotic narrowing of the origin of the internal carotid artery (ICA) ipsilateral to the infarct is found in around 20 to 30% of cases (Ricci *et al.*, 1991). Surgical treatment of severe (greater than 70%) carotid artery stenosis has been shown to reduce the risk of subsequent stroke compared to medical treatment (ECST, 1991; NASCET, 1991; ACAS, 1995; ACST, 2004). Therefore, it is important to establish the degree of carotid stenosis prior to consideration for intervention. While policies for investigation vary, most centers use noninvasive imaging techniques where possible, resorting to catheter angiography only where there is no access to these techniques or where there is nonconcordance of results. Although surgery has long-term benefits, it also carries a significant risk of stroke at the time of the procedure, especially in previously symptomatic carotid artery stenosis (ECST, 1991; NASCET, 1991).

In recent years, the endovascular techniques of percutaneous transluminal angioplasty (PTA) and stenting have been used increasingly to treat arterial stenosis throughout the body. Most notably, percutaneous coronary intervention has become almost universally embraced as the preferred revascularization strategy for patients with coronary artery disease (Boden, 2004). There has been some resistance to treating carotid artery stenosis using endovascular techniques because of the risk of distal embolization to the brain during passage of the catheter through a tight stenosis. Trials were developed to test the safety and efficacy of PTA and stenting in the carotid arteries and, in recent years, equipment has been designed to minimize the risk of cerebral embolism.

WHAT CAUSES CAROTID ARTERY STENOSIS?

Atheroma

Atheroma is the commonest arterial disorder in the developed world and, when complicated by thrombosis and embolism, may result in ischemic stroke, myocardial infarction, and peripheral arterial disease. Atheroma mainly affects the large- and medium-sized arteries and is found particularly at sites of arterial branching such as at the bifurcation of the common carotid artery into the ICA and external carotid artery (ECA) (Heinzlef *et al.*, 1997). Atheroma begins as an intimal fatty streak, and over many years, circulating macrophages adhere to and invade the arterial wall. This leads to an inflammatory response with production of cytokines and activation of T-lymphocytes. Cholesterol is deposited and arterial smooth muscle cells migrate in to the lesion and proliferate. This causes the formation of plaques with a fatty core and a fibrous cap, which spread along and around the arterial wall, encroaching on the media and ultimately leading to narrowing of the vessel lumen and stiffening of the arterial wall (*see* **Chapter 53, Pathogenesis of Atherosclerosis**). The most significant risk factor for developing atheroma is increasing age; hypertension, hypercholesterolemia, diabetes mellitus, and smoking all accelerate this process. Atheroma alone may be asymptomatic, and widespread atheroma is often noted at postmortem in patients who are not known to have had vascular events. However, fissuring or rupture of the fibrous cap promotes platelet adhesion and activation, initiating blood coagulation and the formation of a thrombus (Ware and Heistad, 1993). The thrombosis may initially be incorporated into the plaque but as atherothrombotic plaque grows, the lumen of the vessel may become obstructed causing a narrowing or "stenosis" (Figure 1). In

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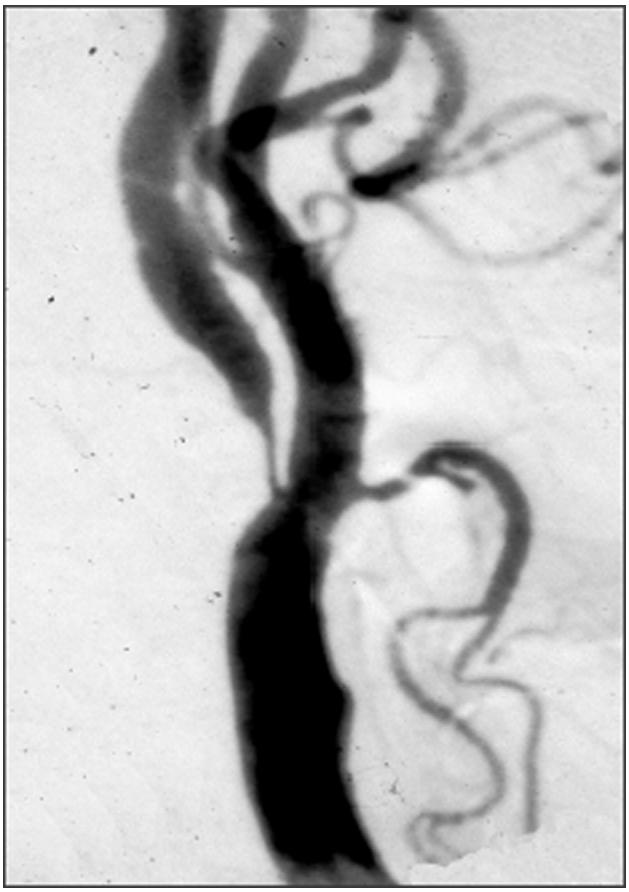

Figure 1 Severe internal carotid artery stenosis

the carotid artery, atherothrombotic plaque usually occurs at the bifurcation and at the distal part of ICA. The atherothrombotic plaque may completely occlude the artery (a process that may be asymptomatic or may result in symptoms secondary to thromboembolism). Embolization from the plaque may cause transient or permanent obstruction of a smaller distal artery, resulting in cerebral or ocular symptoms.

Carotid Dissection

ICA dissection is a much less common cause of carotid stenosis than atheroma and is particularly uncommon in the elderly. In some cases, dissection is associated with underlying connective tissue disorders, including fibromuscular dysplasia, Marfan's syndrome, or Ehlers Danlos syndrome. More commonly, dissection occurs following head or neck trauma associated with sudden rotation of the neck, which may be relatively trivial. The ICA is then torn against the second cervical vertebra and forms a hematoma in the arterial wall, which can narrow the vessel lumen, leading to thrombosis. Alternatively, a free intimal flap may promote thromboembolism. Anterior cerebral circulation symptoms such as hemiparesis and dysphasia may be preceded by diagnostic clues such as orbital or neck pain and sometimes Horner's syndrome resulting from compression or ischemia of the sympathetic chain which surrounds the carotid artery in the neck. It can be difficult to diagnose arterial dissection using noninvasive techniques, and patients are often subjected to catheter angiography with a view to initiating anticoagulation in cases of radiographically proven dissection. However, there is no clear evidence that anticoagulation reduces the subsequent risk of stroke and, therefore, the use of invasive imaging in this context is contentious. Cross-sectional magnetic resonance imaging (MRI) is the investigation of choice in suspected dissection and may show the characteristic crescent-shaped hematoma in the wall of the carotid artery. Ultrasound is less sensitive because the site of the dissection is usually above the bifurcation in the distal carotid artery.

PRESENTATION OF CAROTID ARTERY STENOSIS

The first presentation of a patient with significant carotid artery stenosis may be with temporary or permanent symptoms of cerebral ischemia or visual disturbance. An embolus from ICA stenosis may find its way to the ophthalmic artery (the first branch of the supraclinoid portion of the ICA), causing transient monocular blindness (amaurosis fugax). This is classically described as "a curtain falling across the eye" with complete loss of vision in that eye, which usually lasts for a few minutes. A permanent visual defect may occur if the retinal artery is occluded.

If debris from an atherothrombotic plaque in the carotid artery embolizes to the cerebral circulation, patients usually present with a middle cerebral artery territory syndrome of hemiparesis with or without hemisensory disturbance and cortical signs such as hemianopia or higher cerebral dysfunction (e.g. dysphasia). Less commonly, the embolus occludes one of the anterior cerebral arteries or causes subcortical ischemia mimicking a lacunar stroke (Waterston *et al.*, 1990). The distinction between a transient ischemic attack (TIA) lasting less than 24 hours and stroke is arbitrary. In general, the risk of completed stroke following a TIA of any cause is 8% at 7 days following the initial event, 11.5% at 1 month and 17.3% at 3 months (Coull *et al.*, 2004), but in patients with severe, potentially treatable carotid stenosis, the risks are even higher. Therefore, patients with TIA and those who recover quickly after stroke must be investigated urgently.

Carotid artery stenosis may be found incidentally in a neurologically asymptomatic patient. Usually this occurs when investigating a patient with a carotid bruit or during investigation of a patient with known arterial disease elsewhere in the body. In particular, patients waiting for coronary artery bypass grafting are often investigated for the presence of carotid artery disease prior to their surgery.

INVESTIGATION OF CAROTID ARTERY STENOSIS

Patients should be investigated for carotid stenosis if they have had symptoms referable to the carotid territory and are candidates for surgery or stenting or because they are known to have arterial disease elsewhere in the body and surgery for asymptomatic carotid stenosis would be considered. Investigation for carotid artery stenosis is the same whether for symptomatic or asymptomatic diseases. Listening for a carotid bruits in the neck is a useful start, but is not a reliable screen for carotid stenosis. A localized bruit is usually caused by stenosis of the underlying artery, but the extent and significance of the stenosis cannot be predicted by the presence of a bruit. Indeed, a very tight stenosis may not cause a bruit (Hankey and Warlow, 1990) and a loud bruit can be caused by ECA stenosis, which has no clinical significance.

Doppler Ultrasound

In most patients, it is possible to examine the common carotid artery, the bifurcation, and several centimeters of internal and external carotid arteries beyond the bifurcation in a sequential manner with ultrasound (Sidhu, 2000). The advantage of ultrasound is that it is noninvasive, safe, and relatively inexpensive. Recent advances mean that it has become more accurate at assessing carotid disease, but its utility remains limited by the requirement of a high degree of operator skill and experience and the results are subject to significant interobserver variation. Gray scale and color Doppler imaging are combined to detect stenotic lesions, obtaining a spectral waveform from which a velocity measurement is generated. The most commonly used criteria to grade ICA stenosis are the ICA peak systolic velocity (internal carotid artery peak systolic velocity (ICPSV)) and the ICPSV to common carotid artery peak systolic velocity (CCPSV) ratio with the end diastolic velocity (EDV) used to discriminate borderline measurements (Moneta *et al.*, 1995). Velocities and their corresponding degrees of ICA stenosis are illustrated in Table 1.

There are some technical limitations of ultrasound, for example, acoustic shadowing caused by calcified plaque means that it may not be possible to visualize the area of interest. Also, ultrasound is not good at studying a tortuous vessel where the velocities may be spuriously increased. Because of the potential limitations of ultrasound, most experts recommend that the findings be corroborated with a second imaging modality before considering surgery or stenting for carotid stenosis. However, some vascular units with experienced ultrasonographers rely on Doppler ultrasound alone to select patients with severe carotid stenosis for intervention.

Table 1 Ultrasound criteria for grading internal carotid artery stenosis

Degree of ICA stenosis (%)	IC PSV ($cm\,s^{-1}$)	IC EDV ($cm\,s^{-1}$)	IC PSV/ CC PSV
0–29	<100	<40	<3.2
30–49	110–130	<40	<3.2
50–59	>130	<40	<3.2
60–69	>130	40–110	3.2–4.0
70–79	>230	110–140	>4.0
80–95	>230	>140	>4.0
96–99	"string flow"		
100	"no flow"		

Note: ICA, internal carotid artery; IC PSV, internal carotid artery peak systolic velocity; IC EDV, internal carotid artery end diastolic velocity; CC PSV, common carotid artery peak systolic velocity.

Magnetic Resonance Angiography (MRA)

Magnetic Resonance Angiography (MRA) is a noninvasive technique used for the investigation of arterial pathology in the neck and head. It is often used to confirm the presence of carotid artery stenosis in patients who have undergone preliminary ultrasound examination, but may also be used as a screening investigation. The combination of ultrasound and MRA has been shown to give sensitivities of 100% and specificities between 90 and 98% (De Marco *et al.*, 1996). When both investigations are concordant, the noninvasive approach has largely replaced conventional catheter angiography to investigate patients for carotid stenosis. The technical aspects of MRA are beyond the scope of this article, but the main techniques are time of flight MRA (used because of its superior flow related enhancement) and contrast enhanced MRA (used because it is less susceptible to artifact). One of the limitations of MRA is that some patients find it claustrophobic and are unable to tolerate the examination. In addition, for safety reasons, some patients are unable to undergo MRA, for example, those with cardiac pacemakers and metallic heart valves. There are also a number of technical limitations such as misinterpretation of swallowing artifact or turbulent flow as an arterial stenosis. Where either Doppler or MRA produce poor quality images or when ultrasound and MRA results are nonconcordant, it may be necessary to perform conventional catheter angiography prior to carotid intervention. Catheter angiography may also be necessary to establish the exact degree of stenosis in patients where noninvasive investigations suggest stenosis on the border of surgical significance or to exclude more distal carotid stenosis not visualized by ultrasound or MRA.

Catheter Angiography

Although catheter angiography is regarded by some as the "gold standard" investigation for a patient with carotid artery stenosis, it is invasive and uncomfortable and carries a procedural risk of stroke or TIA of up to 4% in some series (Heiserman *et al.*, 1994). The complications of angiography occur because the catheter dislodges the atheromatous plaque, the arterial wall is dissected, or thrombus forms on the catheter tip. In addition to the thromboembolic risk, there

are the risks associated with the use of intravenous contrast that range from the relatively minor, for example, headache and nausea to more serious complications such as hypotension, bradycardia, and renal failure. Catheter angiography cannot therefore be justified as a screening investigation for carotid stenosis and should always be preceded by noninvasive investigations.

MANAGEMENT OF CAROTID ARTERY STENOSIS

Having established that a patient has carotid stenosis, the next step is to maximize medical treatment of vascular risk factors and consider intervention (surgery or stenting) to reduce the stenosis. The decision to recommend carotid intervention rests crucially on answers to two main questions: (1) What are the risks of stroke if the patient is treated medically? (2) What are the risks of carotid endarterectomy or stenting?

Medical Management

The medical management of a patient with carotid artery stenosis is aimed at preventing stroke in a previously asymptomatic patient (primary prevention) or preventing recurrent stroke in a patient with a history of stroke or TIA (secondary prevention). Medical management includes modification of lifestyle and treatment of vascular risk factors. Patients are strongly advised to stop smoking, reduce their alcohol intake, increase the amount of exercise they take, and consider a low fat diet. Many centers now have specialized multidisciplinary clinics to help with these changes in lifestyle.

Hypertension is the most important vascular risk factor to address (*see* **Chapter 48, Hypertension**). It is now clear from the perindopril protection against recurrent stroke study (PROGRESS) trial that lowering blood pressure in both hypertensive and nonhypertensive patients after TIA and stroke is beneficial regardless of baseline values (Progress Collaborative Group, 2001). Although PROGRESS did not examine patients with carotid stenosis separately, it is unlikely that lowering blood pressure in patients with carotid stenosis will be harmful, so long as blood pressure is not reduced precipitously. The majority of strokes caused by severe carotid stenosis result from thromboembolism, not from reduction in perfusion pressure, because in most cases the Circle of Willis provides sufficient collateral flow.

For many years, it was thought that there was only a weak association between the level of serum cholesterol and the risk of stroke. The Heart Protection Study (HPS) included over 20 000 patients with existing coronary heart disease, other occlusive vascular disease or diabetes mellitus randomized to treatment with a statin, simvastatin 40 mg nocte or placebo (Heart Protection Study Collaborative Group, 2002). There was a reduction in low-density lipoprotein (LDL) cholesterol of 29% compared with placebo, and active treatment was associated with a 24% relative reduction in the risk of the composite end point of major vascular events. In particular, there was a 25% reduction in the relative risk of stroke in the group that were randomized to treatment with a statin (4.3% vs 5.7% $P < 0.0001$) (Heart Protection Study Collaborative Group, 2002). Surprisingly, there was no significant reduction in the rate of stroke in the subgroup of treated patients with previous stroke or TIA, but this may have reflected small numbers and this subgroup still benefited from a reduction in myocardial infarction (Heart Protection Study Collaborative Group, 2004). There was also a halving in the number of patients requiring carotid endarterectomy or angioplasty in the group treated with simvastatin. One can conclude that all patients with carotid stenosis should be treated with a statin provided there are no contraindications.

Diabetes mellitus is an important risk factor for carotid stenosis, and it is logical to ensure as good glycemic control as possible. However, this has only been shown to reduce the risk of microvascular complications of diabetes (retinopathy and renal damage) and not larger vessel disease.

Even if great care is taken to reduce the medical risk factors, pooled data from the major carotid surgery trials have shown that when treated medically, patients with carotid stenosis greater than 50% have a 5-year cumulative risk of ipsilateral carotid ischemic stroke of 21.2% (95% confidence intervals 18.8–23.6) (Rothwell *et al.*, 2004). Hence intervention with surgery or stenting should be considered for these patients after consideration of the risks.

The Benefits and Risks of Surgery for Symptomatic Carotid Stenosis

Large randomized trials have clearly shown the benefits of carotid endarterectomy, compared with medical treatment alone, in severe symptomatic carotid stenosis (ECST, 1991; NASCET, 1991; Mayberg *et al.*, (VA 309), 1991). In the European Carotid Surgery Trial (ECST), over 3000 patients with any degree of carotid stenosis, who had had a TIA or minor stroke in the 6 months prior to randomization, were randomized to receive carotid endarterectomy or best medical management alone. Around the same time, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) randomized over 2800 patients with >30% carotid stenosis who had symptoms within 3 months of randomization to endarterectomy or medical treatment alone. The data from ECST and NASCET have recently been combined together with the much smaller VA 309 trial to provide a very robust data set (Rothwell *et al.*, 2003). ECST and NASCET used different denominators to measure the severity of stenosis, and in the combined analysis, the severity of stenosis was measured using the NASCET method. Results from the combined analysis (data for over 6000 patients) showed a 5-year absolute risk reduction of 16% for ipsilateral ischemic stroke, operative stroke, or operative death in patients with 70 to 99% carotid stenosis treated with endarterectomy compared to those

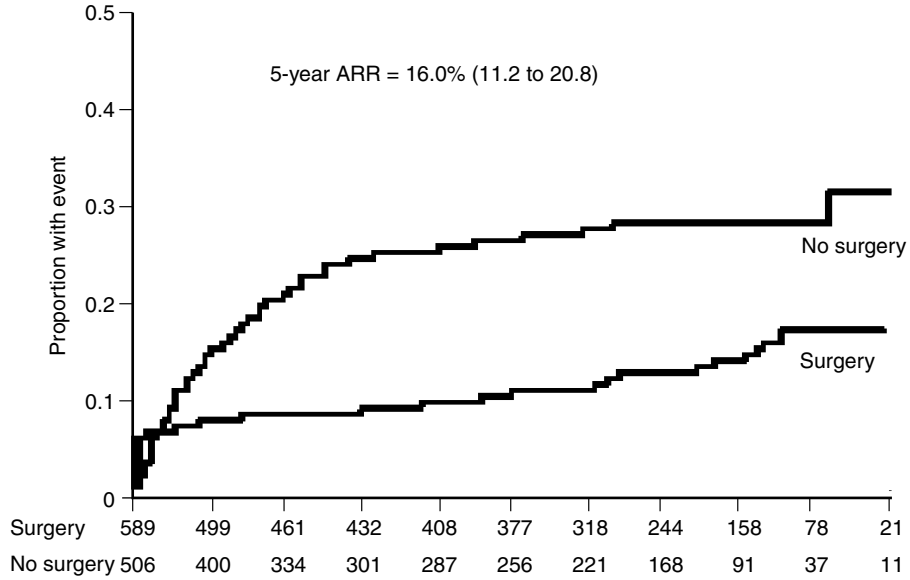

Figure 2 Effects of surgery on ipsilateral ischemic stroke and any operative stroke or operative death in patients with 70–99% symptomatic carotid stenosis in analysis of pooled data from ECST, NASCET, and VA309. ARR = Absolute risk reduction. (Reprinted with permission from Elsevier (The Lancet, 2003, **361**, 107–116))

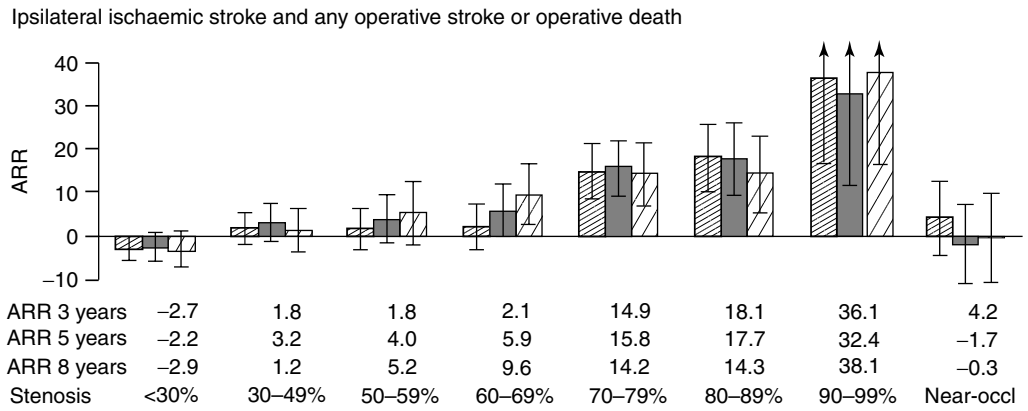

Figure 3 Effect of surgery on absolute risk reduction (ARR) of ipsilateral ischemic stroke and any operative stroke and operative death at 3, 5, and 8 years follow-up by degree of symptomatic carotid stenosis, in analysis of pooled data from ECST and NASCET. (Reprinted with permission from Elsevier (The Lancet, 2003, **361**, 107–116))

treated medically (Figure 2). Surgery increased the 5-year risk of ipsilateral ischemic stroke in patients with less than 30% stenosis, had no effect in patients with 30 to 49% stenosis, was of marginal benefit in those with 50 to 69% stenosis ($n = 1549$, absolute risk reduction 4.6% $p = 0.04$) and was highly beneficial in those with 70% or greater without near occlusion ($n = 1095$, absolute risk reduction 16.0% $p < 0.001$) (Figure 3). In a further analysis, data from ECST and NASCET were combined to determine the overall benefit from surgery in relation to several *post hoc* subgroups. Sex ($p = 0.003$), age ($p = 0.03$), and time from the last symptomatic event to randomization ($p = 0.009$) modified the effectiveness of surgery. Benefit from surgery was greatest in men, those randomized within 2 weeks of their last event and patients aged over 75 years. For patients with 50% or higher stenosis, the number of patients needed to undergo surgery (number needed to treat) to prevent one ipsilateral stroke in 5 years was five for patients aged 75 or older, versus 18 for those younger than 65 years (Rothwell *et al.*, 2004). Despite this, NASCET reported an 8.9% risk of wound complication, 7.5% risk of cranial nerve injury, and 0.9% risk of myocardial infarction following endarterectomy. Therefore, selection for surgery should involve careful assessment of the risk benefit ratio of surgery for the individual according to age, sex, time from last symptoms, and degree of carotid stenosis. In conclusion, patients with severe stenosis of greater than or equal to 70% measured by the NASCET method and recent ipsilateral carotid territory symptoms should be referred for surgery as soon as possible if they are otherwise fit for an

operation. Patients with stenosis between 50 and 70% should be carefully selected for surgery on the basis of their risk factors.

The Benefits and Risks of Surgery for Asymptomatic Carotid Stenosis

The benefits of surgery for asymptomatic stenosis and symptomatic stenosis with symptoms more than 6 months previously are less clear-cut than for symptomatic stenosis despite evidence from two large randomized asymptomatic trials (ACAS, 1995; ACST, 2004). In the Asymptomatic Carotid Atherosclerosis Study (ACAS), over 1600 patients with asymptomatic carotid stenosis of 60% or more were randomized to receive carotid endarterectomy or best medical treatment. The results showed that surgery significantly reduced the overall 5-year risk of ipsilateral stroke or any perioperative stroke or death from 11% to 5.1% ($P = 0.004$), but not the risk of major ipsilateral stroke or any perioperative stroke or death (6.5% in medical group, 3.4% in surgical group $P = 0.12$) (ACAS, 1995). The 30-day risk of stroke or death in the patients who underwent carotid endarterectomy was 1.5%. Another 1.2% suffered a stroke or TIA during preoperative angiography, thus the complication rate in the surgical arm was approaching 3%.

The Asymptomatic Carotid Surgery Trial (ACST) randomized over 3000 patients to a policy of immediate or deferred carotid endarterectomy (until surgery seemed to be more clearly indicated, e.g., when the patient became symptomatic) for asymptomatic 60 to 99% stenosis. The results showed a benefit to immediate surgery in terms of reducing the 5-year risk of all strokes and perioperative death from 11.8% to 6.4% ($P < 0.0001$) (Figure 4) (ACST, 2004). However, subgroup analysis showed no evidence of a benefit in patients older than 75 years (Figure 5) or in women after taking into account the risks of surgery. Once again, there was a definite but less marked benefit in terms of reducing the risk of fatal or disabling stroke (3.5% vs 6.1% $P = 0.004$). The complication rate of stroke or death within 30 days of surgery in the immediate group subgroup analysis was very similar to ACAS at 3.1% (ACST, 2004).

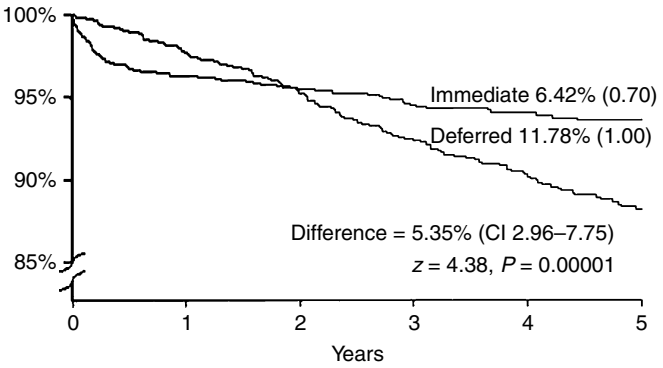

Figure 4 Percentage of patients with asymptomatic carotid stenosis who remain free of any type of stroke or perioperative death 5 years after randomization to immediate or deferred endarterectomy. (Reprinted with permission from Elsevier (The Lancet, 2004, **363**, 1491–1502))

The results from these trials suggest that although surgery for asymptomatic carotid stenosis may be less risky than in symptomatic disease, the benefits in terms of reducing the risk of major stroke or death are less certain. In particular, the rate of stroke in patients with asymptomatic carotid stenosis treated medically is very low at only 2% per annum, and the benefits of surgery rely on having an experienced surgeon with low complication rates. In practice, the results from ACST and ACAS are useful when discussing the treatment options with a patient with asymptomatic carotid stenosis. Patients with less than 60% stenosis or those aged over 75 years should not be offered surgery. Those aged less than

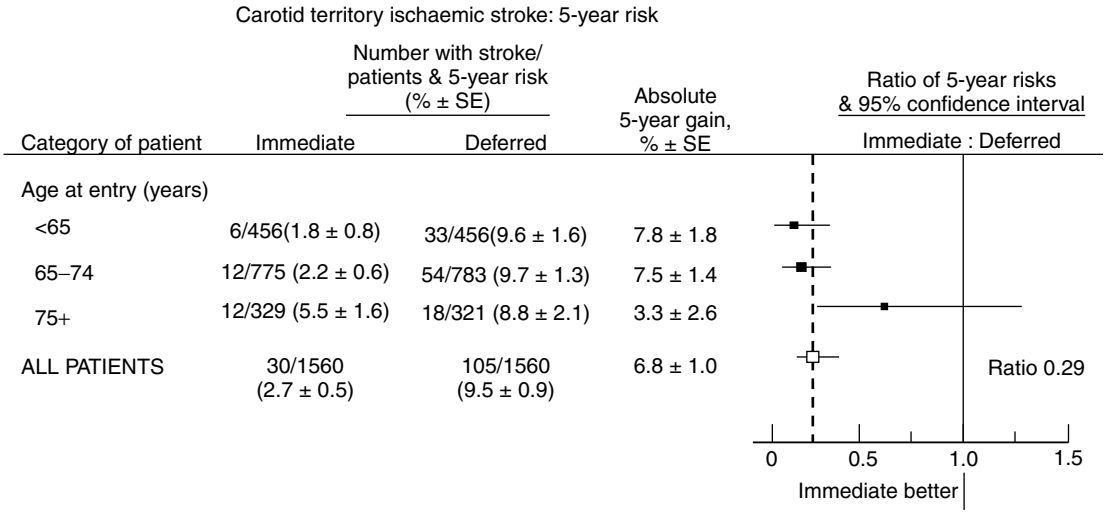

Figure 5 5-year risks of non-perioperative carotid territory ischemic stroke in patients categorized by age at study entry in years. The ratio of 5-year risks (95% confidence interval) in immediate versus deferred endarterectomy is shown. (Reprinted with permission from Elsevier (The Lancet, 2004, **363**, 1491–1502))

75 years and with 60% or more stenosis should have the surgical option discussed with them but should be told that their risk of stroke without surgery is low. Those who do not opt for surgery should be educated about the symptoms of TIA, amaurosis fugax, or stroke, and advised to seek medical attention urgently if they occur.

The Benefits and Risks of Endovascular Intervention for Carotid Stenosis

Endovascular treatment (angioplasty and stenting) is increasingly being used to treat carotid stenosis as a less invasive alternative to carotid endarterectomy. Surgery carries a small but clinically important risk of morbidity and mortality (ECST, 1991; NASCET, 1991; ACAS, 1995; ACST, 2004). Endovascular intervention may avoid some of this morbidity. In particular, it has the advantage of usually being performed under local anesthesia, avoiding the effects of anesthetic drugs and intubation. The risk of potentially fatal complications such as myocardial infarction and pulmonary embolism is also reduced. The use of local anesthesia also means a faster recovery for patients treated endovascularly, reducing the length of hospital stay and potentially reducing costs. However, carotid surgery is increasingly being performed under local anesthetic in some units. The major advantage of endovascular treatment is that there is no need for an incision in the neck, thereby avoiding hematoma, infection, and cutaneous or cranial nerve injury. Complications at the site of endovascular access in the groin are rare and not usually a cause for concern.

The potential pitfalls of endovascular treatment include the fact that there are very few interventionists with extensive experience of angioplasty and stenting in the carotid artery, although an increasing number now have experience using these techniques elsewhere in the body. There has always been concern over the risk that endovascular treatment of carotid artery stenosis may lead to distal embolization to the brain during passage of the catheter through a tight stenosis. In centers where endovascular intervention is being used to treat carotid stenosis, there has been a move away from simple balloon angioplasty of the artery toward stenting with or without prior angioplasty (Figure 6). One reason for this is that stents are thought to cause less carotid dissection, reducing the subsequent thromboembolic risk. However, transcranial Doppler studies have shown that embolization frequently occurs during deployment of the stent and post-stent balloon dilatation (Roubin *et al.*, 2001). This has led to the development of a variety of devices that provide cerebral protection against embolization during endovascular treatment. These consist of various designs of filters placed beyond the stenosis to catch debris during stent deployment and alternative balloon occlusion devices used to occlude the common carotid artery and ECA so that flow is reversed down the ICA and into a catheter placed in the femoral artery during stent insertion. A recent review of the literature suggested that these devices significantly reduce the 30-day risk of stroke or death when compared to procedures carried out without cerebral protection (Kastrup *et al.*, 2003). However, not all series show better outcomes with protection devices and it is possible that they could cause stroke in some cases.

Figure 6 Stent positioned in the internal carotid artery

Although the recovery time following successful endovascular intervention is short, reducing the length of inpatient care, the savings may be overshadowed by the costs of equipment as the preferred technique now involves the use of an expensive stent and cerebral protection device. Another problem with endovascular treatment is the greater potential for restenosis of the treated artery compared to surgery although the clinical significance of this is uncertain. Evidence from case series suggests that early complication rates following stenting are similar to the complication rates following surgery at approximately 6% for symptomatic disease and 1% for asymptomatic disease (Kastrup *et al.*, 2003). This justifies evaluation of stenting for carotid artery disease within the context of large multicenter randomized trials. To date, there have been five completed or stopped randomized trials of carotid endovascular intervention compared with carotid surgery: the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS Investigators, 2001); the WALLSTENT study (Alberts, 2001); the SAPPHIRE study, (Yadav *et al.*, 2004); a single center study based in Leicester United Kingdom (Naylor *et al.*, 1998) and one

Table 2 Main characteristics of completed or stopped randomized trials of endovascular treatment compared with surgery for carotid stenosis

Trial	*N*	Treatment allocated	Overall result	Result influenced by	Status
CAVATAS	504	Surgery or endovascular treatment	Neutral	74% endovascular group received PTA only	Completed
WALLSTENT	219	Surgery or stenting	Negative	Trial suspended, outdated techniques used	Stopped
SAPPHIRE	334	Surgery or stenting with cerebral protection	Positive	Mostly asymptomatic patients. Non-Q wave MI included in primary outcome measure	1-year follow-up completed
Leicester	23	Surgery or stenting	Negative	Single center	Stopped
Kentucky A (symptomatic)	104	Surgery or stenting	Neutral	Single center	Completed
Kentucky B (asymptomatic)	85	Surgery or stenting	Neutral	Single center	Completed

Note: *N* = number of patients randomized. Overall result is positive, negative, or neutral in terms of a benefit of endovascular treatment over surgery.

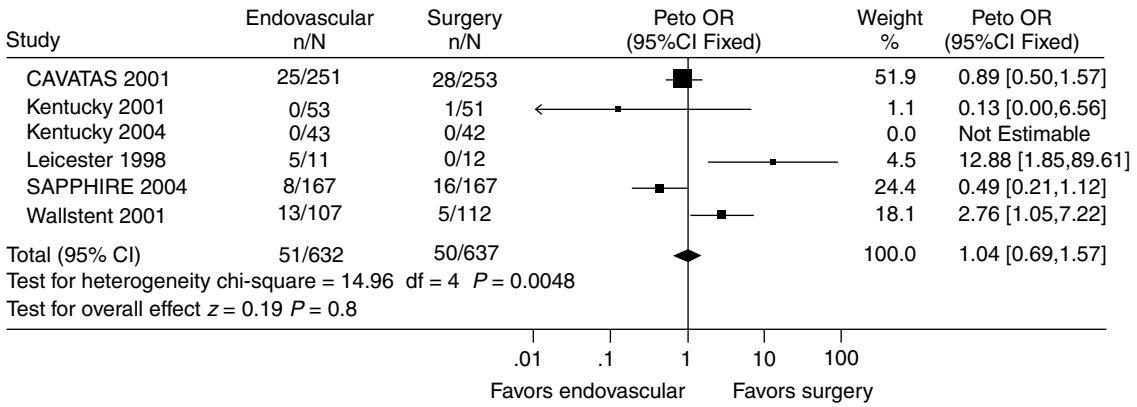

Figure 7 The effect of endovascular treatment versus endarterectomy for patients with carotid artery stenosis on the combined outcome "death or stroke or myocardial infarction within 30 days of procedure." Results are expressed as Peto odds ratio (OR) with a fixed effects model. OR <1 suggest endovascular treatment to be superior to endarterectomy. (From Coward *et al.*, Percutaneous transluminal angioplasty and stenting for carotid artery stenosis Issue 2, 2004. Copyright Cochrane Library, reproduced with permission)

other single center study based in Kentucky, United States, which comprised a symptomatic and an asymptomatic subgroup (Brooks *et al.*, 2001 and Brooks *et al.*, 2004). Table 2 shows the main characteristics of the five trials. 1269 patients were included in these trials. Meta-analysis of 30-day safety data found no significant difference in the odds of treatment related death or any stroke (Odds Ratio (OR) endovascular: surgery 1.33, 95% Confidence Interval (CI) 0.86 to 2.04), or the odds of death, any stroke or myocardial infarction (OR 1.04, CI 0.69 to 1.57) (Figure 7) (Coward *et al.*, 2004). The confidence intervals surrounding the odds ratios are wide, meaning that a significant difference in favor of one treatment or the other cannot be ruled out. In contrast, analysis of the risk of periprocedural cranial nerve injury clearly favored endovascular treatment (OR 0.13, CI 0.06 to 0.25) (Coward *et al.*, 2004). The meta-analysis found significant heterogeneity between the trials for each of the major outcomes. There are a number of reasons for the heterogeneity between trials arising from the fact that both symptomatic and asymptomatic patients were treated, different endovascular techniques were used (simple balloon angioplasty alone or combined with stenting or primary stenting) and also that both completed and stopped trials were included. The meta-analysis concludes that there is currently insufficient evidence to recommend the use of endovascular treatment for carotid stenosis as an alternative to carotid endarterectomy outside of the context of a clinical trial. There is therefore a clear need for more data from randomized trials of carotid stenting to establish its benefits and risks compared with endarterectomy (Brown and Hacke, 2004). However, experienced centers are increasingly using carotid stenting as the treatment of choice for patients with carotid stenosis who are not fit for surgery. Caution should be expressed about treating patients over the age of 80 with stenting as a number of studies suggest that advanced age should be a contraindication. Worldwide, there are currently four ongoing randomized trials of stenting treatment compared with surgery for carotid stenosis. All four are comparing stenting with surgery for symptomatic stenosis only and the combined sample size of the trials is over 7000. This should mean less heterogeneity of outcome data between trials when the results are subject to meta-analysis.

DISCUSSION

Carotid artery stenosis is an important etiological factor that is responsible for 20 to 30% of cases of anterior circulation ischemic stroke. The arterial narrowing is usually caused by atherosclerosis, a process that becomes more prevalent with increasing age. Hypertension, diabetes, and smoking all lead to acceleration of atherosclerosis and carotid stenosis is more common in patients with these risk factors. Control of these

risk factors is therefore an important part of the treatment of carotid stenosis. It is likely that in the future, widespread use of statins and better control of hypertension will reduce the impact of carotid stenosis. However, removal of the stenosis will remain the mainstay of preventive treatment in symptomatic patients. The decision to intervene to reduce the degree of carotid stenosis depends on whether the patient is symptomatic and on the degree of stenosis. All patients with TIA or stroke who might be suitable for carotid surgery or stenting should therefore be investigated for carotid stenosis by a method with acceptable accuracy in determining the degree of stenosis. There are, as yet, no definitive guidelines regarding the investigation of patients who may have carotid stenosis. However, it is now accepted that a policy of using noninvasive imaging techniques (ultrasound and/or MRA) in place of formal catheter angiography should be adopted for screening.

Randomized trials have shown that for recently symptomatic, severe stenosis (70% or more by NASCET method of measurement), surgery reduces the risk of subsequent stroke. Surgery also appears to have some benefit for well-selected patients with moderate symptomatic stenosis (50–70% NASCET method) and those with asymptomatic severe stenosis. Despite these benefits, surgery has consistently been shown to be associated with a significant periprocedural risk of stroke and, therefore, the search for a less risky alternative has led to randomized trials comparing surgery with endovascular intervention, which is now almost invariably carotid stenting. There is currently limited evidence from such trials, suggesting that the risks of endovascular treatment are similar to surgery, but a significant difference in safety between the treatments has not been ruled out. Therefore, it is important that eligible patients with carotid stenosis who are suitable for intervention are currently treated within the ongoing randomized trials of surgery versus stenting. Patients with carotid stenosis who do not fulfill the inclusion criteria for these trials and are not fit for surgery may be suitable for endovascular treatment at experienced centers. However, the results of the trials should determine which treatment is the best option for the majority of patients.

KEY POINTS

- Detection of internal carotid stenosis using noninvasive imaging is an important part of stroke prevention.
- Management involves lifestyle modification, treatment of vascular risk factors and consideration of intervention to reduce the degree of stenosis.
- The decision to intervene depends on the severity of stenosis and on the presence, nature, and timing of any symptoms.
- Carotid endarterectomy reduces the risk of subsequent stroke but even in the best hands is associated with a perioperative stroke risk of 5 to 7% in symptomatic patients and 3 to 4% in asymptomatic patients.
- Stenting shows promise but has not yet been convincingly shown to be equivalent to endarterectomy in randomized trials.

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Acute Stroke

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INTRODUCTION

Management of acute stroke has progressed rapidly over the last 20 years. Randomized controlled trials have shown that care within a stroke unit saves lives and reduces disability (The Stroke Unit Trialists' Collaboration, 1997) and such specialist units are now commonplace in developed countries. Furthermore, advances in the practice of care, brain imaging techniques, nutrition, and drug therapy has led to a proactive approach to management of patients. This chapter will discuss the epidemiology, clinical presentation, relevant investigations, and management of acute stroke and also the emerging treatments such as thrombolysis.

EPIDEMIOLOGY

Stroke is the leading cause of adult disability and an important cause of death in the developed world. Incidence progressively rises with increasing age, but subsequently declines after the age of 85 (Rothwell *et al.*, 2004a). Recent data suggests that over the last 20 years the incidence of major stroke in the over 65 age-group is decreasing (Rothwell *et al.*, 2004a) and this is thought to reflect advances in the control of vascular risk factors, such as hypertension (Table 1). However, in view of the aging population, the absolute number of older adults suffering a stroke is likely to increase and may place great financial burden on the state. Approximately 80% of strokes are due to cerebral ischemia and 15% due to primary intracranial hemorrhage. A further 5% are due to subarachnoid hemorrhage; however, this condition will not be discussed in this chapter.

ISCHEMIC STROKE

Pathogenesis

Ischemic stroke is frequently caused by thrombus formation on atheromatous plaques. Atheromatous plaques are commonly present at the bifurcation of major vessels such as the common carotid artery and the basilar artery, and the origins of the anterior, middle, and posterior cerebral arteries. Thrombus may either occlude the artery at the site of formation or, alternatively, fragment and occlude distal arteries. Other common causes of ischemic stroke are cardiac embolism or lacunar infarction, however, rare causes also need to be considered (Table 2).

Cerebral infarction causes an area of irreversible damage to brain tissue. Interest has been focused on the area surrounding this ischemic core, which may possibly be salvageable should cerebral blood flow be restored. This area, known as *the ischemic penumbra*, decays progressively over several hours following stroke (Kidwell *et al.*, 2003), hence any potential form of imaging and subsequent intervention to prevent further tissue damage would need to be performed rapidly.

Clinical Presentation

Stroke is defined by the World Health Organization as *the clinical syndrome of rapid onset of focal cerebral deficit, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one* (Warlow *et al.*, 2003). This definition distinguishes stroke from transient ischemic attack, the latter characterized by full recovery within 24 hours.

It is essential to obtain a detailed history and conduct a thorough examination of those who present with suspected stroke. If the patient is dysphasic, confused, or comatose, the history should be obtained by proxy. Even though stroke is classically associated with sudden onset of focal neurological features, a staggered or progressive course is possible. In the United Kingdom, ischemic stroke is commonly classified according to the Oxfordshire Community Stroke Project (OCSP) into anterior circulation infarction, posterior circulation infarction (POCI), or lacunar infarction (Bamford *et al.*, 1991). Accurate identification of the subtype of stroke

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Table 1 Proposed risk factors for ischemic stroke in the United Kingdom for those aged 65 and above (Rodgers *et al.*, 2004; Warlow *et al.*, 2003)

Atrial fibrillation
Previous transient ischemic attack/stroke
Cardiovascular disease (myocardial infarction, angina, or heart failure)
Smoking
Hypertension
Left ventricular hypertrophy
Peripheral vascular disease
Diabetes
Alcohol excess
Hyperlipidemia
Obesity

Table 2 Causes of ischemic stroke in the elderly

Atheromatous disease
Lacunar infarction
Cardiac embolus
Atrial fibrillation
Mural thrombus following acute myocardial infarction
Bacterial endocarditis
Prosthetic valve thrombosis
Inflammatory vascular disease
Vasculitis (e.g. polyarteritis nodusum)
Giant cell arteritis
Trauma (e.g. strangulation)
Angiography/cardiac surgery
Cardiac arrest/hypoxia
Prolonged hypotension
Syphilis
Paradoxical embolus
Hyperviscosity syndrome

enables estimation of prognosis and influences management decisions.

Anterior Circulation Infarction

Occlusion of the proximal middle cerebral or internal carotid artery causes total anterior circulation infarction (TACI) (Bamford *et al.*, 1991). This results in a clinical syndrome of contralateral hemiparesis, homonymous hemianopia, and impairment of one or more of the domains of higher mental function, such as dysphasia or visuospatial defect.

Occlusion of distal tributaries of the middle cerebral artery (MCA) results in partial anterior circulation infarction (PACI) (Bamford *et al.*, 1991). Diagnosis requires the presence of two of the three components of TACI or a higher mental defect alone. PACI may present as the combination of expressive dysphasia and contralateral hemiparesis, affecting predominantly the face and arm following occlusion of the anterior divisions of the MCA. Alternatively, occlusion of the posterior divisions of the MCA results in receptive dysphasia and homonymous visual field defect.

PACI may result from occlusion of the anterior cerebral artery characterized by a clinical syndrome of contralateral hemiparesis, predominantly affecting the leg, urinary incontinence, lack of motivation, and motor dyspraxia.

Posterior Circulation Infarction

Posterior circulation infarction is caused by occlusion of the vessels of the brain stem resulting in a wide variety of clinical syndromes (Bamford *et al.*, 1991). Palsy of the extraocular muscles with contralateral hemiparesis, bilateral motor or sensory deficit, isolated homonymous visual field defect, and cerebellar syndrome are examples of POCI. Occlusion of the basilar artery or both vertebral arteries causes a frequently fatal syndrome of coma, pinpoint pupils, quadriplegia, and cranial nerve palsies.

Occlusion of the posterior inferior cerebellar artery results in a classical, but rare, clinical syndrome of vertigo, ipsilateral facial spinothalamic sensory loss, Horner's syndrome, dysphagia, ataxia, and spinothalamic sensory loss of the contralateral limbs.

Lacunar Infarction

Lacunar infarction is a consequence of occlusion of small perforating arteries by lipohyalinosis or microthrombi and causes a range of clinical syndromes (Bamford *et al.*, 1991). These include pure motor stroke characterized by varying degrees of paresis of two or three ipsilateral body areas (face, arm, leg). Lacunar stroke may also present as pure sensory stroke or sensory-motor stroke. Ataxic hemiparesis is characterized by hemiparesis with ipsilateral cerebellar features and dysarthria.

Differential Diagnosis

It is important to remember that approximately 5% of patients presenting with suspected stroke are later shown to have an alternative diagnosis (Table 3). Many of the conditions that masquerade as stroke may prove fatal if diagnosis is delayed, illustrating the necessity to conduct thorough clinical assessment for all patients.

Stroke usually presents with sudden onset of focal neurological signs, although a similar presentation may rarely be the result of hemorrhage into a tumor. A history of falls and head injury, particularly associated with fluctuating neurological signs, may be indicative of subdural hematoma. Meningitis may present with fever, focal neurological signs, neck stiffness, and loss of consciousness and diagnosis should not be delayed. Urgent serum glucose should be obtained for all patients, as hypoglycemia requires urgent treatment.

Table 3 Differential diagnosis of stroke in the elderly

Cerebral tumor
Subdural hematoma
Cerebral abscess
Encephalitis
Meningitis
Head injury
Hypoglycemia
Epilepsy with Todd's paresis

Ischemic stroke is usually a consequence of atheromatous disease, but may also be caused by other rare and sometimes treatable conditions (Table 2). Giant cell arteritis and vasculitis uncommonly present as a stroke, but are treatable with corticosteroids or immunosuppressants. Bacterial endocarditis is a rare cause of embolic stroke and early recognition of this condition will allow appropriate commencement of antibiotic therapy. Strangulation may cause arterial dissection or occlusion, subsequently resulting in stroke.

Investigations

All patients require their measurements of serum urea, electrolytes and creatinine, full blood count, clotting screen, erythrocyte sedimentation rate, and serum glucose to be carried out. Electrocardiograph is required to determine the presence of cardiac arrhythmia including atrial fibrillation or evidence of recent myocardial infarction. A chest X ray is indicated if cardiac failure or pneumonia is suspected. Selected investigations include lipid profile, syphilis serology, and autoantibodies.

Brain Imaging

The purpose of brain imaging is to rapidly assist the distinction of brain infarction (Figure 1) from hemorrhage (Figure 2) and exclude other potentially treatable pathologies. Should infarction be suspected, the early introduction of aspirin may improve prognosis (Sandercock *et al.*, 2004; International Stroke Trial Collaborative Group, 1997). In some situations, urgent scanning is advisable and the indications are shown in Table 4. Otherwise, imaging should ideally be arranged within 24 hours following the onset of stroke (Intercollegiate Stroke Working Party, 2004).

The modality of brain imaging depends upon the clinical circumstances. Computerized tomography (CT) scan is currently easily obtainable as an emergency in most hospitals in the United Kingdom and may rapidly and safely be performed on acutely ill patients (Wardlaw and Farrall, 2004). CT is reliable for the identification of acute hemorrhage, visualized as a hyperdense homogenous lesion (Figure 2), and is also effective in identifying subdural hematomas and many cerebral tumors. CT has limited accuracy in identifying infarcts within the first few hours following stroke, however, this may not necessarily be problematic in clinical practice as cerebral infarct may be inferred by a classical presentation and an unremarkable brain scan.

Magnetic resonance imaging (MRI) is gaining increasing popularity, particularly with the advent of the newer techniques of diffusion and perfusion weighted imaging. MRI is

Table 4 Indications for urgent CT head for patients presenting with suspected acute stroke

Patient taking anticoagulation therapy
Bleeding diathesis
Depressed level of consciousness
Proposed urgent anticoagulation or thrombolytic therapy
Progressive or fluctuating neurological signs
Suspected cerebellar stroke
Presence of "thunderclap" headache
Presence of meningism: stiff neck, photophobia, Kernig's sign positive

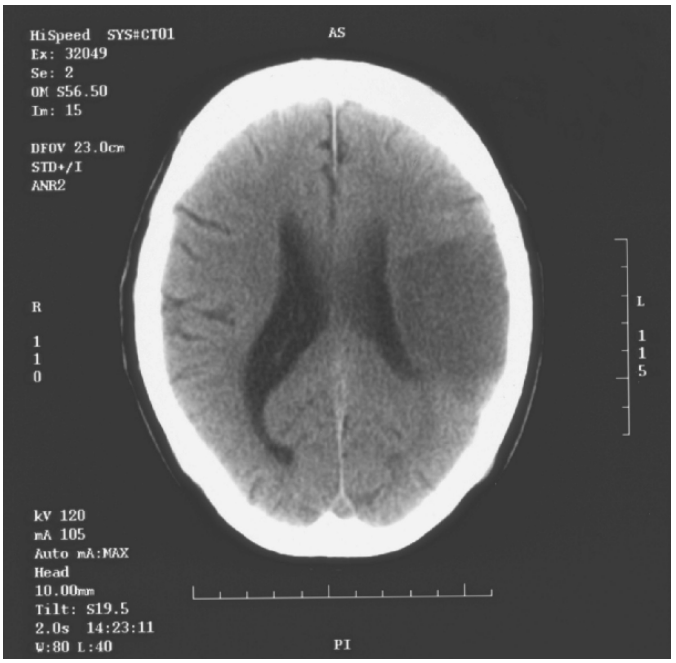

Figure 1 CT brain scan showing an area of low attenuation in the left temporal lobe consistent with an infarct

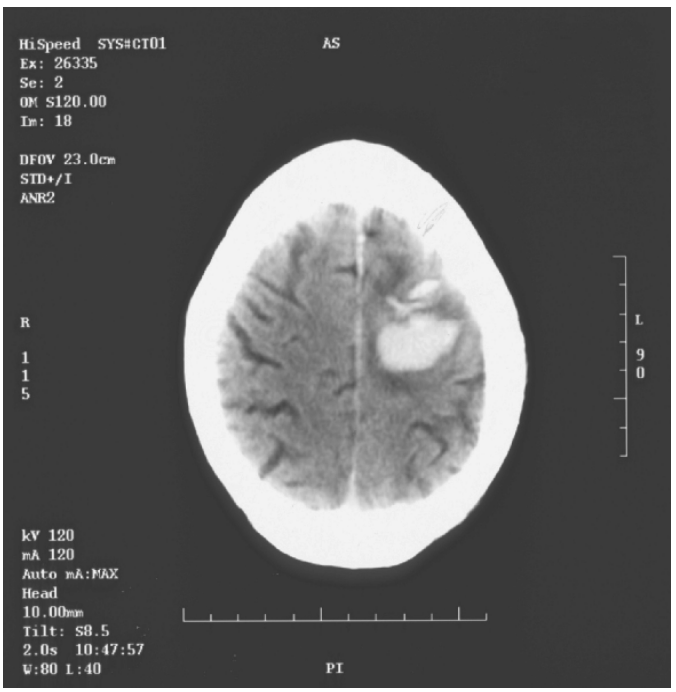

Figure 2 CT brain scan demonstrating an area of high attenuation in the left parietal region, consistent with a recent intracerebral hemorrhage

more accurate at identifying brain stem lesions and smaller cerebral infarcts that are undetectable with CT.

MRI has disadvantages. Patients are placed in an enclosed structure and the noisy environment may be unsuitable for the distressed patient. Furthermore, monitoring of vital signs may be difficult and for many patients MRI is contraindicated, for example, if a permanent pacemaker or metallic foreign body is present. There are concerns that MRI may be unreliable in identifying intracranial hemorrhage during the first few hours following a stroke. However, this may not cause difficulties in clinical practice as illustrated by a recent study reporting that multisequence MRI is of nearly equivalent accuracy compared to CT if performed within 6 hours from the onset of stroke (Fiebach *et al.*, 2004).

MRI is the investigation of choice to reliably distinguish infarct from hemorrhage, should brain scanning be delayed for 8 days or later (Wardlaw *et al.*, 2003). The reason for this is that several days after cerebral hemorrhage, MRI is able to detect the characteristic pattern formed by hemosiderin, a breakdown product of hemoglobin, deposited within macrophages. In contrast, CT is unable to reliably distinguish hemorrhage from infarction several days after the stroke and is not recommended for this purpose (Wardlaw *et al.*, 2003).

Brain Imaging and Thrombolysis

The proposed mechanism of thrombolysis is that by restoring cerebral perfusion, the ischemic penumbra is salvaged. This results in reduction of the size of infarct expansion (Parsons *et al.*, 2002) and improved patient outcome (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995) as compared with the use of placebo. Thrombolysis is only effective if administered within 3 hours following ischemic stroke (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995); hence, it is necessary for the rapid organization of effective brain imaging.

Early identification of cerebral infarction may assist decisions to thrombolyze, and diffusion weighted imaging is proving more reliable than CT in the identification of infarction within a few hours following the onset of stroke (Fiebach *et al.*, 2002). Furthermore, combination of diffusion and perfusion weighted MRI images may determine the extent of the ischemic penumbra (Kidwell *et al.*, 2003; Parsons *et al.*, 2002), hence it may be useful identifying subgroups of patients who are more likely to benefit from thrombolysis.

Management

Monitoring Progress

Following admission to hospital, stroke unit care involves frequent monitoring of physiological variables such as oxygen saturations, pulse, blood pressure, blood glucose, body temperature, and level of consciousness. Regular review by specialist medical staff and other members of the multidisciplinary team enable the early recognition and treatment of coexisting conditions (Table 5) in order to maximize prospects of recovery. Issues of stroke unit management that are of particular importance are discussed as follows:

Table 5 Acute stroke: important coexisting conditions

Cardiac
Myocardial infarction/acute coronary syndrome
Congestive cardiac failure
Arrhythmia (mainly atrial fibrillation)
Neurogenic pulmonary edema
Respiratory
Aspiration
Community or hospital acquired pneumonia
Pulmonary embolus
Metabolic
Dehydration
Electrolyte disturbance
Hyperglycemia
Gastroenterological
Peptic ulceration (bleeding, perforation)
Ischemic bowel
Urological
Urinary retention
Urinary incontinence
Miscellaneous
Pressure ulceration
Deep vein thrombosis

Airway and Oxygenation

The initial priority of acute stroke management is to ensure that the airway is patent and the patient receives adequate oxygen therapy. The airway may be obstructed as a consequence of reduced levels of consciousness or secretions and may be alleviated by careful positioning of the patient and nasopharyngeal suction.

Oxygen saturation is measured easily with pulse oximetry and if reduced (i.e. less than 92%) should prompt a search for a cause and oxygen should be prescribed. Hypoxia may be due to pneumonia, aspiration, heart failure, pulmonary embolus, or alternatively, the patient may suffer from a chronic respiratory illness. Arterial blood gases are required to detect associated carbon dioxide retention and are particularly valuable if the patient has a history of chronic obstructive pulmonary disease. For carefully selected patients with respiratory failure, invasive or noninvasive ventilation may be indicated.

Coma

Deterioration in the level of consciousness following stroke is a frequently encountered clinical scenario and may be because of intracranial pathology such as cerebral edema or recurrent infarction (Table 6). It is, however, essential to exclude important medical conditions such as metabolic disturbance, sepsis, hypo or hyperglycemia, or respiratory

Table 6 Neurological complications of acute stroke

Recurrent infarction
Hemorrhagic transformation of infarct
Recurrent intracranial hemorrhage
Cerebral edema
Brain herniation
Acute hydrocephalus
Epileptic seizures

failure, which may also account for clouding of consciousness. Sedatives, hypnotics, or opiates may affect the level of consciousness and caution is advised before using these drugs.

Arterial Blood Pressure

A finding of elevated arterial blood pressure in the acute aftermath of a stroke should be followed by a reassessment of the patient in order to identify any source of pain or distress such as acute urinary retention. Rarely, aortic dissection may present as a combination of hemiparesis and severe hypertension and this should be excluded.

Controversy remains as to the merits of lowering arterial blood pressure immediately after stroke. Cerebral autoregulation is impaired, and pharmacological blood pressure reduction may thus alter perfusion of the ischemic penumbra, and limited evidence shows this may be associated with an increased risk of early neurological deterioration (Castillo *et al.*, 2004). Furthermore, randomized controlled trials have failed to establish the merits of early reduction of arterial blood pressure with antihypertensive medication because of small patient numbers (Boysen, 2004).

Consequently, on the basis of current evidence, it is usually undesirable to lower blood pressure during the acute phase of stroke. Exceptions are if arterial blood pressure is extremely high, for example, 240/130, or if there is evidence of malignant phase hypertension, acute myocardial infarction, severe left ventricular failure, aortic dissection, and unstable angina (Robinson and Potter, 2004). Elevated blood pressure falls during the 7 days after stroke and tends to plateau thereafter (Harper *et al.*, 1994), hence it is probably safe to initiate antihypertensive medication 1 to 2 weeks following stroke. A common dilemma is whether to continue the patient's usual antihypertensive treatment in the immediate aftermath of stroke and trials are in progress to resolve this issue.

Hypotension may be potentially dangerous as cerebral perfusion may be compromised, particularly if the patient has severe stenosis of intracranial arteries. This view is supported by data obtained from the International Stroke Trial (IST), which reported that blood pressure at the lower end of the spectrum (systolic blood pressure <120 mm Hg) at randomization was associated with poor outcome (Leonardi-Bee *et al.*, 2002). Furthermore, evidence suggests that the avoidance of dips in diastolic blood pressure below 80 mm Hg may improve patient survival (Indredavik *et al.*, 1999).

Hypotension may be a marker of serious coexisting pathology and attempts should be made to identify, and if possible, correct the cause. Dehydration, particularly if a long delay preceded hospital admission, will respond to the use of intravenous fluids. Other causes of hypotension are pulmonary embolus, gastrointestinal hemorrhage, acute myocardial infarction, and aortic dissection. Preexisting cardiac impairment and overzealous treatment with hypotensive agents may contribute to hypotension and the patient's medication regime may require reassessment.

Metabolic Considerations

Management of hyperglycemia following acute stroke is controversial. For many patients, hyperglycemia is a transient phenomenon, possibly a reflection of endogenous catecholamine and corticosteroid release poststroke. This is illustrated by the observation that elevated glucose levels tend to fall during the first few hours following hospital admission (Lindsberg and Roine, 2004; Gray *et al.*, 2004). Hyperglycemia after stroke may also be a reflection of established or newly diagnosed diabetes.

Hyperglycemia at the time of hospital admission is associated with a poor outcome and correlates with expansion of infarct size (Lindsberg and Roine, 2004; Baird *et al.*, 2003). It is still not known if strict pharmacological control of hyperglycemia improves survival and the results of a randomized controlled trial is awaited (Gray *et al.*, 2004). In the meantime, management depends upon local guidelines, but one strategy is to maintain euglycemia with variable dose insulin and dextrose-potassium infusions (Gray *et al.*, 2004).

Serum electrolytes and renal function may be deranged because of a variety of factors including dehydration and diuretic usage necessitating the need for regular monitoring of urea, electrolytes, and creatinine. Patients may be at risk of dehydration as a consequence of dysphagia, but are also susceptible to fluid overload because of injudicious fluid replacement or heart failure. Monitoring of fluid balance by hospital staff and regular clinical assessment is required to ensure that the euvolemic status is maintained.

Fever

Metanalysis has confirmed that fever after stroke is strongly associated with increased morbidity and mortality (Hajat *et al.*, 2000); however, it is still not known if measures to normalize fever improve outcome. Fever ($>37.5\,^{\circ}$C) should prompt clinical examination to establish a source such as infection, inflammatory disease, or venous thromboembolic disease. This should be combined with the option of prescription of antipyretic medication such as oral or rectal paracetamol (acetaminophen).

Physical Therapy

Early mobilization is critical in the absence of objective contraindications and is related to a favorable outcome (Indredavik *et al.*, 1999). A policy of initially moving the patient out of bed within 24 hours of stroke and subsequent

mobilization may reduce the risk of pneumonia, venous thromboembolic disease and pressure ulcers, not to mention the benefits for patient morale.

Venous Thromboembolic Disease

Deep vein thrombosis and pulmonary embolus are common and serious complications of stroke. Elastic compression stockings reduce risk of deep vein thrombosis postoperatively (Amaragiri and Lees, 2004) and, by inference, are recommended to be used in the aftermath of stroke (Intercollegiate Stroke Working Party, 2004). The use of unfractionated heparin or low molecular heparin is currently not recommended for the prevention of venous thrombosis because of the lack of evidence of overall benefit (International Stroke Trial Collaborative Group, 1997; Coull *et al.*, 2002).

Antithrombotic/Anticoagulant Therapy

The benefits of early aspirin therapy is illustrated by the IST and the Chinese acute stroke study (International Stroke Trial Collaborative Group, 1997; Coull *et al.*, 2002). IST reported that for patients administered 300 mg of aspirin within 48 hours of stroke, 2.8% suffered a recurrent stroke within 14 days compared to 3.9% in the placebo group (International Stroke Trial Collaborative Group, 1997). This equates to a small, but significant benefit of aspirin with no significant excess of intracranial hemorrhage. Furthermore, meta-analysis shows that at follow-up for up to 6 months, early aspirin therapy resulted in 13 per 1000 treated patients alive and free of stroke (Sandercock *et al.*, 2004). Aspirin should thus be administered as soon as possible for patients with ischemic stroke and if the patient is dysphagic, this may be delivered through enteral or rectal routes.

IST demonstrated that unfractionated heparin reduces the risk of recurrent stroke and pulmonary embolus, yet because of an unacceptably high risk of hemorrhagic complications (International Stroke Trial Collaborative Group, 1997), this treatment is not recommended. There is also insufficient evidence to support the efficacy of low molecular weight heparin (Gubitz *et al.*, 2004; Coull *et al.*, 2002). Some physicians propose that it is possible that certain subgroups may benefit from rapid anticoagulation. These include stroke patients with a suspected cardioembolic source, those with severe stenosis of large arteries (Coull *et al.*, 2002), and those with crescendo transient ischemic attacks and treatment may be considered on a named-patient basis.

Thrombolytic Therapy

Interest is growing in the use of thrombolytic therapy for the treatment of ischemic stroke. One trial assessing thrombolysis with recombinant tissue plasminogen activator (rTPA) up to 3 hours following ischemic stroke reported that 50% of those in the treatment group recovered to a level of minimal or no disability at 3 months compared to 38% in the placebo group (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). The main adverse effect of thrombolysis was intracranial hemorrhage, occurring in 6.4% of thrombolyzed patients, compared to 0.6% of those randomized to placebo (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). At present, it is not clear if the benefits of thrombolysis persist if administered up to 6 hours poststroke (Wardlaw *et al.*, 2004), and further trials are in progress.

If thrombolysis were to be introduced into standard clinical practice, this would require major reorganization of stroke services. Greater availability of urgent brain imaging and resident expertise to interpret the findings may be required in collaboration with education of the public and the primary care staff regarding the necessity for rapid referral.

Neurosurgical Intervention

Neurosurgical intervention may be considered for a small number of patients. Cerebellar infarction may cause acute hydrocephalus and urgent decompression surgery should be considered. Another important consideration is patients who develop malignant cerebral edema following anterior infarction. Cerebral edema reaches peak mass at day three to day five following infarction and, if particularly severe, may cause deterioration of consciousness, eye and head deviation and, later, transtentorial herniation. Decompressive hemicraniectomy may be considered (Foerch *et al.*, 2004; Schwab *et al.*, 1998) and further management may be discussed with a local neurosurgical unit.

Dysphagia and Nutrition

Patients may not be able to swallow immediately after a stroke because of a number of factors including reduced level of consciousness, oral ulceration, poor dentition, and oropharyngeal dysphagia. Dysphagia following stroke is common and swallow assessments should be performed as soon as possible after admission. If swallow is impaired or absent, the use of intravenous fluids to maintain hydration is required in the first instance.

Bedside swallow assessments are based on the detection of signs that signify a high risk of aspiration. Patients with decreased level of consciousness, poor or absent voluntary cough, moist or bubbling voice, or evidence of chest infection are particularly at risk (Smithard *et al.*, 1998; Ramsey *et al.*, 2003). Under specialist supervision, swallow may be cautiously evaluated by administering a teaspoon of water 3 times; the absence of laryngeal movement and the presence of cough suggest that swallow is unsafe (Smithard *et al.*, 1998). The gag reflex, formally used frequently by physicians, is now considered a poor indicator of the ability to swallow (Ramsey *et al.*, 2003). There are several bedside swallow assessments in current usage; however, no universally agreed protocol exists, and sensitivity in the detection of risk of aspiration may be as low as 47% (Smithard *et al.*, 1998; Ramsey *et al.*, 2003).

Videofluoroscopy is viewed by some as the gold standard investigation for the assessment of swallow. This involves the patient standing or sitting at 45–90 degrees and food and liquid of different consistencies mixed with barium are ingested, allowing assessment of the oral and pharyngeal phases of swallow (Ramsey *et al.*, 2003). The disadvantages of this investigation are that the patient is required to maintain posture and only reflects swallow over a brief period of time and thus may not be representative of the circumstances at ward level (Ramsey *et al.*, 2003). Furthermore, interobserver disagreement may limit the usefulness of this test (Ramsey *et al.*, 2003). Other techniques include fibro-optic endoscopy that allows direct visualization of the swallow process (Ramsey *et al.*, 2003).

After swallow assessment, dysphagic patients may be able to tolerate a diet of modified consistency. The precise consistency will vary for each patient, and in view of the likelihood of the degree of dysphagia fluctuating (Smithard *et al.*, 1997), regular swallow assessments by speech and language therapists or appropriately trained staff are required. A pureed diet consisting of thick homogenous textures may be appropriate initially, but as dysphagia resolves, this may be altered to minced, soft textured food. Fluids may also require modification to varying degrees of viscosity.

For those patients unable to sustain adequate nutrition orally, enteral feeding should be considered. The rationale is to avoid malnutrition, which is associated with a poor prospect of functional recovery and increased risk of infections and pressure ulcers (Davalos *et al.*, 1996). The precise timing of initiation of enteral feeding is debated, without firm consensus. Approximately one half of dysphagic patients improve at the end of the first week (Smithard *et al.*, 1997), hence it may be reasonable to wait until after this time to institute enteral feeding if required. Factors that may promote a decision for early insertion of feeding tubes include preexisting malnutrition and the necessity to continue essential medication such as antiparkinsonian or antiepileptic drugs.

Enteral feeding is commonly accomplished by the insertion of a nasogastric (n/g) tube, however, many patients resist insertion and attempt removal resulting in the disruption of feeding regimes. Some of these problems may be circumvented by the insertion of a percutaneous endoscopic gastrostomy (peg) tube. The optimal timing of peg insertion is not clear. However, one randomized controlled trial comparing peg and n/g tube insertion within 14 days following stroke did show improved nutritional status and lower fatality, at 6-week follow-up, for the former group (Norton *et al.*, 1996) and further trials are in progress.

Aspiration pneumonia is the consequence of poorly coordinated swallowing allowing ingested material or gastric contents to enter the airway. Neither n/g tube (Dziewas *et al.*, 2004) nor peg tube feeding (James *et al.*, 1998) precludes development of this complication. Rapid identification with clinical examination supported by chest radiography is vital, and management options include institution of chest physiotherapy, oxygen supplementation, nebulizers, and appropriate intravenous antibiotics. Aspiration pneumonia may also develop without immediate clinical features, so-called silent aspiration, although it is not clear if this has a negative impact on prognosis (Ramsey *et al.*, 2003).

HEMORRHAGIC STROKE

Spontaneous intracranial hemorrhage is commonly a consequence of hypertension, although bleeding disorders, anticoagulant therapy, cerebral amyloid angiopathy, and arterio–venous malformations are important causes. Hemorrhage most frequently occurs in the basal ganglia, and less commonly, in the pons, thalamus, cerebellum, and subcortical areas.

Intracranial hemorrhage may present in a similar manner to ischemic stroke. Features suggestive of hemorrhagic stroke, in favor of ischemic stroke, are loss of consciousness at the time of the event, early onset of severe headache, nausea and vomiting, and neck stiffness. However, clinically it is not possible to reliably differentiate these conditions without brain imaging.

Cerebellar hematoma presents as sudden onset of headache, truncal ataxia, clouding of consciousness and conjugate gaze palsy and may be followed by a rapid neurological deterioration consequent upon the development of acute hydrocephalus.

Management of acute primary intracranial hemorrhage is generally similar to that for ischemic stroke, with a few important exceptions. Antiplatelet, anticoagulant, and thrombolytic therapy is usually contraindicated. Dilemmas arise if venous thrombosis or pulmonary embolus complicate recovery and the physician is placed in a difficult position balancing the risks and benefits of anticoagulation. Insertion of veno-caval filters or the use of a course of low molecular weight heparin instead of warfarin are options to be considered (Kelly *et al.*, 2003), however, at present, there is little consensus as to the correct management that should be pursued.

Neurosurgical management is an important consideration. Evacuation of cerebellar hematoma is potentially lifesaving with the prospect of good functional recovery and this opportunity should not be missed. For intracranial hemorrhage at other sites, no randomized controlled trial has demonstrated the efficacy of surgery. However, it is possible that some patients with superficial hemorrhage may benefit from neurosurgical intervention, and advice may be obtained from a specialist unit.

ORGANIZATION OF ACUTE STROKE SERVICES

Numerous randomized controlled trials have established that stroke unit care improves outcome (The Stroke Unit Trialists' Collaboration, 1997; Kalra *et al.*, 2000, 1993). Metanalysis shows that at medium follow-up of 1 year, 20.4% of patients treated in a stroke unit were dead as compared to

25.5% of those receiving general ward care (Number needed to treat (NNT) = 22) (The Stroke Unit Trialists' Collaboration, 1997). With respect to functional dependency, 40.1% of stroke unit treated patients were unable to go home, compared to 47.2% in general wards (NNT = 14) (The Stroke Unit Trialists' Collaboration, 1997). The success of stroke unit care has precipitated recommendations encouraging all patients hospitalized with stroke to receive this specialist care (Intercollegiate Stroke Working Party, 2004).

There are many reasons that account for the superiority of stroke unit care. Stroke unit staff of all disciplines receive focused training and usually have developed a special interest in stroke medicine (The Stroke Unit Trialists' Collaboration, 1997; Indredavik *et al.*, 1999). Multidisciplinary team meetings are conducted more frequently and relatives are involved with practical aspects of rehabilitation (The Stroke Unit Trialists' Collaboration, 1997; Indredavik *et al.*, 1999). Interestingly, studies have shown that the duration and frequency of occupational therapy and physiotherapy are not consistently greater with stroke unit care (The Stroke Unit Trialists' Collaboration, 1997; Indredavik *et al.*, 1999; Kalra *et al.*, 1993); however, rehabilitation provided may be targeted toward the specific needs of each individual patient (The Stroke Unit Trialists' Collaboration, 1997; Kalra *et al.*, 1993).

An important difference between stroke unit and general ward care is greater emphasis on teamwork and integration of nursing staff with therapists (The Stroke Unit Trialists' Collaboration, 1997; Indredavik *et al.*, 1999; Kalra *et al.*, 2000; Langhorne and Pollock, 2002). This may be illustrated by activities such as swallow assessments and regular changes in diet consistency, necessitating regular collaboration of speech and language therapy, dietetic, and nursing staff. Early mobilization is a feature of stroke unit care, requiring not only intensive physiotherapy but also nursing staff involvement in order for the mobilization to continue successfully, throughout the day.

Intensive monitoring of physiological variables such as oxygen saturation, blood pressure, and temperature characterize stroke unit care (Indredavik *et al.*, 1999; Langhorne and Pollock, 2002). A proactive approach to the correction of hypotension with intravenous fluids, reduction of fever, stabilization of high blood glucose, and greater attention to measures to prevent aspiration may promote recovery (Indredavik *et al.*, 1999; Langhorne and Pollock, 2002). The underlying reason for the success of stroke units may, however, be because of factors that are unmeasurable such as dedication of staff to the care of patients with stroke and their ability to promote patient morale.

CLINICAL GUIDELINES

Stroke medicine is a rapidly evolving speciality and it may be difficult for medical staff to incorporate all the recent developments into everyday clinical practice, potentially compromising patient care. This situation may be alleviated by reference to clinical guidelines. Clinical guidelines provide recommendations for many aspects of care, such as relevant investigations, treatment, and provision of nutrition (Intercollegiate Stroke Working Party, 2004; Adams *et al.*, 2003).

Clinical guidelines are based upon the best available evidence. The results of randomized controlled trials and meta-analysis are commonly utilized as a source of recommendations; however, for many aspects of care this data is not available, and guidelines may refer to high-quality observational studies or a consensus of expert opinion. The source of evidence is provided in clinical guidelines in order for physicians to assess the merits of each recommendation. It is important to remember that clinical guidelines are not rigid rules and are not able to provide recommendations for all clinical scenarios. Medical staff may wish to deviate from clinical guidelines depending upon the circumstances of each individual patient.

CARE PATHWAYS FOR ACUTE STROKE

Integrated care pathways are commonly utilized in an attempt to improve efficiency and organization of multidisciplinary rehabilitation and facilitate discharge planning. Care pathways cover the many aspects of patient care such as medical investigations and treatment, management of urinary incontinence, and timing and nature of intervention by therapists.

Trials have demonstrated that the utilization of care pathways for acute stroke results in improved documentation by staff and a reduction in certain complications such as urinary tract infection compared to conventional care (Kwan *et al.*, 2004). However, there is little evidence to suggest that this translates to improvement in important outcome measures such as mortality, destination after discharge, and length of stay (Kwan *et al.*, 2004; Sulch *et al.*, 2000, 2002). Of further significance, there is evidence that the use of care pathways may negatively affect quality of life of the patient (Sulch *et al.*, 2000, 2002). This is possibly a reflection of the lack of flexibility of care pathways to cater for the complex psychological and physical needs of each individual patient.

SECONDARY PREVENTION OF ISCHEMIC STROKE

Advice on lifestyle modifications, that is, smoking cessation, regular exercise, weight reduction if obese, and avoidance of excess alcohol and salt may be commenced while the patient is recovering from stroke. One to 2 weeks after stroke, it is safe to treat hypertension. Controversy remains as to the most effective first line agent; however, there is compelling evidence supporting the use of thiazide diuretics, indapamide, and angiotensin converting enzyme inhibitors (Yusuf *et al.*, 2000; PROGRESS Collaborative Group, 2001; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002).

For patients with ischemic stroke that are in sinus rhythm, antiplatelet therapy is indicated. Aspirin is the most intensively studied drug and the optimal dose is 75–150 mg

(Antithrombotic Trialists' Collaboration, 2002); however, addition of modified-release dipyridamole to aspirin reduces the risk of further stroke compared to aspirin or dipyridamole alone (Diener *et al.*, 1996). One trial supported a small benefit of use of clopidogrel, compared to aspirin, for prevention of vascular events, and clopidogrel may be considered for patients hypersensitive or intolerant to aspirin (CAPRIE Steering Committee, 1996). A combination of aspirin and clopidogrel is not recommended because of the excess risk of bleeding complications (Diener *et al.*, 2004). Statin therapy should be considered for patients with total cholesterol $>3.5\,\mathrm{mmol\,l^{-1}}$ (Collins *et al.*, 2004).

For patients with atrial fibrillation, warfarin therapy should be commenced, provided no contraindications are evident. As a result of concerns causing hemorrhagic transformation in the immediate aftermath of stroke, anticoagulation should be delayed for a few days following a minor stroke or 2 weeks following a major stroke.

For patients who present with infarction of the anterior cerebral circulation and who have mild or no disability, carotid Doppler should be performed and if stenosis of the ipsilateral carotid artery is greater than 70%, CEA is indicated (Intercollegiate Stroke Working Party, 2004; European Carotid Surgery Trialists' Collaborative Group, 1998).

The relative benefits of stroke prevention of CEA decline if surgery is delayed. This view is supported by post hoc analysis of randomized controlled trials comparing CEA to placebo, reporting an absolute risk reduction of 30% if surgery is performed within 2 weeks of stroke, compared to approximately 4% if delayed by 4–12 weeks (Rothwell *et al.*, 2004b). Therefore carotid Doppler with a view to CEA should ideally be arranged without delay for those who have little or no disability (Intercollegiate Stroke Working Party, 2004). Patients over 75 years benefit the most from CEA (Rothwell *et al.*, 2004b), hence, age is definitely not a barrier to this treatment.

PROGNOSIS OF ACUTE STROKE

Patients and relatives are eager to be provided with information concerning long-term prognosis at the time of acute stroke. Prognostic indicators are also valuable to hospital staff to ascertain prospects for effective rehabilitation, assist decisions reflecting destination after discharge, and to spare patients with poor prognosis unnecessary interventions.

Several features obtained at the time of admission to hospital, which may predict long-term outcome, have been evaluated. Primary intracranial hemorrhage is associated with higher disability and fatality compared to cerebral infarct (Barber *et al.*, 2004). The clinical features of urinary incontinence (Taub *et al.*, 1994) and low level of consciousness (Henon *et al.*, 1995) at the time of onset of stroke are predictors of poor recovery, although they lack specificity (Counsell *et al.*, 2004). Demographic characteristics such as older age is a frequently cited predictor for the lack of prospects of recovery (Kammersgaard *et al.*, 2004; Hankey *et al.*, 2002), but studies have revealed conflicting results once other confounding variables have been accounted for (Taub *et al.*, 1994; Kammersgaard *et al.*, 2004; Epstein, 2004; Hankey *et al.*, 2002). Multiple coexisting medical conditions (Ween *et al.*, 1996), recurrent stroke (Hankey *et al.*, 2002), and preadmission dependency (Kammersgaard *et al.*, 2004; Hankey *et al.*, 2002) increase the risk of an unfavorable outcome. A variety of social factors such as living without a caregiver before admission, predict nursing home entry after discharge (Epstein, 2004; Ween *et al.*, 1996).

The OCSP classification is commonly utilized to predict prognosis in the United Kingdom (Table 7; Bamford *et al.*, 1991). For patients with TACI, the prognosis is usually poor. Approximately 60% are dead at 12 months, mainly because of complications of stroke such as chest infections and venous thrombosis, and only less than 5% achieve functional independence (Bamford *et al.*, 1991). For PACI, POCI, and lacunar infarction (LACI), survival prospects are better and more than 50% are independent at 12 months (Bamford *et al.*, 1991). The recently developed six simple variables (SSV) model has been shown to be superior to the OCSP for predicting functional outcome (Counsell *et al.*, 2004), but requires further evaluation before this is used in clinical practice.

The Orpington prognostic scale utilizes the variables of motor deficit in the affected arm, proprioception, mobility, and cognition (Kalra *et al.*, 1994) and if performed within 2 weeks of acute stroke is able to predict the degree of functional dependency at 3 and 6 months (Studenski *et al.*, 2001). It is still not proven that modern models of predicting recovery are more reliable compared to informal judgment by experienced clinicians.

Risk of recurrent stroke is estimated at 14% in the first year, highest for those suffering POCI or PACI (Bamford *et al.*, 1991). Conversely, patients with LACI are at low risk of recurrent stroke, but are likely to develop serious cardiovascular events (Bamford *et al.*, 1991).

CONCLUSION

Acute stroke is a medical emergency and requires rapid assessment to confirm diagnosis, and frequent monitoring of physiological variables in order to detect and subsequently treat complications early. Close liaison between members

Table 7 Case fatality and functional status at 1 year poststroke for the 543 patients recruited by the Oxfordshire Community Stroke project. Extracted from the OCSP; (Bamford *et al.*, 1991)

	Stroke classification			
	LACI (%)	PACI (%)	TACI (%)	POCI (%)
1 year dead	11	16	60	19
1 year functional independence	60	55	4	62
1 year functional dependence	28	29	36	19

of the multidisciplinary team enables effective prevention of aspiration, attention to nutrition, and early mobilization. Patients suffering acute stroke should be admitted to a stroke unit, and in this enriched environment dedicated and specialist staff pay particular attention to the many aspects of patient care.

KEY POINTS

- Stroke is an important cause of death and disability in the older population.
- Determination of the subtype of acute stroke enables prediction of long-term prognosis.
- Early brain imaging is required to distinguish infarction from hemorrhage.
- Administration of aspirin therapy within 48 hours following ischemic stroke improves outcome.
- Early mobilization, attention to nutrition and prevention of complications of acute stroke is fundamental to good management.
- Stroke Unit care saves lives and reduces disability.

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Secondary Stroke

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RISK OF RECURRENCE

Nearly one-third of strokes are recurrent events. The risk of recurrent stroke is greatest soon after the initial event and subsequently declines with time, while the risk of other cardiovascular events, for example, myocardial infarction increases with time. One-year stroke survivors have a 10% annual mortality rate which is predominantly due to cardiovascular disease rather than stroke and is approximately double that of those of similar age who have not had a stroke (Hankey *et al.*, 2000).

Secondary prevention therefore aims to reduce the risk of not only recurrent stroke but also ischemic heart disease and vascular death (Figure 1). Intermittent claudication (Hazard ratio (HR) 1.9 95% Confidence Intervals (CI) 1.2–2.9), urinary incontinence (HR 2.0 95% CI 1.3–3.0), previous transient ischemic attack (TIA) (HR 2.4 95% CI 1.4–4.1) and prestroke disability (HR 2.0 95% CI 1.2–3.2) are independent predictors of long-term mortality among stroke survivors (Hankey *et al.*, 2000).

RISK OF STROKE FOLLOWING TIA

Although most symptoms and signs resolve within an hour of onset, a TIA is a warning sign of increased stroke risk which needs to be taken seriously. The risk of stroke is greatest within the first few days of onset of symptoms: 8% (95% CI 2.3–13.7%) at 7 days; 11.5% (95% CI 4.8–18.2%) at 1 month and 17. 3% (95% CI 9.3–25.3%) at 3 months (Coull *et al.*, 2004; Figure 2).

One study reported a 5.3% risk of stroke within 2 days (Johnston *et al.*, 2000). Those who were aged over 60 years, diabetic, had symptoms lasting longer than 10 minutes, or who had weakness and/or speech impairment during the episode were at greatest risk (Johnston *et al.*, 2000). The 90-day stroke risk for patients who had all of these characteristics was 34%. Other factors which are associated with a significantly increased risk of stroke following TIA are frequent episodes, cortical rather than ocular TIAs, ulcerated plaque, and severe carotid stenosis. It is therefore important that patients with TIA are seen, diagnosed, investigated, and treated urgently to optimize secondary prevention. Guidelines highlight the need for rapid access TIA clinics (Royal College of Physicians, 2004).

RECURRENT ISCHEMIC STROKE

Neurological deterioration within the same vascular territory as the initial stroke is not always due to recurrence. Initial deterioration may be due to cerebral edema or hemorrhagic transformation of an infarct. Infection, metabolic disturbance, or other intercurrent illness can cause worsening of neurological signs and deterioration in functional abilities that can wrongly be attributed to recurrent stroke. Treatable nonneurological causes of deterioration, for example, chest or urinary tract infection should be sought especially when there is no clear history of sudden onset of worsening of symptoms. The 90-day recurrence rate following ischemic stroke is 15.1% (95% CI 12.3–17.9) (Coull and Rothwell, 2004). Recurrence rates vary according to stroke subtype: partial anterior circulation infarction (PACI) 22.9% (95% CI 17.5–28.2); posterior circulation infarction (POCI) 19.5% (95% CI 13.0–25.9); lacunar infarction (LACI) 5.4% (95% CI 1.5–9.3); total anterior circulation infarction (TACI) 3.9% (0.1–7.6) (Coull and Rothwell, 2004). These differences relate to the etiology of the stroke subtype. Patients with a PACI are more likely to have carotid stenosis which is associated with a higher recurrence rate. POCIs are associated with large vessel atherosclerosis. Recurrent events have higher levels of death and disability than first stroke.

RECURRENT INTRACEREBRAL HEMORRHAGE

Between 10 and 20% of strokes are due to primary intracerebral hemorrhage whose key risk factors are age, male

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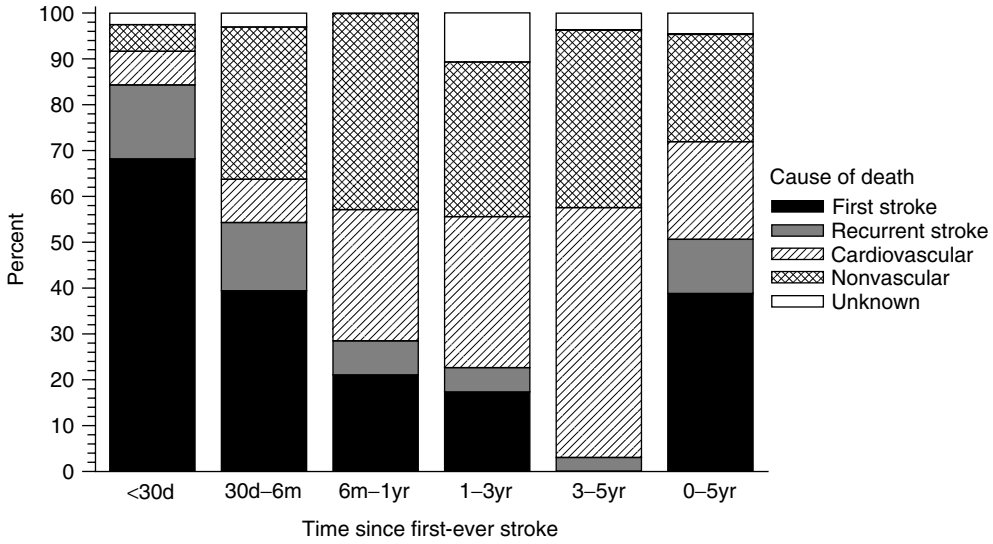

Figure 1 Histogram showing the proportion of patients dying from different causes during different time intervals from the onset of their first-ever stroke (Reprinted from Hankey GJ *et al.*, Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study, *Stroke* 2000; **31**(9): 2080–2086, with permission from Lippincott Williams & Wilkins)

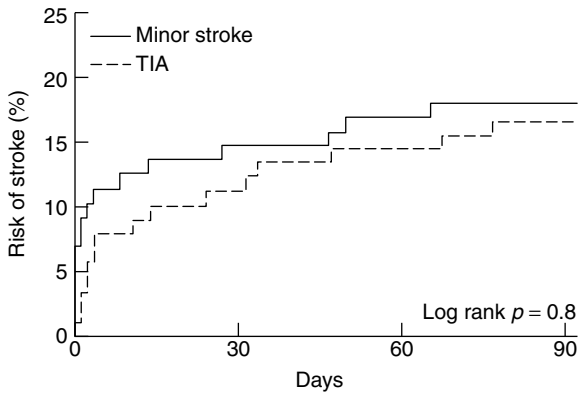

Figure 2 Cumulative risk of stroke after a transient ischemic attack (TIA) or minor stroke (Reprinted from Coull AJ *et al.*, Population based study of early risk of stroke after transient ischemic attack or minor stroke: implications for public education and organisation of services. *BMJ* 2004; **328**: 326–328, with permission from the BMJ Publishing Group)

sex, hypertension, and high alcohol intake (Ariesen *et al.*, 2003). There is no reliable evidence to indicate that the risk of recurrence of hemorrhagic stroke is different from ischemic stroke (Dennis, 2003). Blood pressure lowering reduces the risk of recurrence (PROGRESS Collaborative Group, 2001). It should not be assumed that recurrent stroke is always due to the same etiology as the initial event and a CT or MRI head scan is necessary to distinguish cerebral infarction from hemorrhage following a further event. A systematic review of recurrent stroke after primary intracerebral hemorrhage found that 59% were hemorrhagic, 26% were ischemic and 15% were of unknown etiology (Bailey *et al.*, 2001). As there are a number of conditions which may cause intracerebral hemorrhage, for example, hypertension, bleeding disorder, anticoagulants, amyloid angiopathy, aneurysm, and arteriovenous malformation, the risk of recurrence is likely to relate to the etiology of the initial hemorrhage. Cerebral hemorrhage associated with amyloid angiopathy should be considered following a recurrent cerebral hemorrhage affecting different parts of the brain.

INTERVENTIONS TO REDUCE VASCULAR RISK FOLLOWING TIA OR ISCHEMIC STROKE (FIGURE 3)

Until fairly recently, aspirin was the only treatment which had been shown to be effective for secondary prevention. There are now a number of high-quality randomized controlled trials that have demonstrated the effectiveness of other antiplatelet agents, for example, dipyramidole MR and clopidogrel; lowering of blood pressure; lowering of cholesterol; warfarin for those in atrial fibrillation; and carotid endarterectomy for severe carotid stenosis (Warlow *et al.*, 2003).

There is an ongoing debate about the significance and clinical implications of the results of a number of recently published trials. Although the benefits of addressing individual risk factors have been clearly demonstrated, it is not yet known how effective a combined approach to the management of multiple risk factor will be, following a stroke or TIA. This is a particular issue for older people in whom side effects and complications of polypharmacy are more likely, for example, falls. Similarly, the optimal timing for starting a number of these treatments, for example, blood pressure and cholesterol lowering following stroke or TIA is unclear.

Patients should be involved in discussions about the nature of their stroke or TIA; the risk of recurrence; what can be done to reduce their risk of further events; and the pros

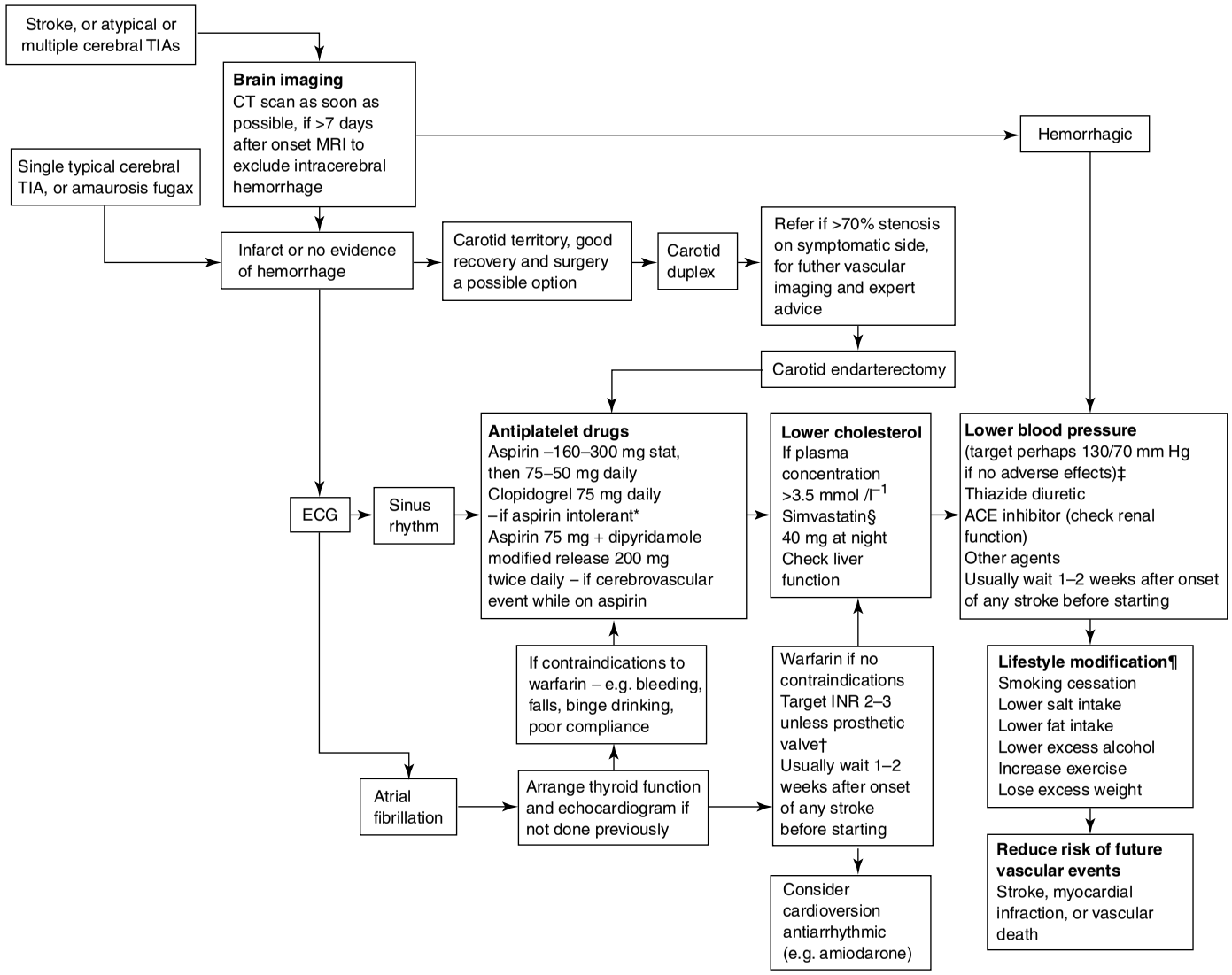

Figure 3 Guidelines for secondary prevention after stroke or transient ischemic attack (Reprinted with permission from Elsevier (*The Lancet*, 2003, **362**, 1211–24)). ACE, angiotensin converting enzyme; INR, international normalised ratio. Currently there is evidence to support combinations: *Aspirin and clopidogrel only in patients with unstable angina with electrocardiographic or enzyme changes; †Warfarin and aspirin in patients with prosthetic heart valves; ‡Take care in lowering blood pressure if the patient has postural hypotension, abnormal renal function, or severe carotid stenosis; §Consider pravastatin for use in combination with warfarin or digoxin; ¶No clear randomised evidence, but most believe this strategy to be helpful

and cons of different treatment options to enable them to make an informed choice about their treatment (Thomson, 2002). Patients should be given the opportunity to decide what is right for them, for example, some patients do not want to risk the bleeding complications of warfarin regardless of potential benefits. Written information, videos, decision analysis, and computer-aided risk communication may be helpful in enabling patients reach their decision. As optimal secondary prevention may involve a patient taking a number of new medications, for example, one or more antiplatelet drugs, a statin, or one or more antihypertensive agents, a staged approach to starting new treatments should be considered so that should side effects occur, they can be correctly attributed to.

ANTIPLATELET THERAPY

Antiplatelet agents, for example, aspirin, dipyramidole, and clopidogrel are modestly effective in secondary prevention following ischemic stroke or TIA. All inhibit platelet aggregation but differ in their mechanism of action. Secondary prevention with antiplatelet agents results in a reduction of 36 serious vascular events per 1000 patients treated (Antithrombotic Trialists' Collaboration, 2002). In clinical trials, the excess risk of major extracranial bleeding associated with antiplatelet treatment was 5 per 1000. This figure may be higher in clinical practice, especially for older people. When commencing any antiplatelet agent, medication should be reviewed and where possible, nonsteriodal anti-inflammatory drugs should be discontinued or changed to an alternative one, for example, paracetamol to reduce the risk of gastrointestinal hemorrhage.

ASPIRIN

Aspirin inhibits platelet activity by blocking cyclo-oxygenase. Aspirin reduces the risk of stroke by 20% following TIA or ischemic stroke. A daily dose of 160–300 mg should be given once intracerebral hemorrhage has been excluded. This is the recommended dose for treatment of acute ischemic stroke which is usually reduced to a maintenance dose of 75–150 mg for secondary prevention within 2 weeks of the acute event. In general, aspirin doses above 75 mg are unlikely to be more effective for secondary prevention and are associated with an increased risk of gastrointestinal bleeding. If a patient develops dyspepsia while taking aspirin, the following could be considered prior to considering an alternative drug: reduce dose if taking more that 75 mg per day; take aspirin with food; use enteric-coated preparation; use aspirin in combination with an antacid or acid suppressant. For patients with a history of aspirin-induced ulcer bleeding (whose ulcer has healed) aspirin plus omeprazole is associated with a lower incidence of recurrent bleeding than clopidogrel (0.7% vs 8.8% $p = 0.001$) (Chan *et al.*, 2005).

DIPYRAMIDOLE

Dipyramidole reduces platelet aggregation by inhibiting adenosine reuptake and phosphodiesterase. It is also a vasodilator and so should be used with caution in patients with severe coronary artery disease or recent myocardial infarction. Unlike aspirin and clopidogrel, dipyramidole has not been shown to reduce vascular risk for those with ischemic heart disease. The place of dipyramidole in the secondary prevention of stroke is controversial. Until publication of the European Stroke Prevention Study-2 (ESPS-2), dipyramidole was believed to be ineffective in secondary prevention following stroke (Diener *et al.*, 1996). This study had four treatment groups: aspirin 25 mg bd; dipyramidole MR 200 mg bd; aspirin 25 mg bd plus dipyramidole MR 200 mg bd; and placebo. Previous studies had not used the modified release (MR) preparation of dipyramidole. ESPS-2 found that dipyramidole was as effective as aspirin for secondary prevention in terms of reduction of stroke (12.8% dipyramidole versus 12.5% aspirin). The combination of aspirin and dipyramidole was significantly more effective than either drug used alone for patients of all ages (Sivenius *et al.*, 1999). For combination therapy, stroke occurred in 9.5% giving a relative risk (RR) of 0.76 (95% CI 0.63–0.93) when compared to aspirin. There was no difference in mortality or levels of myocardial infarction between treatment groups. Bleeding rates were similar for the combination of aspirin and dipyramidole (8.7%) and aspirin alone (8.2%), but were significantly less for those who were treated with dipyramidole alone (4.7%). One-third of patients were unable to take dipyramidole because of its causing a headache and patients should be warned of this side effect. A meta-analysis of individual patient data from randomized controlled trials found that the combination of aspirin plus dipyramidole was superior to either aspirin or dipyramidole alone in reducing the composite outcome of nonfatal stroke, nonfatal myocardial infarction or vascular death (Leonardi-Bee *et al.*, 2005).

CLOPIDOGREL

Clopidogrel is a theinopyridine derivative which selectively and irreversibly inhibits the binding of adenosine phosphate (ADP) to its platelet receptor. Clopidogrel can be prescribed to patients who are allergic to aspirin. Contraindications include active bleeding and severe liver impairment. For patients taking clopidogrel, the risk of bleeding is increased after trauma or surgery and it is currently recommended that clopidogrel should be stopped 7 days before elective surgery/dentistry and avoided for the first few days after myocardial infarction and 7 days after ischemic stroke. Patients should be advised that it may take longer than usual to stop bleeding and asked to report unusual bleeding to their doctor. The CAPRIE Study (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) which involved patients with ischemic stroke, myocardial

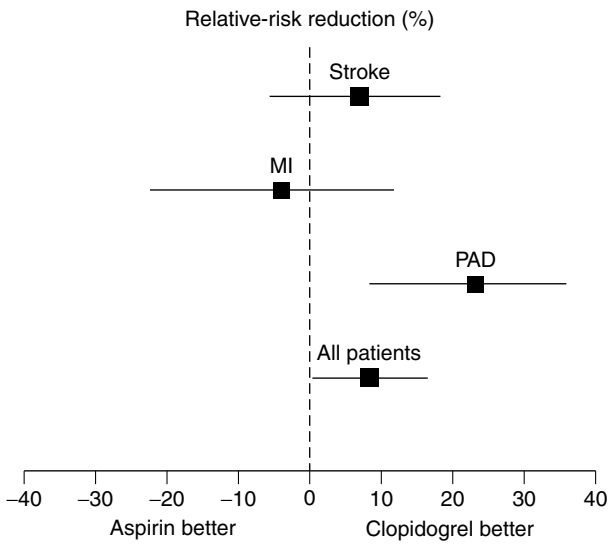

Figure 4 CAPRIE Study: RR reduction and 95% CI by disease subgroup MI : myocardial infarction; PAD; peripheral arterial disease (Reprinted with permission from Elsevier (*The Lancet*, 1996, **348**: 11329–1339))

infarction, and peripheral vascular disease found that rates of ischemic stroke, myocardial infarction, or death were less in those treated with clopidogrel 75 mg od (5.3%) than with aspirin (5.8%) (CAPRIE Steering Committee, 1996; Figure 4). Although the RR reduction was statistically significant (8.7% (95% CI 0.3–16.5)) the absolute risk reduction was small −0.5%. We would need to treat 200 people with clopidogrel rather than aspirin to prevent one of these events per year and clopidogrel is considerably more expensive than aspirin (Hankey *et al.*, 1999). A subgroup analysis according to disease subgroup raised further issues. Surprisingly, the treatment effect was different for those with peripheral vascular disease, myocardial infarction, and stroke. Statistically significant benefits were seen for those with peripheral arterial disease who received clopidogrel but not for those with myocardial infarction or stroke.

This result should be treated with caution as the analysis was not prespecified in the protocol and the study did not have adequate statistical power to consider each subgroup separately. A further CAPRIE analysis which looked at patients with a history of prior ischemic stroke and/or myocardial infarction found that the event rate (ischemic stroke, myocardial infarction, vascular death) was 8.8% for those treated with clopidogrel and 10.2% for those treated with aspirin ($p = 0.045$) (Ringleb *et al.*, 2004). Rates of gastrointestinal hemorrhage were significantly lower in the clopidogrel group (2.0%) than the aspirin group (2.7%) ($p < 0.05$). Levels of indigestion, nausea, and vomiting were also less with clopidogrel (15.0% vs 17.6% ($p < 0.05$)).

The combination of aspirin and clopidogrel has been shown to be useful in the treatment of unstable angina and following percutaneous coronary intervention. However, current evidence suggests that aspirin and clopidogrel should not be used together following TIA and ischemic stroke. The MATCH study (Management of Atherothrombosis with Clopidogrel in High-risk patients) compared the effects of aspirin plus clopidogrel with clopidogrel alone in ischemic stroke, myocardial infarction, vascular death, or rehospitalization for acute ischemia in high-risk patients with TIA or ischemic stroke (Diener *et al.*, 2004). Although event rates were similar for both treatment groups (aspirin and clopidogrel 16%, clopidogrel 17% ($p = 0.26$)) life threatening bleeds were significantly higher in those who received combination therapy (aspirin and clopidogrel 3%, clopidogrel 1% ($p < 0.001$)). Further information will be available from the ongoing CHARISMA trial which is comparing clopidogrel plus aspirin with aspirin.

ATRIAL FIBRILLATION

Up to 24% of patients with ischemic stroke have atrial fibrillation and recurrence rates are higher in these patients compared to those in sinus rhythm (Wolf *et al.*, 1991). Those with atrial fibrillation due to valvular heart disease have the highest stroke risk. Stroke associated with atrial fibrillation is usually caused by an embolism from a clot in the left atrium but is due to atherosclerosis in approximately one-third of cases. Risk of recurrence following stroke related to nonvalvular atrial fibrillation (NVAF) is 12% per annum, but rates are increased in patients who are aged over 75 years, hypertensive or diabetic, and those who have left ventricular dysfunction on echocardiogram (Cerebral Embolism Task Force, 2000).

Warfarin is much more effective than aspirin in preventing recurrent stroke in patients with NVAF (Figure 5). Warfarin inhibits vitamin K–dependent coagulation factors (factors II, VII, IX and X) and protein C and protein S in the liver. Although warfarin reduces the risk of recurrent stroke (odds ratio (OR) 0.36 95% CI 0.22–0.58) and vascular events (OR 0.55 95% CI 0.37–0.82), it is associated with increased risk of major bleeding (OR 4.32 95% 1.55–12.10) (Saxena and Koudstaal, 2004).

The benefits of prevention of further stroke need to be balanced against the risk of complications for individual patients, for example, risk of bleeding, history of falls, or cognitive impairment. As the risk of hemorrhagic conversion of an infarct is greatest within the first few weeks after stroke, it is generally recommended that anticoagulation should not commence until 1–2 weeks poststroke. The target INR for those with NVAF is 2.5 (range 2.0–3.0). Aspirin is an alternative for those who are unable to or do not wish to take warfarin but it is a less effective treatment. Compared to warfarin, aspirin was associated with 60 more recurrent strokes per year per 1000 patients treated (Koudstaal, 2000).

Direct thrombin inhibitors (DTI) for example, ximelagatran, which prevent the formation of fibrin and activation of other coagulation factors are currently being evaluated. Unlike warfarin, DTIs are prescribed as a fixed dose and do not need regular blood tests or monitoring. Two trials, SPORTIF III and SPORTIF V (Stroke prevention using oral

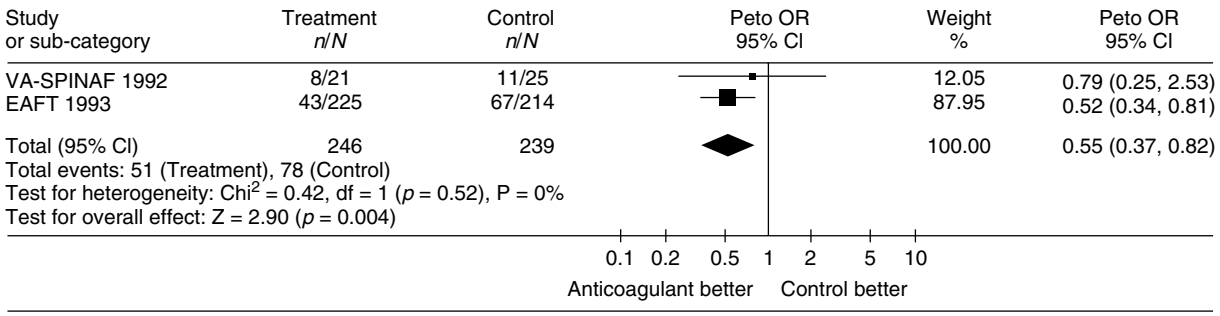

Figure 5 Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attack (Reprinted from Saxena R, Koudstall, PJ. Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attack. *Stroke* 2004; **35**: 1782–1783, with permission from Lippincott Williams & Wilkins)

thrombin inhibition in atrial fibrillation) found that ximelagatran was as effective as warfarin in preventing stroke and systemic emboli in patients with atrial fibrillation (Executive Steering Committee on behalf of the SPORTIF III investigators, 2003). In addition, bleeding rates were significantly lower with ximelagatran. However, ximelagatran was associated with raised levels of liver alanine aminotransaminase (ALT) which usually resolved spontaneously or after stopping the drug.

WARFARIN FOR PATIENTS WHO ARE IN SINUS RHYTHM

Warfarin is not recommended for routine use in secondary prevention following stroke for patients who are in sinus rhythm as the risk of bleeding outweighs any benefits (Algra *et al.*, 2003). Anticoagulation can be used for secondary prevention following cardiac embolism, for example, mural thrombus and for crescendo TIAs. If there is no ongoing structural problem, for example, left ventricular aneurysm, then anticoagulation should probably be for a fixed period, for example, 3–6 months when warfarin should be replaced with an antiplatelet drug.

BLOOD PRESSURE

Hypertension is the most important modifiable risk factor for the primary prevention of stroke (Collins *et al.*, 1990). The benefits of blood pressure lowering for secondary prevention are substantial following both ischemic and hemorrhagic stroke (PROGRESS Collaborative Group, 2001; Figure 6) Rashid *et al.*, 2003). Long-term lowering of blood pressure significantly reduces the risk of stroke for patients with raised and normal blood pressure. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) recruited patients who had suffered a stroke in the previous 2 weeks to 5 years. The intervention group received perindopril 4 mg o.d. with or without indapamide 2.5 mg o.d, the control group received placebo. The average blood pressure reduction with combination therapy was 12/5 mmHg and this was associated with a RR reduction of stroke of 43% (95% CI 30–54) and major vascular events of 40% (95% CI 29–49%).

This benefit was seen for both patients who were initially hypertensive and those who were normotensive. Treatment with perindopril alone resulted in an average reduction in blood pressure of 5/3 mm Hg, which was not associated with a reduction of risk of further stroke or vascular events. A similar reduction in recurrence rate for both hypertensive and nonhypertensive patients was seen in the HOPE trial which evaluated another angiotensin converting enzyme inhibitor, ramipril (Heart Outcomes Prevention Evaluation Study Investigators, 2000). Whether the reduction in stroke recurrence and major vascular events seen in these studies is due to the particular drug(s), a class effect of the drugs, or simply because of blood pressure lowering is unclear. (MacMahon *et al.*, 2004; Anderson, 2004; Bath, 2003; Davis and Donnan, 2003; Wennberg and Zimmerman, 2004) However, unlike some other antihypertensive drugs, ACE inhibitors improve endothelial dysfunction, decrease thrombotic activity, and do not alter cerebral autoregulation (Muir, 2004). Current evidence supports an ACE inhibitor plus a diuretic as first-line treatment with careful monitoring to identify side effects, for example, cough or renal failure. If blood pressure remains high, that is, over 140/85 mmHg (or 130/80 mmHg for diabetics), then other antihypertensive medication should also be considered. The effect of blood pressure lowering within the acute phase after stroke is unknown and trials are ongoing. Blood pressure lowering for secondary prevention should probably start 1–2 weeks after the acute event. Rapid reduction in blood pressure should be avoided as this may result in side effects including ischemic stroke due to cerebral hypoperfusion. Older patients are particularly prone to side effects which include electrolyte imbalance, falls, and postural hypotension, and the risks and benefits of aggressive blood pressure lowering needs to be carefully considered for these individuals.

CHOLESTEROL

Unlike ischemic heart disease, cholesterol has not been shown to be a major risk factor for stroke. However,

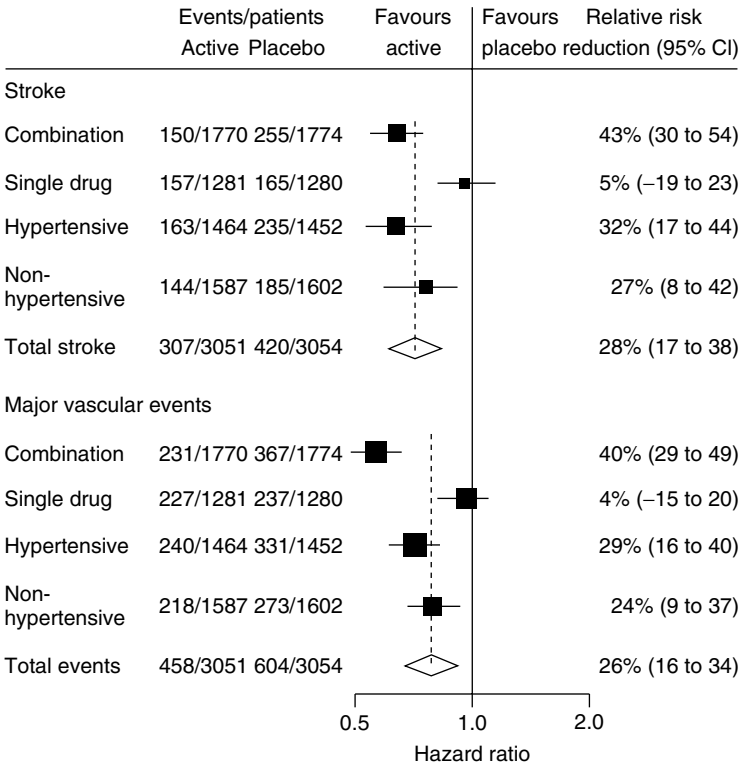

Figure 6 PROGRESS: Effects of study treatment on stroke and major vascular events in subgroups of patients (Reprinted with permission from Elsevier (*The Lancet*, 2001, **358**, 1033–1041))

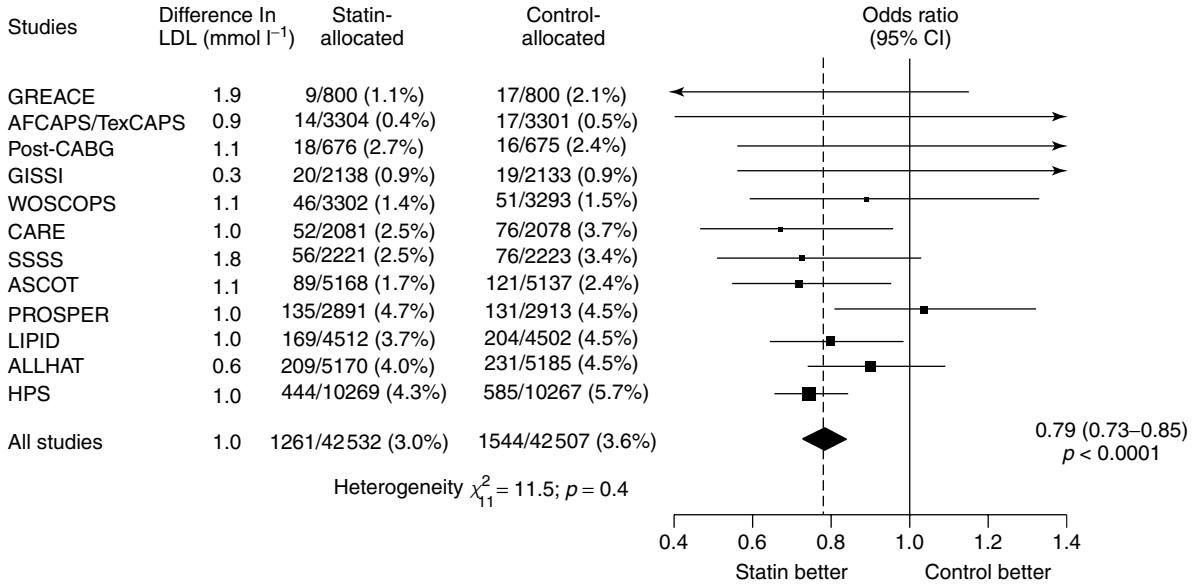

Figure 7 Meta-analysis of effects of statin allocation on stroke in major randomized trials (Reprinted with permission from Elsevier (*The Lancet*, 2004, **363**, 757–767))

cholesterol lowering is associated with better outcomes following stroke, and statin therapy has been shown to reduce the progression of carotid atherosclerosis (MacMahon *et al.*, 1998; Heart Protection Study Collaborative Group, 2002; Heart Protection Study Collaborative Group, 2004; Figure 7). Statins are 3-hydroxy-3-methylglutaryl coenzyme A (MHG-CoA) reductase inhibitors which apart from lowering cholesterol modify endothelial function, inflammatory responses, and thrombus formation. There are important benefits of cholesterol lowering following stroke and TIA regardless

of whether or not the patient is known to have coronary heart disease. A reduction of 1.0 mmol l^{-1} (39 mg dl^{-1}) LDL cholesterol is associated with a 21% (95% CI 15–27) reduction in the incidence of stroke.

The Heart Protection Study found that a daily dose of 40 mg simvastatin reduced the RR of nonfatal myocardial infarction, coronary death, stroke, and revascularization by 24% (95% CI 19–28) in patients at high risk of occlusive vascular disease (nondisabling stroke, TIA, ischemic heart disease, diabetes, hypertension) (Heart Protection Study Collaborative Group, 2002; Figure 8). Patients with disabling stroke were excluded, as were those who had had a TIA or stroke within the previous 6 months. The event rate was 19.8% in the simvastatin group compared with 25.2% in the placebo group, giving an absolute reduction in event rate of 5.4% ($p < 0.0001$). The absolute risk reduction for fatal and nonfatal stroke was 1.4% (4.3% simvastatin and 5.7% placebo). This benefit was largely due to a reduction in the incidence of ischemic stroke but the frequency of TIA, carotid endarterectomy, and carotid angioplasty were also reduced. It had been suggested that lipid lowering may result in higher rates of hemorrhagic stroke but this was not the case. Similar benefits were seen for older and younger people. Patients with nonfasting blood total cholesterol levels of at least 3.5 mmol l^{-1} (135 mg dl^{-1}) were recruited and there was no lower threshold for the beneficial effect of simvastatin. As with blood pressure lowering, similar benefits are seen for treating patients with "normal" as well as raised cholesterol levels. The treatment effects of simvastatin for patients with and without cerebrovascular disease have been compared in a secondary analysis (Heart Protection Study Collaborative Group, 2004).

The results of a subgroup analysis that was not prespecified should always be treated with caution and such results usually provide more questions than answers. This was the case for the Heart Protection Study (Figure 9). Although rates of reduction of coronary artery disease and revascularization with simvastatin were similar for both those with and without cerebrovascular disease, those who were randomized to simvastatin following stroke or TIA did not have a reduced risk of stroke compared to the placebo (RR 0.98 95% CI 0.79–1.22).

Statins can cause myositis and patients should be advised to report unexplained muscle pains. Liver function tests should be monitored and statins should be used with caution in patients with a history of liver disease or a high alcohol

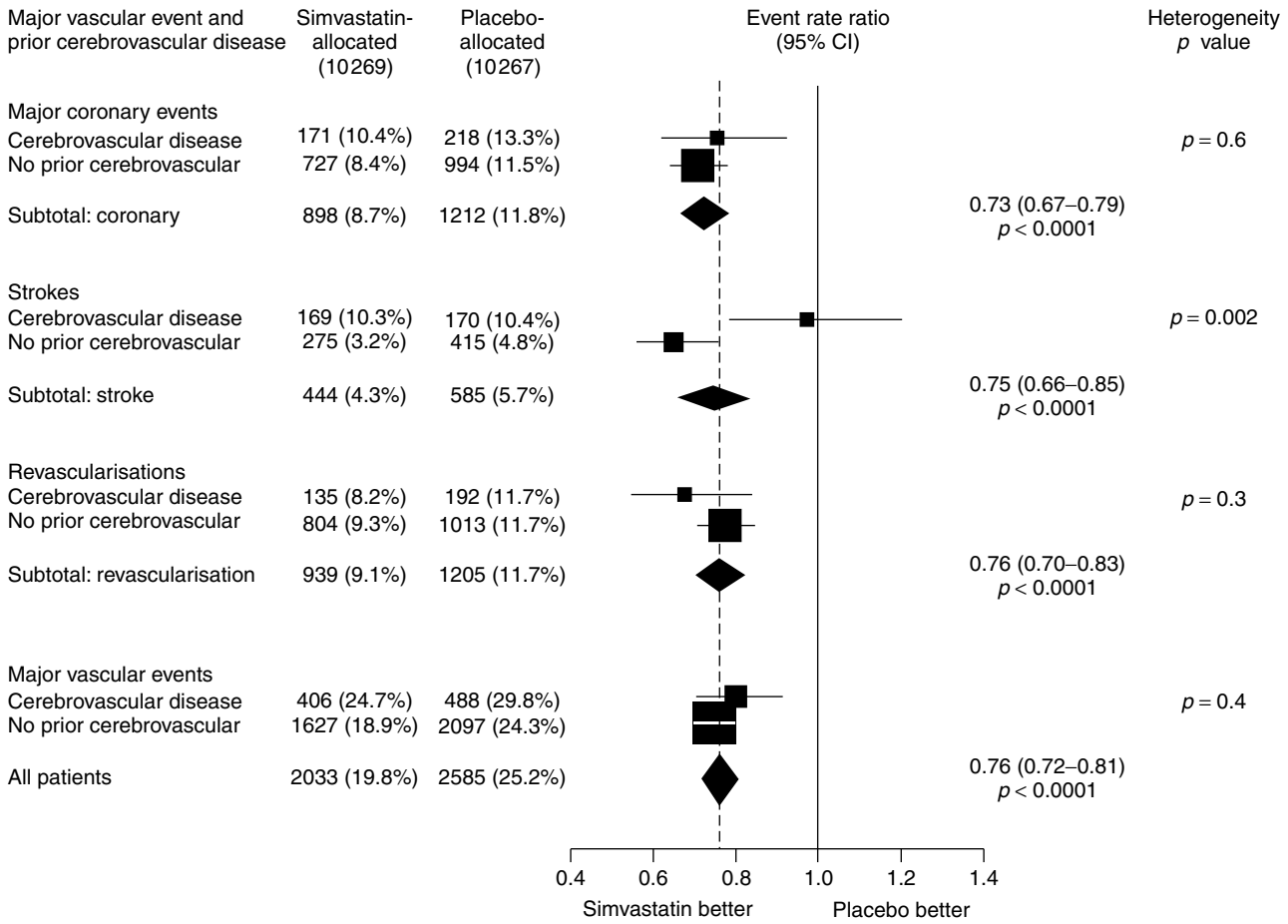

Figure 8 Heart Protection Study: Effects of simvastatin allocation on first major coronary event, stroke, or revascularization in participants subdivided by prior cerebrovascular disease (Reprinted with permission from Elsevier (*The Lancet*, 2004, **363**, 757–767))

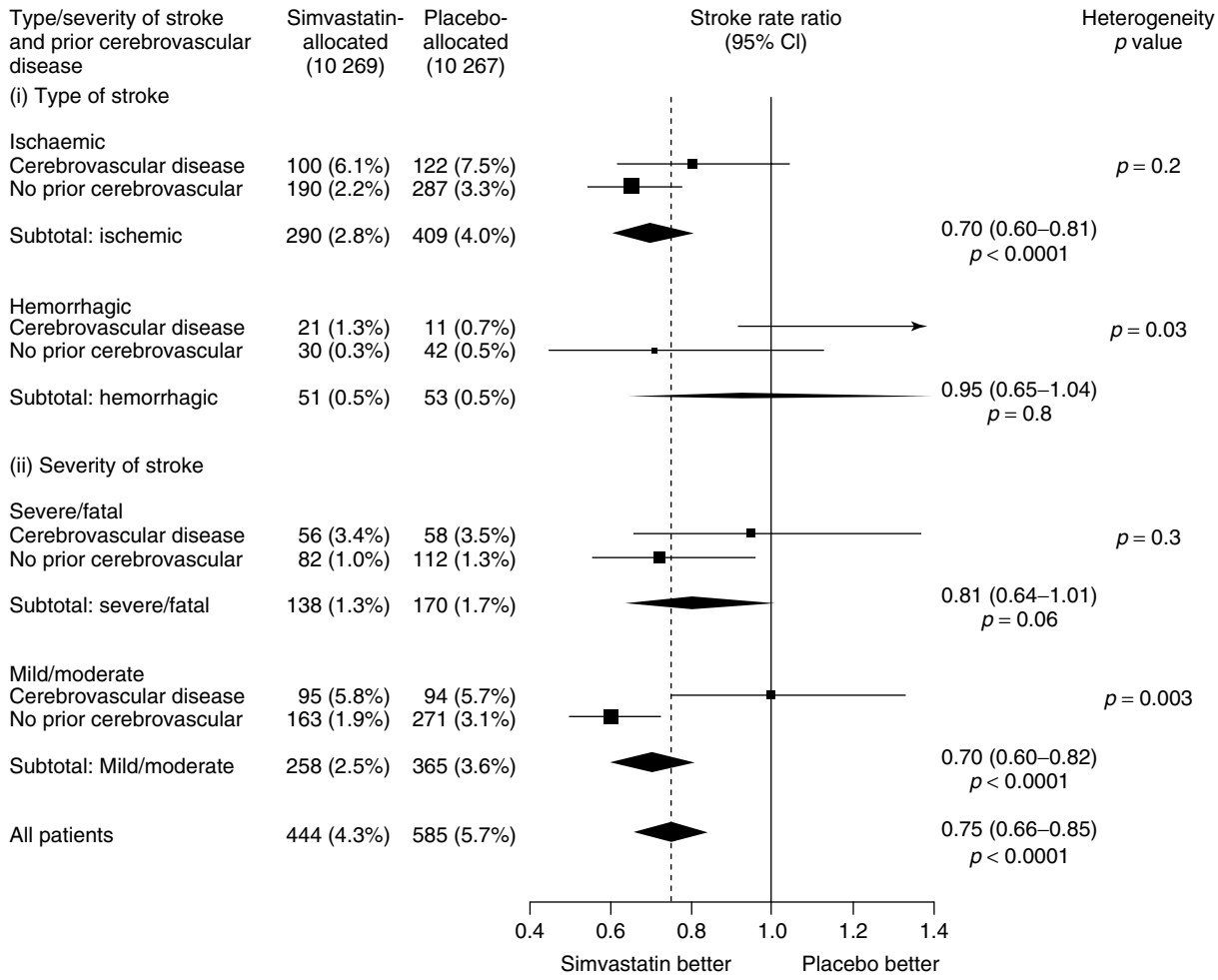

Figure 9 Heart Protection Study: Effects of simvastatin allocation on type and severity of stroke in participants subdivided by prior cerebrovascular disease (Reprinted with permission from Elsevier (*The Lancet*, 2004, **363**, 757–767))

intake. Simvastatin enhances the effect of warfarin, so an alternative, for example, pravastatin should be considered for patients who are already taking anticoagulants.

Further research is needed to establish the efficacy of cholesterol lowering during the first few weeks after stroke when the risk of recurrence is greatest (Coull, 2004). The effect of lipid lowering for patients with a hemorrhagic stroke remains unclear.

DIABETES

Cohort studies have shown that the RR of stroke in patients with diabetes is 1.5–3.0 (Sacco, 1997). Patients with diabetes have an increased prevalence of hypertension, obesity, and abnormal blood lipids, all of which are associated with an increased risk of stroke. There is a high prevalence of undiagnosed diabetes mellitus, particularly in older people (Gray *et al.*, 2004). Intensive blood glucose control substantially reduces the risk of microvascular complications in type 2 diabetes but not macrovascular disease (UK Prospective Diabetes Study (UKPDS) Group, 1998). Aggressive multiple risk factor modification, especially control of blood pressure and lipids are of paramount importance in reducing the risk of stroke in these patients (Gaede *et al.*, 2003). Stroke patients with diabetes have significantly worse outcomes in terms of both death and disability and are at a higher risk of recurrence (Olson *et al.*, 1990; Megherbi *et al.*, 2003).

HOMOCYSTEINE

Homocysteine is derived from dietary methoinine which is an amino acid found predominantly in animal protein (Hankey and Eikelboom, 1999). Although there is epidemiological evidence of a dose response relationship between increasing levels of plasma homocysteine and cardiovascular risk, it is unclear if reduction of plasma homocysteine leads to a reduced risk of atherothrombotic disease (The Homocysteine Studies Collaboration, 2002; Hankey and Eikelboom, 2004; Figure 10).

Current evidence does not support the routine use of folic acid and B vitamins (which are cofactors for the

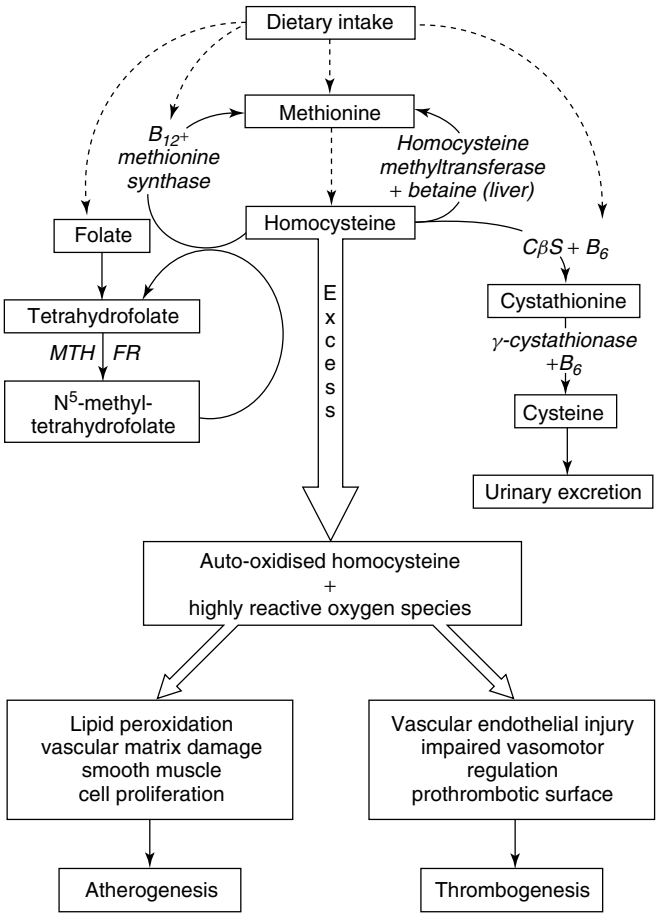

Figure 10 Homocysteine metabolism and possible mechanism of atherothrombotic disease (Reprinted with permission from Elsevier (*The Lancet*, 1999, **354**, 407–415))

enzymes which metabolize homocysteine) to reduce plasma homocysteine in patients with stroke or TIA. The Vitamins in Stroke Prevention Study (VISP) randomized patients with recent ischemic stroke to receive either high- or low-dose vitamin supplements (folic acid, vitamin B12, vitamin B6 and riboflavin) (Spence *et al.*, 2001). VISP found that reduction of plasma homocysteine was not associated with reduction of recurrent stroke, coronary events, or death (Toole *et al.*, 2004). Further data will be available upon completion of the VITAmins TO Prevent Stroke (VITATOPS) trial, which is a randomized controlled trial looking at the effect of folate and vitamin B supplements (vitamin B12 and vitamin B6) or placebo upon stroke, myocardial infraction, or vascular death in patients with recent TIA and stroke (The Vitatops Trials Study Group, 2002).

ANTIOXIDANT VITAMINS

Diets that are high in fruits and vegetables are associated with lower rates of cardiovascular disease. Although antioxidants slow the rate of progression of atherosclerosis as shown in animal studies, supplementation of antioxidant vitamins (vitamin E, vitamin C and β-carotene) has not been shown to be effective in reducing the risk of recurrence or cardiovascular events following stroke (Heart Protection Study Collaborative Group, 2002).

CAROTID ENDARTERECTOMY

Carotid endarterectomy is a surgical procedure to remove atheromatous material from within the common or internal carotid artery. Trials from Europe and North America have demonstrated the benefit of this operation for patients with a carotid territory TIA or nondisabling stroke who have a severe (70–99%) symptomatic ipsilateral carotid stenosis and to a lesser extent, moderate (50–69%) stenosis (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; European Carotid Surgery Trialists' Collaborative Group, 1991). These trials used different methods to measure carotid stenosis but measurements can be converted with a simple formula (Rothwell *et al.*, 1994). Carotid endarterectomy reduces the risk of death or disabling stroke by 48% (95% CI 27–73%) for patients with a severe stenosis which has been symptomatic within the previous 4–6 months (Cina *et al.*, 1999). Beyond this time period, the stenosis is regarded as asymptomatic. For patients with carotid occlusion or mild carotid stenosis, the risks of surgery outweigh the benefits. The benefits of carotid endarterectomy are greater for older than for younger people. For those aged 75 years and older with a 50% or higher stenosis, the number needed to treat (NNT) to prevent one ipsilateral stroke in 5 years is 5 compared to 18 for those younger than 65 years (Rothwell *et al.*, 2004). Surgery should be undertaken as soon as possible from onset of symptoms to achieve maximum benefit. The NNT to prevent one ipsilateral stroke in 5 years is 5 if carotid endarterectomy is undertaken within 2 weeks of symptoms compared to 125 if the operation is undertaken after 12 weeks. In clinical practice, only about 4% of patients with carotid territory TIA have a relevant severe stenosis.

Carotid Doppler ultrasound is the first-line investigation to identify carotid stenosis, but because occasionally there may be false-positive results, most clinicians require a confirmation by a further investigation, for example, repeat Doppler by a different operator or MR angiogram. In deciding whether or not to undergo carotid endarterectomy, patients need to consider the potential long-term benefits of stroke prevention versus the early risks of surgery. The risk of perioperative stroke is 5–7%, but local complication rates should be discussed with prospective patients. Carotid endarterectomy can also be performed under local anesthetic, hence avoiding the risk associated with general anesthetic. This approach is being evaluated by a large randomized trial general versus local anaesthetic for carotid surgery (GALA) which is comparing the outcomes of local versus general anesthetic for carotid endarterectomy (Rerkasem *et al.*, 2005).

CAROTID ANGIOPLASTY AND STENTING

Carotid angioplasty and stenting can be performed percutaneously under local anesthetic and therefore can potentially avoid some of the complications associated with surgery and general anesthetic, for example, neck wound infection and dysesthesia, cranial nerve palsies, and myocardial infarction (CAVATAS, 2001). Stenting can also be used for some lesions which are not suitable for surgery. Trials comparing carotid endarterectomy with carotid angioplasty and stenting suggest that they have similar short- and long-term outcomes (Coward *et al.*, 2004). Large randomized studies are ongoing in the United States (CREST), Europe (ICSS), France (EVA-3S), Germany, and Austria (SPACE).

PATENT FORAMEN OVALE AND ATRIAL SEPTAL ANEURYSM

Patent foramen ovale (PFO) and/or atrial septal aneurysm (ASA) have been shown to be associated with cryptogenic stroke in older people in some studies (DiTullio *et al.*, 1992; De Belder *et al.*, 1992) but not in others (Jones *et al.*, 1994). However, patients aged over 65 with a PFO-related stroke have a recurrence rate of 31.0% compared to 11.3% for other cryptogenic strokes (HR 3.32 (95% CI 1.22−8.89)) (Homma *et al.*, 2004). This may not be a true reflection of the recurrence rate, as a significant proportion of patients were treated with warfarin −38% of patients with and 42% without a PFO (Homma *et al.*, 2004). Interestingly, younger patients with cryptogenic stroke PFO were not at increased risk of stroke recurrence (Homma *et al.*, 2004). Older people may be at higher risk of paradoxical embolism through a PFO because both right ventricular pressure and the prevalence of venous thromboembolism increase with age (Brendan *et al.*, 2001; Schina *et al.*, 1993). Treatment options include antiplatelet therapy, anticoagulation, and closure of PFO by interventional radiology or surgical techniques. In terms of available procedures for closure of PFO, percutaneous catheter closure is the preferred option. None of these techniques have been evaluated in older people and the optimal treatment of PFO and/or ASA in younger people is controversial. Randomized controlled trials are ongoing and it is important that studies recruit significant numbers of older people who are at greatest risk.

LIFESTYLE

Risk of stroke recurrence is higher among smokers than nonsmokers (Burn *et al.*, 1994). Despite this, 22% of stroke survivors continue to smoke, even at one year after stroke (Redfern *et al.*, 2000). While in the general population, the risk of stroke falls to that of nonsmokers within 5 years of stopping smoking, it is unclear whether the same risk reduction applies to those who have had a stroke (Wannamethee *et al.*, 1995). Nicotine replacement therapy, intensive support, and bupropion have all been shown to increase smoking cessation rates (Raw *et al.*, 1999). Heavy alcohol intake is associated with stroke recurrence (Sacco *et al.*, 1994). Activity is reduced after stroke because of the neurological deficit, emotional and social barriers, and comorbidity, especially ischemic heart disease. Exercise programs have been shown to improve physiological parameters and risk factors following stroke but to date there are no randomized controlled trials to evaluate the effect of exercise programs on stroke recurrence.

IMPLEMENTATION

Despite clinical evidence and cost-effectiveness of interventions, national strategies, and guidelines for the primary and secondary prevention of stroke implementation remains poor in a number of areas (ACS/ADA/AHA Collaborative Writing Committee, 2004). This unfortunately is particularly true for older people who, despite having the most to gain from secondary prevention, are the least likely to receive it.

SUMMARY

The risk of stroke recurrence is greatest within the first few weeks of onset of symptoms. Modification of classical risk factors such as hypertension, cholesterol, diabetes, obesity, and smoking can significantly reduce the risk of stroke recurrence and other vascular events. In addition, lowering of "normal" blood pressure and cholesterol is beneficial. Antiplatelet agents reduce the risk of recurrence but are associated with an increased risk of gastrointestinal bleeding. Warfarin is the optimal treatment to prevent further stroke for patients in atrial fibrillation. Carotid endarterectomy is effective for carefully selected patients, particularly when undertaken early. The risks and benefits of these treatments need to be carefully considered in older people, particularly those with significant comorbidity. The pros and cons of treatment options should be discussed with patients to achieve maximum benefit.

KEY POINTS

- Nearly one-third of strokes are recurrent events.
- Antiplatelet agents, for example, aspirin, dipyramidole, and clopidogrel reduce the risk of recurrence following TIA and ischemic stroke.
- Warfarin is the optimum treatment for secondary prevention following ischemic stroke for patients in atrial fibrillation.

- Lowering of blood pressure and cholesterol should be considered following stroke for patients with normal as well as raised values.
- The benefits of carotid endarterectomy for carefully selected patients are greatest within the first few weeks following TIA and nondisabling stroke.

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Communication Disorders and Dysphagia

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COMMUNICATION

Effective communication allows an individual to convey successfully a message or meaning to another person, and for that meaning to be correctly interpreted. Communication is one of the most fundamental characteristics of higher cognitive functioning and is dependent upon symbolic encoding, either in sounds, script, or gesture. These complex acts are supported by virtually every aspect of brain function with the afferent sensory stimuli being processed through association regions, being integrated with stored memories and emotions along with immediate factors relating to attention, arousal, and motivation which can stimulate a verbal or gestural response governed by different environmental and behavioral conditioning.

In its simplest form, communication requires an individual to be able to receive a message from another, either auditorily or visually; to interpret this message and to generate an appropriate response which is encoded into sounds, gestures, or written letters in order to respond. Thus, the term "language" refers to a code used to represent and communicate ideas and feelings. Language may be verbal or nonverbal, for example, written words, sign language, gestures. But all modes are governed by rules shared within cultures. The expression of language verbally is speech which comprises sounds (phonology), written symbols (as in letters in writing) or agreed body movements for signs (e.g. sign language or gestures).

AGING AND COMMUNICATION

There is evidence that language is an inherent capacity and that the neural basis for language is not only a dynamic process but prewired biologically. Researchers have investigated the capacity for language in different animal species and while some animals, particularly apes, can be taught to use symbols, man appears to be specifically, physically, and neurologically adapted for speech and language. Much work has been done on the development of language from birth during its rapid acquisition stage. Less work has been conducted on examining the effects of aging on communication processes later in life. However, it is clear that changes in vision and hearing, laryngeal function, and cognitive function impact upon the effectiveness of communication. For example, less cognitive agility may reduce the facility to make inferences when complex language structures are used; the use of stereotypical phrases to fill in language when original vocabulary is less available and a slight deepening and huskiness in the voice may all be associated with normal communication changes associated with age. Many of these will be subtle and will not be evident in casual conversation (Civil and Whitehouse, 1991).

The impact of age-associated changes to the sensory systems are likely to have a profound effect on communication, but it is difficult to define exactly when the normal deterioration in hearing and eyesight becomes pathological and affects communication more extremely (Gulya, 2002).

Hearing

The prevalence of hearing impairment depends upon the criteria used to define it. However, many studies have indicated that between 30 and 40% of older people have a hearing loss of 25-dB hearing level. This level would affect the ability to hear normal conversation. While men are more likely to have more severe hearing level loss than women, increasing age is by far the major determinant in predicting who is likely to have a hearing difficulty. A decrease in overall hearing acuity is often accompanied by disproportionate difficulty in discriminating higher-frequency sounds and a

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lowering of the threshold at which sounds cause discomfort. These age-related changes are called *presbycusis*. Distortions of the speech signal result in misinterpretation and misunderstanding, which have implications for communicative functions as well as cognition and mood. Hearing loss can be profoundly isolating and reduce enjoyment in many activities and is frequently associated with depression (Dalton *et al.*, 2003). For many elderly individuals, communication problems and related psychosocial difficulties resulting from hearing impairments could be reduced significantly by the use of hearing aids. However, a high proportion of those provided with hearing aids do not use them. One study indicated that only 21% of hearing impaired elderly individuals provided with a hearing aid used them. Improved usage is associated with an education program accompanied by the provision of a hearing aid. This should include information on how to physically manipulate the aid itself as well as giving encouragement to develop the necessary tolerance in order to get accustomed to the different auditory input provided through a hearing aid. Thus, provision of a hearing aid is not an end in itself and is unlikely to lead to successful improvement in communication (Lesner and Kricos, 2003).

Vision

The chapter would be incomplete without mentioning the contribution of vision to communication but, as this is less profound, only a summary will be provided. Visual changes occur with age and affect depth perception, color sensitivity, the ability to focus and the ability to adapt to changes in lighting. In addition, a number of diseases such as cataract, glaucoma, and macular degeneration may affect vision and are associated with increasing age. Vision obviously affects reading and writing, but reduced ability, to see gestures and facial expression or to recognize people, can impair the communication process in a more subtle manner (Gravell and Stevens, 1998). One of the concerns to speech and language therapists is that visual and hearing impairments can profoundly affect an individual's response to rehabilitation of acquired dysphasia or dysarthria. Detailed speech and language assessments usually require reasonable vision and hearing; thus, patients with defects in these may be more difficult, not only to treat, but also to evaluate and diagnose.

Cognition

Age-related cognitive decline is examined in depth elsewhere in this book (*see* **Chapter 90, Delirium**).

There is a close relationship between thought and language and it has been suggested that various types of cognitive decline, including specific dementia types lead to fundamentally different communicative symptoms. However, with cognitive decline, pragmatic dysfunction leading to incompetence in communicative process, is more frequently evident than linguistic difficulty. Thus, a person may have appropriate language structure, but may use the language in a way that does not communicate effectively, either by ignoring the context, lacking coherence, or showing difficulty in sticking to a topic.

Studies have indicated that certain cognitive abilities such as accessing vocabulary, may be insensitive to age-related changes until the age of 75–85 (Bouchard-Ryan, 1991). The main difficulty in normal aging is associated with slowing of processing time and less resistance to distraction (Vliet *et al.*, 2003).

Persons with age-related cognitive disorders affecting communication can be assisted by speech and language therapists. The therapist will undertake a differential communication assessment and advise the patient and carers on strategies to improve effectiveness of interaction. These strategies include: reducing the use of pronouns such as "he" or "she" and referring to people or things by name; avoiding open-ended questions, for example, giving definite options; encouraging gesture and using communication prompts such as pictures and charts (Enderby, 1997).

Motor Speech

Power and range of movement may be affected by age; this can subtly change respiration, phonation, and articulation, allowing the listener to frequently identify a speaker that they cannot see as being older or younger. The voice becomes less robust with the onset of tremulous, frail, or a thinned quality. It is possible that these changes are associated with some adaptation of the laryngeal cartilages, thickening of the vocal folds and reduction in respiratory support.

Depression

There is high prevalence of depression in older people and depression has an impact on communication leading to reduced communication, less interest in the communication of others and a general withdrawal from social groups. Depression has been associated with grieving over loss of functions (such as hearing, and physical dependence), loss of autonomy and control over life, loneliness, and anxiety about the future. Depression can be so profound that it can mimic a cognitive dysfunction and aphasia and in all cases will mean that rehabilitation of another specific communication disorder will be rendered more difficult. Identifying whether depression is a component of the communicative disorder is essential as its treatment can assist with general management of other physical deficits.

DIAGNOSIS AND ASSESSMENT OF COMMUNICATION DISORDERS

The specific communication disorders associated with age-related pathologies are dysphasia, dysarthria, and dyspraxia. Dysphasia is commonly a consequence of left-hemisphere

stroke which can also give rise to dyspraxia. Dysarthria is more commonly a symptom with bilateral hemisphere damage or damage to the cerebellum or extra pyramidal system as a consequence of head injury, brain tumor, or progressive neurological diseases such as Parkinson's disease.

Dysphasia

Dysphasia is a disorder of language which affects the ability to understand, or to express oneself in speech or writing. While the term "aphasia" denotes a greater severity, the terms are now frequently used interchangeably. Dysphasia is usually of sudden onset and results from focal brain damage. Traditionally, aphasia has been classified according to localization theory. Wernicke's aphasia is correlated with damage to the left posterior region of the perisylvan cortex or primary language area. A lesion in this area frequently produces disturbances of auditory comprehension, inability to repeat and name objects, but with the preservation of verbal fluency. Paraphasic errors and indefinite pronouns pervade expressive language of Wernicke's aphasic patients, who often retain inappropriate, but rich, intonation. In contrast, Broca's aphasia is classically associated with lesions localized to the left anterior region of the perisylvan cortex. Broca's aphasia is associated with less disordered comprehension, severe word finding problems and marked impairment of fluency. Thus, the patient will give the appearance of struggling for speech. Studies have indicated that the more profound, debilitating aphasia (Wernicke's) is associated with increasing age. Thus, a high proportion of stroke patients over the age of 80 will have Wernicke's aphasia affecting their comprehension ability profoundly. One of the hypotheses for this age-related shift in aphasia type is that cerebral damage has a more posterior focus with advancing age, which could be associated with etiological changes.

More recently, speech and language therapists have adopted a cognitive neuropsychological model to diagnosing and managing dysphasia as this approach is of more direct assistance in planning and targeting therapeutic intervention. This model is based on the assumption that language system is organized in an integrated and modular manner, and that this can be selectively impaired by brain damage. Thus, once the particular modules have been identified by assessment, then treatment can either stimulate the use of this linguistic deficit, or teach strategies to overcome, or bypass that aspect of the system. Much research, most of single case studies, has identified particular patterns of language associated with disruptions to the neurolinguistic structure and report varying degrees of success in focusing therapeutic intervention (Hicklin *et al.*, 2002; Nickels, 2002; Franklin *et al.*, 2002).

It is important for all health-care professionals to be able to have a good understanding of the communicative ability of a patient with aphasia – particularly, confidence in the level of comprehension, in order that the patient is engaged in decisions and giving informed consent appropriately. There are several bedside screening tests which can assist with identifying the level and nature of dysphasia, for example, Frenchay Aphasia Screening Test (Enderby *et al.*, 1986). The more formal speech and language therapy assessments provide a detailed description of the neurolinguistic and functional aspects of the aphasia which would inform speech therapy intervention, for example, The Comprehensive Aphasia Test (Swinburn *et al.*, 2004).

A review of recent research indicates that when all other factors (e.g. health, education, and social status) are held constant, chronological age alone is not a good predictor of either severity or prognosis in aphasia, with some very elderly patients improving and recovering remarkably well. However, the risk of concomitant problems is greater with increasing age and these may well contribute to a less good outcome. For example, patients who have aphasia alongside age-related memory problems or hearing loss provide more challenges to rehabilitation.

A systematic review for the Cochrane collaboration of aphasia or treatment by speech and language therapists identified 19 randomized studies of which 12 published sufficient data to inform the review (Greener *et al.*, 1998). These studies included comparison of speech and language therapy with no treatment, informal support, counseling as well as comparing the outcomes of different styles of intervention. The latest randomized controlled trial (RCT) reviewed in this series was published in 1993 with most recent research investigating aphasia favoring different methodologies to the RCT which, in the Cochrane meta-analysis, resulted in the conclusion that the client group and intervention were so heterogeneous that no meaningful conclusion could be drawn.

The use of computers to deliver therapy to people with aphasia is growing in popularity. Many studies indicating that language treatment can be made accessible for frequent practice can be adapted to address different deficits and language styles, are favored by clients and users, and can implement structured approaches to neurolinguistic learning. Single case and group studies using both qualitative and quantitative methodologies indicate encouraging progress with computer delivered treatment (see *Aphasiology*, **18**:3, 2004 – special edition). However, there is growing recognition relating to the social consequences of aphasia to the patient and the family, and increasing evidence that a holistic life-long approach to support the persons with aphasia improves the quality of life, preventing isolation, depression, and withdrawal from society (Parr *et al.*, 1997).

Assessment of mental competence and comprehension is important in some cases where the need for informed consent, power of attorney or testamentary capacity are being considered. While observation and subjective opinion may lead to a particular conclusion, it is essential to support and/or test this with objective tests and consider other influences, for example, social pressures, perseveration, fatigue, and poor attention span which may affect ability (Enderby, 1997).

Dyspraxia of Speech

Dyspraxia of speech refers to the inability to carry out fine voluntary movements necessary for speech, while frequently

voluntary and automatic movements of the same muscles remain intact. Thus, a patient may be unable to stick his tongue out on command but is able to lick his lips to remove a crumb (oral dyspraxia). Muscular weakness may be absent or insufficient to account for the speech difficulty and the patient may produce expletives or automatic speech (as in counting) clearly but is unable to imitate sounds and words (verbal dyspraxia). Speech is characterized by effortful groping and patients have difficulty in imitating and repeating sounds and words. Patients with dyspraxia frequently do not have difficulty with other oral motor tasks such as controlling saliva or swallowing, and this can help distinguish dyspraxia from dysarthria where those functions are frequently abnormal. Dyspraxia rarely exists without some degree of dysphasia and may lead to individuals being thought of as having more language impairment than is the case; it is primarily associated with cortical damage.

Dysarthria

Speech requires accurate motor programming, initiation, and control of fine movements of the lips, tongue, palate, and larynx, which act in harmony with timing of inspiration and expiration. This results in the precise articulation, pitch and tonal quality, resonance and phrasing which are associated with normal speech. Disease processes of the central or peripheral nervous system can affect this choreography and produce a motor speech disorder termed *dysarthria*. Again, the term anarthria usually indicates a more severe form of the disorder.

The different types of abnormal speech can indicate the level of underlying neurobiological dysfunction. For example, difficulties with initiating speech, reducing volume, and increasing speed of speech are associated with damage to the extrapyramidal system and frequently associated with Parkinson's disease (hypokinetic dysarthria). However, a strained, strangled voice with reduced resonance and imprecise articulation may be associated with upper motor neurone damage (spastic dysarthria). Table 1 indicates the different types and qualities of speech associated with different pathologies.

Dysarthria can be discriminated from dyspraxia, as frequently, patients with dysarthria will have problems with swallowing and dribbling. Dysarthria can be discriminated from dysphasia in that patients with dysarthria alone will have no language deficit and should be able to write down responses to questions and use gestures normally as long as other mechanisms are intact.

Table 1 Characteristics of dysarthria types

Flaccid dysarthria	Spastic dysarthria
Normal respiratory support for speech	Poor phonation and information
Normal speaking rate	Reduced alternating movements (undershoots target)
Some isolated areas of severe involvement	Slow speaking rate
Asymmetry of facial musculature	Hypernasality
Reduced phonation time	Speech labored and effortful
	Imprecise articulation
Extrapyramidal hyperkinetic dysarthria	Ataxic dysarthria
Increased (festinate) speaking rate	Poor control of phonation and intonation (often loud)
Weak phonation	Variable accuracy of articulation
Flat intonation	Poor alternating movements of articulators
Poor respiratory support	Normal resonance
Poor oral movements	Irregularity of speech pattern
Mixed dysarthria	
Profound deficit in oral motor tasks	
Poor lip seal	
Palatal movement OK in swallowing – poor in speech	
Severe hypernasality	
Slow labored speech lacking force	

SWALLOWING

The Normal Swallow

Swallowing involves a process of transporting saliva, food and drink from the mouth to the stomach, and it involves the protection of the respiratory system from being entered by anything other than air. Normal swallowing is easy, quick, and unconsciously performed, but it is a highly complex process carried out more than a thousand times a day in normal adults just to clear saliva from the mouth to the esophagus. In the one second it takes to swallow to clear the mouth of saliva, over 40 paired muscles are used (Rubin and Bradshaw, 2000). The mouth, nose, and pharynx are both airways and food ways and are involved in speech. The mechanisms for using these cavities appropriately can be affected by central and peripheral neural or structural damage. Swallowing necessitates cessation of respiration with closure of the airway, while the pharynx is being used to transport saliva, liquids, or foodstuff. Alterations in tone, pressure, or timing can cause aspiration, that is, the leakage of food or fluid into the airway. This will commonly cause coughing or choking as the system acts in a coordinated fashion to expel the foreign material and return it to the pharynx. However, silent aspiration can occur where food or liquid do not stimulate coughing or choking and penetration of the material is unimpeded.

Oral Phase

Swallowing is frequently described as having three phases, the oral phase, the pharyngeal phase, and the esophageal phase. In the oral phase, food is taken into the mouth, chewed, and moved back to the opening of the pharynx. The lips seal the oral cavity and the hyoid rises. At the start of the oral propulsion phase, the soft palate will seal off the nose prior to the tongue propelling the bolus into the pharynx. The oral phase is mainly under voluntary control and can

be disturbed if the lips are affected and unable to make a good seal – this delays the initiation of the swallow. Facial palsy can lead to some of the bolus being deposited within the buccal sulcus and poor tongue movements will result in poor bolus control (Figure 1).

Pharyngeal/Esophageal Phases

The pharyngeal phase is considered to start when the bolus touches the posterior pharyngeal wall. The nasal pharynx is sealed more tightly through the raising of the soft palate and the laryngeal inlet is sealed through raising the larynx, closure of the vocal folds and tilting of the epiglottis. Descending movements of the pharyngeal constrictor muscles squeeze the bolus down. The esophageal phase is seen as the last phase of swallowing; it is the involuntary transport of the bolus through the esophagus to reach the stomach. Anatomically, the esophagus starts at the upper esophageal sphincter; this sphincter is frequently called the PE segment (pharyngoesophageal segment) or otherwise known as the *crycopharyngeal sphincter*. This sphincter at rest is contracted and the bolus alone will not stimulate its release. It relaxes in concert with the pharyngeal bolus transport and opens in unison with the anterior movement of the larynx. It protects the pharynx from regurgitated food and prevents air entering the esophagus during breathing. The timing of the opening and closure of this sphincter can be problematic in many neurological diseases. If this sphincter is not released in a timely fashion, patients will complain that they have difficulty in pushing food down into their throat or they may have overspill aspiration with the bolus not clearing through the pharynx into the esophagus before the airway becomes patent. The aging process alone affects deglutition with an increase in chewing movements in order to form a bolus and to initiate swallowing, a slowed swallowing propulsion time and reduction in pharyngeal and esophageal peristalsis. There is evidence that, with increasing age, the normal elderly aspirate increasingly, but this may not give rise to any symptoms. The mechanisms for tolerating increasing aspiration are not fully understood.

DYSPHAGIA

The broad term "dysphagia" can encompass problems at the oral, pharyngeal, or esophageal stages of swallowing and should not be confused with difficulties of feeding or eating, which may be associated with anorexia, psychological problems or difficulties in transporting food from the plate to the mouth. Symptoms associated with dysphagia include: choking during eating or drinking, difficulty in swallowing certain food types, an inability to swallow saliva, nasal regurgitation of food or drink, and discomfort during swallowing. While dysphagia should not be defined by the presence or absence of aspiration, patients with feeding or swallowing problems need to be assessed in order to identify the risk of aspiration, as this is particularly associated with increased morbidity.

Persons with dysphagia are more at risk of malnutrition, dehydration along with aspiration that can lead to aspiration pneumonia. All these complications can lead to poor outcome and can ultimately be the cause of death, but additionally, there are profound social and psychological effects of swallowing disorders. Coughing and choking can be frightening for both the patient and carers. Dribbling/drooling can be socially offensive and embarrassing and have a severe effect on the quality of life of the patient.

Clinically, dysphagia is common and presents a "major diagnostic and therapeutic challenge" (Nilsson *et al.*, 1998). Interdisciplinary management of dysphagia is advocated (Carrau and Murry, 1999); the aim of this management is to protect the patient from complications of dysphagia, maintain adequate nutrition and ensure that patients and carers are fully aware of the nature of deficit and methods of managing the problems.

Assessment will in the first instance be done at the bedside (see BOX 1), and will take account of the oral and laryngeal structures and movements, dental state, cognition, posture, and other issues which can contribute to the safety of the patient to progress with oral feeding. It is important to note that the absence of the gag reflex does not automatically indicate a major swallowing problem, just as the presence of

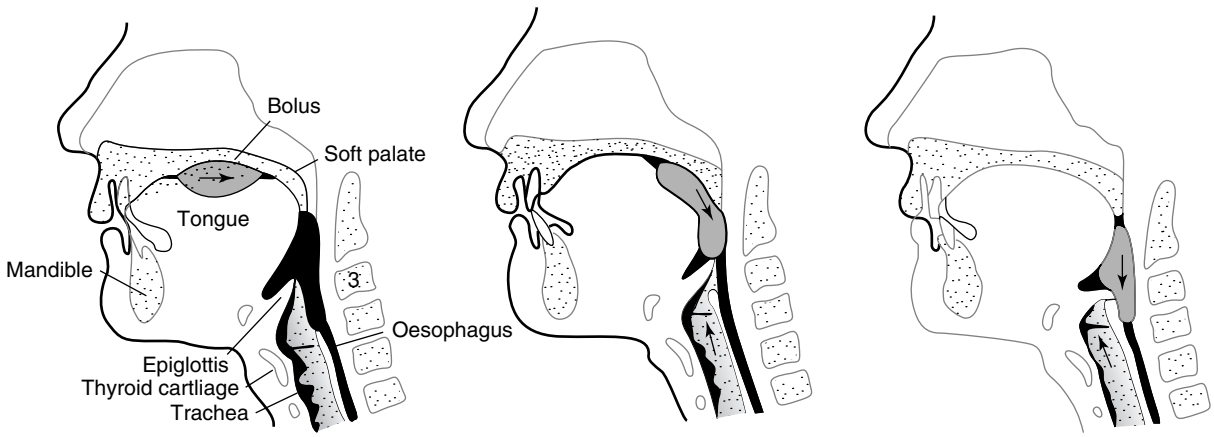

Figure 1 Normal swallowing process

the gag does not indicate safe swallowing. Other factors, such as the bolus control, clarity of the voice (is it wet and gurgly after a test swallow) the effectiveness of the cough (is the cough firm and effective) are all important. A therapist will frequently give different trial swallows of food substances (semisolid, firm, etc.) and liquid. Certain food substances may be more easily and safely transported and, therefore, there could be recommendations of the consistency of oral intake. If it is clear from the bedside assessment that there is a danger of aspiration, it may be necessary to request further assessment in a videoflouroscopy clinic which can determine more objectively the type and nature of the aspiration, and whether positioning the patient or changing the consistency of the bolus can moderate such risk. However, there are certain guidelines that can assist with management of any person with dysphagia. It is important to remember that it is very difficult to swallow safely if one is not fully conscious and aware. Furthermore, if a patient is unable to sit upright or cough purposefully, the likelihood of aspiration is increased.

BOX 1 Bedside Swallow Assessment

Risk Indicators

- Weak husky voice (dysphonia)
- Inability to cough voluntarily
- Weak cough – no effective expulsion
- Pooling of food or saliva in mouth/cheek
- Frequent coughing/choking even on saliva
- History of recent chest infection
- Complaints of difficulty with swallowing
- Reports having to gulp/or abnormal sensation
- Reports difficulty with some types of food

Observation

Try teaspoons of water, if successful, try teaspoons soft puree and then if successful, foods with more substance

Observe:

- Patients report negative sensation
- Poor lip closure/degree of leakage
- Untimely or absent elevation of larynx
- Residue in mouth following swallow
- Lack of clarity of voice, following swallow
- Choking/coughing before, during or after swallow

Any of above would indicate necessity for more in-depth dysphagia assessment.

Videoflouroscopy to assess swallowing is not infallible. The procedure can produce false positives as well as false negatives. For examples: the trial swallows may not produce, for recording, evidence of dysphagia which in some patients only occurs with fatigue after several mouthfuls – a false negative. However, on other occasions, aspiration may be observed, which is asymptomatic or induced by the tension of the situation or unpleasantness of the radio-opaque material – a false positive. The indications from videoflouroscopy must be placed in the context of the history of the patient.

Some patients are able to eat more efficiently and safely, certain food textures. For example, persons with either reduced oral sensation, buccal control, or inadequate laryngeal lift may aspirate more on fluids rather than on semisolids. Fluids do not stimulate the swallow reflex so rapidly, cannot be formed into a bolus, overflow into the pharynx and larynx without needing propulsion and leak into larynx more readily. Thus, some patients may be advised to avoid liquids, but may manage a soft pureed diet. Other patients may have difficulty maneuvering, or forming a bolus due primarily to the involvement of tongue, lips and jaw, and these clients may need to avoid foods requiring chewing.

Problems with communication and/or swallowing are profoundly disabling to the patient and cause great anxiety to relatives. While some of these components may not resolve spontaneously or with treatment, they all deserve appropriate assessment and intervention aimed at improving the management of the symptoms, improving the quality of life by maximizing function, and reducing secondary sequelae.

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KEY POINTS

- Communication and swallowing impairments are profoundly disabling.
- Discriminating between dysphasia, dysarthria, and dyspraxia is important for neurological diagnosis and therapeutic intervention.
- Patients need their level of comprehension to be assessed objectively as it is frequently not what it seems.
- There is evidence that some patients continue to improve communication skills with therapy beyond the period of spontaneous recovery.
- Appropriate identification and management of dysphagia reduces mortality and morbidity.

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Stroke Rehabilitation

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INTRODUCTION

Stroke is the leading cause of severe disability in most of the developed world. In England and Wales alone, there are about 300 000 stroke survivors living in the community, of whom half are unable to use public transport, one quarter need help from community services, and one twentieth require institutional care (Wade, 1994). Stroke is also an expensive disease; for every patient who experiences a stroke, the cost to the UK National Health Service is £15 300 and, when informal care costs are included, the figure increases to £29 400 (2001/2002 prices) (Youman *et al.*, 2003). Recent years have seen several developments to improve the management of stroke patients and reduce mortality, disability, and costs associated with this disease. These range from advances in imaging techniques which improve diagnostic capabilities (Kidwell *et al.*, 2000) and acute interventions aimed at reducing the size of brain injury (Wardlaw *et al.*, 2000) to improved acute care (Evans *et al.*, 2001) and organized rehabilitation aimed at reducing residual dependence (Stroke Unit Trialists' Collaboration, 1999). Despite the proven efficacy of thrombolysis and optimism about physiological manipulations in the acute phase of stroke, these interventions will have only a modest impact on eventual outcome in the vast majority of stroke patients because of the limitations on their use (Lindsberg and Kaste, 2003). On the other hand, over 30 randomized controlled trials provide a sound foundation for evidence-based practice in stroke rehabilitation, supplementing, and often confirming decades of clinical experience. Hence, early and planned multidisciplinary rehabilitation remains the cornerstone of stroke management in the foreseeable future because it is applicable to most stroke survivors and has a strong evidence base for effectiveness in all patients, regardless of stroke severity.

THE NEUROLOGICAL BASIS OF RECOVERY

The principle that underlies all rehabilitation is that the brain has an inherent capacity to recover lost function after stroke (Weiller *et al.*, 1993). This is based on observations that most survivors regain some or many of the functions lost as a result of the stroke. Recovery is of two types; intrinsic, which involves a degree of return of neural control, and adaptive, in which alternative strategies, usually behavioral changes, are used to overcome disability. The majority of patients show some degree of both intrinsic and adaptive recovery, the proportion of each being dependent upon factors such as age, the severity of stroke, cognitive abilities, and rehabilitation input after stroke. Intrinsic mechanisms include restitution, which is the restoration of function of partially damaged pathways and strengthening of existing pathways, mediated by local changes in blood flow, metabolism, or neurotransmitter concentrations. Diaschisis or substitution is the development of new, but functionally related, pathways in the unaffected areas of brain to take over the lost function (Steinberg and Augustine, 1997). Studies in experimental models have shown a number of cellular and histological changes, such as axonal sprouting and formation of new dendritic connections, in the unaffected hemisphere of chronic stroke models, which probably are responsible for long-term recovery in these animals (Steinberg and Augustine, 1997). The degree of recovery due to intrinsic mechanisms may be incomplete in a significant number of patients. In these circumstances, reeducation in compensatory techniques, either by changed use of the affected side or retraining of the unaffected side, becomes an important behavioral adaptation to improve function and reduce the level of disability posed by the impairment (Wade, 1999).

The development of advanced neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (MRI), has helped to demonstrate the processes of reorganization of neural activity after stroke in human subjects (Dettmers *et al.*, 1997; Cramer *et al.*, 1997). These studies have shown that unilateral motor tasks are associated with activation (increased metabolic activity) primarily in the contralateral sensorimotor cortex and the ipsilateral cerebellum in healthy subjects (see Figure 1). The contralateral premotor cortex, ipsilateral somatosensory cortex, and bilateral supplementary motor

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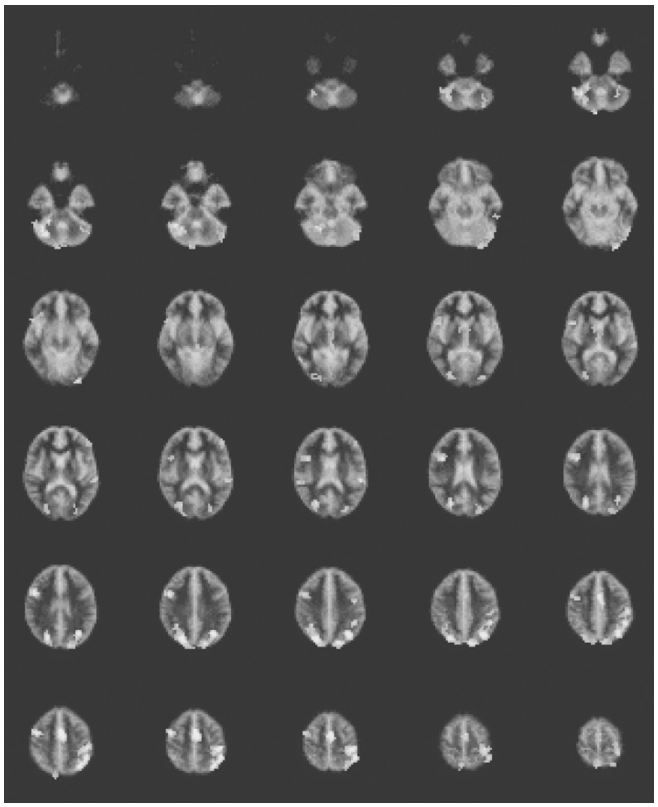

Group brain activation map in 5 subjects showing activation of the cerebellum,superior temporal gyrus, prefrontal cortex, SMA, PMC, lateral premotor cortex And somatosensory cortex on performance of the CRT.

Figure 1 Activation on Functional MRI during a choice reaction task (CRT) in a normal subject

areas also participate in hand and finger motor tasks, particularly when the task increases in complexity. In recovered stroke patients, activation on these tasks is seen in the peri-infarct cortex and supplementary areas of the affected side (see Figure 2), and also in additional regions including the ipsilateral sensorimotor and premotor cortex (see Figure 3). The cerebellum, thalamus, and prefrontal areas play an important part in restoration of function. The process of reorganization is dynamic, there is an evolution of changes with time, and several different patterns have been described. These include activation, and later extinction, of bilateral cerebellar and prefrontal areas, an initial increase followed by a decrease in activation of motor areas, and progression from early contralesion activity to late ipsilateral activity (Marshall *et al.*, 2000; Pineiro *et al.*, 2001; Johansen-Berg *et al.*, 2002; Small *et al.*, 2002). All these changes appear to be associated with good recovery, although their exact significance and relevance to recovery remains a subject of debate. It is now clear that there are multiple motor circuits in the brain, which serve similar functions. Conventional pathways dominate in healthy subjects and inhibit the activity of alternate pathways in other areas of the brain. Disruption of traditional pathways in cerebral ischemia reduces or eliminates the inhibition normally exerted by these pathways and allows activation of alternate pathways in the premotor areas of the affected side and primary motor areas on the unaffected side. Hence, the paradigm for function has shifted from strict cerebral localization to that of interactive functioning of diverse cortical areas activated by the constantly changing balance of inhibitory and excitatory impulses.

An important concept in rehabilitation is that of "brain plasticity," which implies that it is possible to modulate or facilitate reorganization of cerebral processes by external inputs. This concept is supported by early studies that show that activation can be facilitated by sensory stimulation, repetitive movement of the affected limbs, or the use of drugs that modify neurotransmitter release (Hamdy *et al.*, 1998; Nudo *et al.*, 1996a; Gledmacher, 1997). Absence of adequate external inputs may have a negative effect – primate studies have shown that lack of afferent stimulation because of loss of voluntary activity impedes recovery in function after induced ischemic injury to the brain (Nudo

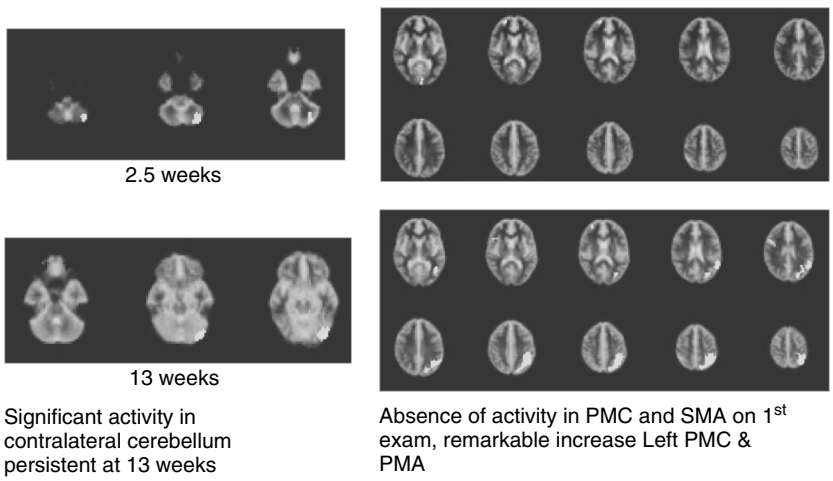

Figure 2 FMRI on CRT using affected hand in a patient with small lacunar infarct in the left internal capsule

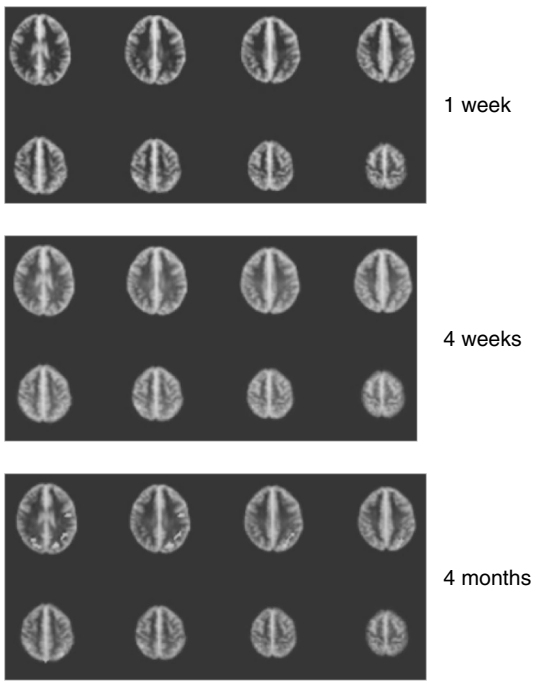

Figure 3 FMRI on CRT using affected hand in a patient with cortical infarct in the right hemisphere

et al., 1996b). The timing and intensity of intervention may also be important: early attempts at intensive movement training in experimental models have resulted in an increase in the size of the cortical lesion (Kozlowski *et al.*, 1996). This emerging picture fits in well with theoretical concepts about motor learning, which emphasizes the importance of repetition, attention, and goal-directed activity (Pomeroy and Tallis, 2000a).

The observations made in animal experiments have been replicated in human studies, which have shown that increased intensity of therapy leads to greater recovery in stroke patients (Feys *et al.*, 1998; Kwakkel *et al.*, 1999; Lincoln *et al.*, 1999). A significant increase in the cortical representation of the thumb of the affected side was seen on transcranial magnetic studies following 12 days of constraint therapy (Liepert *et al.*, 2000). Functional magnetic resonance imaging (FMRI) studies have also shown increased activation of the contralateral motor cortex after 2 weeks of intensive treatment to the affected limb (Johansen-Berg *et al.*, 2002). A small FMRI study has demonstrated that drugs can modify reactivation and recovery; a single dose of fluoxetine resulted in significantly greater activation in the ipsilesional primary motor cortex and significantly improved motor skills on the affected side in patients with pure motor hemiparesis (Pariente *et al.*, 2001). This study supports findings of other small clinical studies showing improved motor outcome in patients receiving norepinephrine enhancing agents during rehabilitation (Gledmacher, 1997).

To summarize, advances in basic sciences and clinical research are beginning to merge and show that the human brain is capable of significant recovery after stroke, provided that the appropriate treatments and stimuli are applied in adequate amounts and at the right time. There is also evidence to suggest that advances in pharmacotherapeutics and robotic assistive technology can further enhance and hasten the process of recovery, which will change the focus of rehabilitation from intuitive methods employed at present to new strategies firmly rooted in the neuroscience of recovery.

PATTERNS OF RECOVERY

Recovery is the fastest in the first few weeks after stroke, with a further 5 to 10% occurring between 6 months and 1 year. About 30% of survivors are independent within 3 weeks, and by 6 months this proportion rises to 50% (Wade and Langton Hewer, 1987). Late neurophysiologic recovery can continue for several years but it is at a much slower rate and seldom results in dramatic changes in overall functional ability (Skilbeck *et al.*, 1983). Completeness of recovery depends largely on the severity of the initial deficit. The more severe the initial deficit, the less likely it is that complete recovery will occur. The pattern of recovery is not uniform and shows considerable variation between individuals and also between different deficits in the same individual. There is currently no validated method for predicting the precise mode or degree of recovery for a given individual. In addition, there can be considerable variation in day-to-day progress of individual patients, which may mask overall recovery or at times give rise to false optimism. This problem can be overcome by monitoring patients over time, as overall trends are more important than "one-off" assessments. Recovery may be affected adversely by the development of stroke-related complications. Comorbidity in elderly patients is another variable that affects overall recovery and rehabilitation.

The rate of recovery varies for different impairments and disabilities. Some problems such as homonymous hemianopia, dysphagia, and sitting balance resolve very quickly in stroke survivors, whereas arm paralysis and language impairment recover more slowly and less completely. Perceptual problems may persist or take a very long time to recover. If all stroke survivors are considered, 62% are independent in self-care at 3 months and 66% at the end of 1 year, despite persistence of neurologic deficit in some patients (Kotila *et al.*, 1984).

OBJECTIVES OF REHABILITATION

Rehabilitation in stroke is not simply a matter of being treated by a therapist or a group of therapists, but involves a whole range of approaches to managing disability, provided by a coordinated multidisciplinary team and tailored to restore

patients to their fullest possible physical, mental, and social capability (Harvey, 1998). The goals of rehabilitation are to:

- maximize patients' role fulfillment and independence in their environment within the limitations imposed by the underlying impairment and availability of resources;
- make the best possible physical, psychological, and social adaptation to any difference between the roles desired and the roles achieved following stroke;
- ensure the long-term well-being and quality of life of stroke survivors and their families by providing the necessary knowledge, skills, and support using a range of health, social, and voluntary services resources.

An important objective of the rehabilitation process is to monitor the relevance, quality, and the effectiveness of the services provided in order to ensure that they meet the expectations of patients and their families, and obtain the best possible value for the money and effort being expended.

The revised World Health Organization International Classification of Impairments, Disabilities, and Handicaps (ICIDH) provides a conceptual model for stroke rehabilitation. In this model, the terms disability and handicap have been replaced by limitations in activities and restriction in participation. The focus of attention shifts from pathology to handicap and from patient to environment during the course of rehabilitation (Duncan *et al.*, 2000). The key areas that rehabilitation impacts upon are limitation of activity (disability) and restriction of participation (handicap). Disability is the lack of ability to perform an activity in the manner or within the range that the person was able to accomplish prior to the stroke and relates to function. In this context, the ability to undertake basic activities of self-care is fundamental to any physical rehabilitation program. Handicap is the social consequence of disability and constitutes the limitations faced by stroke patients in fulfilling their normal role in the society. It is not always possible to differentiate handicap from disability, and most pragmatic approaches tend to combine these two dimensions, referring to them as *social disability*.

Rehabilitation in stroke is essentially a multidisciplinary activity that has been described as a problem-solving educational process focusing on disability and intended to reduce handicap (Wade and de Jong, 2000). The basic principles that should be applied throughout rehabilitation of stroke patients are:

- documentation of impairments, disabilities, and handicaps and, where possible, measuring them using simple, valid scales;
- maximization of independence and minimization of learned dependency;
- adopting a holistic approach to patients, which takes into account their physical and psychosocial background, support mechanisms, as well as their environment;
- supporting caregivers and helping them to develop physical and psychological skills to provide long-term, sustainable support to stroke patients.

PROCESS OF REHABILITATION

Rehabilitation has four important components: assessment, planning, intervention, and evaluation.

Assessment

Assessment is fundamental to ascertain the precise nature and severity of deficits and define treatment goals prior to commencement of a rehabilitation program because it provides a logical basis for treatment and management of stroke patients. The major reasons for undertaking assessments in stroke patients are to:

- define the type of patient, the extent of disability, and the potential for recovery and/or responding to intervention (prognostication);
- identify main areas of difficulty and their underlying causes as well as the expectations of the patient and the family;
- monitor the process of rehabilitation (evaluation) and assess the degree of recovery or residual disability at the end of the rehabilitation process (outcome).

A large number of neurologic, physical, and functional assessments are currently available and can be divided into global assessments (which determine the overall impact of stroke) and specific assessments (which deal with a single level or domain of impairment or disability). Composite scores for global disease severity are unreliable because of the dominance of speech and language function over other indexes and because, when quite different disabilities are combined into one score, much specific information is lost (Wade, 1992). Most scores also mix a variety of impairments and disabilities without considering their interactions.

The importance of knowing what information is wanted and why, that is, the purpose of a measure, is central to choosing any measure in rehabilitation. It is also important to decide on the least amount of information that is needed to achieve this purpose. The necessary characteristics of suitable measures are validity, reliability, sensitivity, simplicity, and communicability. It is best to use existing measures wherever possible provided that they are valid for the purpose in mind, reliable in the circumstances proposed, and relevant to the objectives of intervention. Moreover, the use of established measures makes communication and interpretation of data easier.

Planning

Planning is the process of goal setting based on identification of aims, objectives, and targets (Wade, 1998). Goals can be set at different levels; most patients will have immediate goals that relate to basic personal activities of daily living (ADL) such as achievement of sitting balance, independent transfers, and independence in toiletting activities. As

patients continue to improve, goals need to be set for higher levels of function, which incorporate not only independence in household activities but also the ability to undertake social, leisure, and occupational pursuits. The ultimate goal of the rehabilitation program is to improve overall well-being and participation, but many rehabilitation programs often stop once patients have achieved independence in personal ADL. It is important that planning takes into account not only the immediate needs of the patients but also their potential needs when they return to their own environment. This often involves adapting rehabilitation to the home setting and addressing the needs of caregivers, many of whom will play an important role in providing ongoing support and management of disability at home (Dewey *et al.*, 2002). The areas of practical importance in goal setting are as follows:

- *Accommodation*: Where will the patient live and what physical adaptations will be needed?
- *Personal support*: What is the level of support available for existing caregivers and what extra help will be essential for the patient?
- *Life satisfaction*: What roles will the patient be fulfilling within his or her social setting and how will they be occupying their time?

Many difficulties arise in stroke rehabilitation because the goals of intervention are not set in advance or because these goals have not been discussed and agreed on by all relevant parties. Goals of rehabilitation vary according to the expectations of those involved. The goal of hospitals may be to discharge patients as soon as possible, whereas the goal of patients may be to return to their previous functional status even if this is unattainable. The goal of caregivers may be to minimize the level of input they need to provide even at the cost of institutionalization. Many of the difficulties ultimately faced in managing patients and in evaluating the effectiveness of interventions can be traced back to conflicts between the goals and objectives of different parties. An essential function of the whole rehabilitation team is to identify and modify unrealistically high (and sometimes unjustifiably low) expectations of patients and their families by making them more aware of the nature of residual deficit and expected prognosis as soon as these are reasonably clear. The two major problems that arise in goal setting include failure to use a common language in communication between various professionals or between professionals and patients and, second, failure to agree on a time frame within which the rehabilitation process must be accomplished.

Intervention

The minimum requirement of any stroke intervention is to provide the care that is necessary to maintain *status quo* and prevent deterioration of the patient's condition or functional ability due to poor management or complications. Further intervention should be aimed at facilitating recovery and improving outcome by minimizing disability and preventing handicap. Although a large amount of time and resources are devoted to various therapy interventions after stroke, most of the current practices are not rooted in neurophysiology and many lack strong clinical evidence to support their application to stroke patients (Pomeroy and Tallis, 2000a). Obtaining evidence on therapy interventions is not easy; it will be unacceptable to design trials that compare therapy with no therapy, even when there is no objective proof of its effectiveness. In addition, all patients have different treatment needs that require different interventions and at different times, which makes it impossible to design a standardized protocol to be tested in a randomized controlled fashion.

Of the few trials that have compared different therapeutic techniques, none have shown conclusively that one technique is superior to any other in the major areas of physical therapy or in speech and language function (Cifu and Stewart, 1999). The amount of formal therapy received by stroke patients is small and may be as little as 45 minutes each working day or 3 to 4% of a patient's waking time each week, even at specialized facilities (Wade *et al.*, 1984). A small but well-designed randomized controlled study has shown a small but definite relationship between the amount of therapy given and the amount of improvement in functional ability, which was independent of changes in attention or adaptive mechanisms (Kwakkel *et al.*, 1999). Evidence from the bulk of clinical and functional imaging studies suggest that more intense therapy over a shorter period of time provides a better outcome compared with less intense treatment given over longer durations (Teasell and Kalra, 2004). In addition to quantity, the quality of interventions is equally important. Evidence suggests that task-specific approaches, especially with stroke motor therapy, can be more efficacious than traditional approaches that focus on impairment (Teasell and Kalra, 2004).

Of the newer treatments that are available for stroke rehabilitation, treadmill training and constraint therapy are fast becoming popular at many centers. Treadmill training has been shown to improve gait and walking speeds significantly in hemiparetic patients when used as an adjunct to conventional treatment. There are many approaches to gait training, but the most effective combination of training parameters, for example, amount and timing of body support during the gait cycle, belt speed, and acceleration, remains unknown (Pohl *et al.*, 2002). The applicability of treadmill training in clinical practice is limited by the availability of specialist equipment, and the technique may be suitable only for a small proportion of young stroke patients with relatively modest impairments. Constraint therapy is based on the assumption that immobilization of the unaffected side to prevent learned "nonuse" and promote use of the affected limb results in faster (and more complete) recovery. However, there is little objective evidence to support this approach. A recent meta-analysis has shown that recovery is proportional to the amount of exercise given to the affected limb (van der Lee, 2001). It is likely that comparable benefits can be achieved by less hazardous and less frustrating conventional therapy methods (van der Lee, 2001). This is supported by studies from stroke

rehabilitation centers, which show that early, intensive therapy has a positive effect on the speed of functional recovery and discharge from the hospital (Kalra, 1994).

There is consensus that well-organized and well-planned rehabilitation guided by well-defined goals based on adequate assessment and sensitive negotiation with patients and caregivers reduces disability and long-term institutionalization. There is, however, no evidence supporting any specific treatment technique for stroke patients. A pragmatic functional approach individualized for each patient's needs is recommended, and strict adherence to theories with little scientific basis or clinical evidence of effectiveness should be discouraged. There is also evidence suggesting that early, intensive intervention by therapists may speed recovery and hasten discharge from the hospital without increasing the total amount of therapeutic input.

Evaluation

Evaluation is the process of monitoring a patient's progress (or lack of it) and assessing the effectiveness of the rehabilitation process itself. Objective assessment of effectiveness of stroke rehabilitation has proved difficult for several reasons. These include the confounding effect of spontaneous recovery from stroke, difficulty in defining the extent of need, and perceptions of good outcome, which may vary with the perspective of different observers. The wide variety of impairments and disabilities associated with stroke, as well as the large number of instruments available to measure each impairment and disability, have also contributed significantly to the lack of a common assessment for outcome in stroke rehabilitation. A sensible approach is to use simple assessments more frequently during the rehabilitation process to monitor and adjust the treatment program. A review of studies on stroke rehabilitation has shown the predominance of ADL scales in monitoring rehabilitation (Kwakkel *et al.*, 1996). This may be because the level of independence in ADL is not only the basis for more complete recovery but is also important in determining the care needs of, and resource use by, patients who continue to be dependent. Widespread use of ADL scales is further supported by the general agreement on the core ADL components (bladder and bowel function, feeding, cleanliness, dressing, and mobility), high inter-rater reliability in clinical settings, which is not influenced by the method of data collection, and communicability within multidisciplinary teams. On the other hand, ADL scales blur the distinction between impairment and disability, have a low ceiling effect, and cannot identify the reasons why patients fail to achieve goals.

There is little consensus on the most relevant outcome, the method of measurement, or the most appropriate timing of such assessment in stroke patients (Duncan *et al.*, 2000). The perception of a favorable outcome may vary depending upon professional, patient, or carer perspectives and how long after stroke it is assessed. Although it has been recommended that outcomes should be measured at different levels within the ICIDH framework, patients will value their ability to undertake desired activities or to participate in social roles more than improvements in specific areas of performance. Even within the ICIDH framework, the rate and extent of change may vary between the different levels and continue over months. Consequently, it is important to consider the timing of any assessment and the influence of factors known to affect the chosen outcome measures. Measures at the level of activities (disability) are widely used for outcome and have the advantage of objectivity, reliability, and sensitivity besides being simple and relevant to the patient. Measurement of participation and quality of life, however, may be more relevant and appropriate over the longer term. Appropriate timing of assessments is important and the natural history of recovery from stroke must be considered when selecting the time of assessment. Spontaneous recovery, especially in patients with greater severity of stroke, may not plateau until 6 months after the event. Most experts agree that 6 months is the most appropriate time point at which to measure neurological and functional outcome. Wider interactions with environment and society become important after this stage and measurement of participation, life satisfaction, and emotionality should preferably take place at a time when the patient's social condition has stabilized.

COMMON PROBLEMS IN STROKE REHABILITATION

Stroke-related disorders that are important during rehabilitation include visual problems (hemianopia or inattention), dysphagia with the risk of aspiration and infection, communication problems, venous thrombotic disease, urinary and bowel problems, spasticity and contractures, pressure sores, shoulder pain, associated reactions, cold hemiplegic arm, and edema of the limbs. The main neurologic complications include depression, seizures, behavioral changes, and central pain. Stroke patients are also at a higher risk of falls, which, in association with osteoporotic bone changes in the hemiplegic limb, often result in fractures on the stroke side. Various studies have shown that complications occur in about 60% of stroke patients who are undergoing rehabilitation and are more frequent in patients with severe disability (Langhorne *et al.*, 2000).

Dysphagia (*see* Chapter 73, Communication Disorders and Dysphagia)

Swallowing problems are associated with increased incidence of aspiration, chest infection, dehydration, and malnutrition. The presence of dysphagia, in itself and in association with its complications, is linked with poor outcome following stroke (Kidd *et al.*, 1995). Most swallowing difficulties in acute stroke are transient and resolve within 2 weeks of the acute episode. The remainder respond well to compensatory techniques and dietary modifications under the supervision of

speech and language therapists and dietitians, which remain the mainstay of treatment of dysphagia in stroke patients. Patients with persistent dysphagia require alternative means of nutrition (e.g. nasogastric tubes, percutaneous endoscopic gastrostomy (PEG)). Other measures to alleviate swallowing problems include stimulation of the pharynx by mechanical or thermal means, cortical stimulation with magnetic fields to stimulate the swallowing reflex, and insertion of artificial electrical pacemakers to trigger laryngeal elevation.

Dysphasia (*see* Chapter 73, Communication Disorders and Dysphagia)

Dysphasia is a defect in language function manifesting as impairment in speech production, comprehension, reading, or writing in the absence of motor disturbances of voice production or writing, visual or auditory deficits, and intellectual or cognitive impairment. Impaired ability to understand speech is common in dysphasic patients. The difficulty in comprehension increases with increasing linguistic complexity of the speech presented and length of sentences used. The extent to which a dysphasic patient can understand what is being said is frequently overestimated, which can result in misunderstandings between patients and their families or professionals involved in patient care. It is important that communication problems are identified early in stroke patients because many therapy interventions are dependent on this function.

The more severe forms of dysphasia are often easy to diagnose on clinical examination in most stroke patients. The diagnosis of mild dysphasia may be more difficult, especially if the patient has a high-level language deficit. It is also important to differentiate dysphasia from confusion secondary to cognitive impairment. Inquiries about the patient's language background (native language, profession, social, and educational status), previous speech problems, and hand dominance should be part of the examination. Problems in comprehension are particularly difficult to assess. A bedside measure can be obtained by assessing the patient's ability to respond to commands of increasing complexity, either in content or in linguistic structure. It should be remembered that in some patients, errors may occur because of dyspraxia or memory problems. All patients suspected of having dysphasia should be assessed by speech and language therapists regardless of the severity of the impairment. Appropriate treatment of dysphasic patients consists of individualized therapy programs supervised by speech and language therapists, development of simple communication strategies to enable multidisciplinary rehabilitation, and educating caregivers in communication techniques appropriate to the patient's level of impairment.

Perception

Perception is an important but neglected aspect of stroke management. The outcome of rehabilitation frequently depends on effective management of perceptual problems rather than on motor recovery alone. Despite this, perceptual problems are poorly understood and difficult to assess objectively because of the paucity of valid assessment instruments. Their management is equally difficult and a subject of great controversy. Perceptual problems after stroke can be divided into (1) neglect, which is the disregard of, and failure to attend to, one half of external space; (2) agnosias, which comprise problems with interpreting sensory data from the environment or the body (visual, tactile, autotopagnosia); and (3) apraxias, the collection of problems involving the formulation, initiation, or sequencing of motor activity. Visuospatial dysfunction can be particularly disabling in stroke patients, as it affects their ability to judge distances and relationships between objects or between self and objects in a three-dimensional setting, causing severe restrictions in daily living activities. Patients with anosognosia are also difficult to rehabilitate because of the lack of awareness of any problems.

It is not known whether these deficits respond to general stimulation or to specific remedial measures. Recent research suggests that neglect may be amenable to therapeutic interventions such as prism correction, electrical stimulation, and increasing attentional activities, but further studies are required to confirm these findings. Although visuospatial problems delay or compromise functional recovery in most patients, some individuals eventually make full functional recovery despite residual impairments. There is no effective treatment for apraxia. Management currently focuses on increasing the patient's awareness of the condition and its effects. This requires early recognition of the problem and teaching of adaptive skills and coping strategies to patients and their relatives.

Tone and Spasticity

The management of muscle tone is an integral part of therapy input in stroke patients. Muscle tone is a dynamic, complex process that is part of an overall pattern of posture and movement, which plays a vital role in recovery from stroke. Appropriate management of tone is one of the fundamental principles of the Bobath method of facilitative physiotherapy, which gives priority to normalization of tone and improving symmetry even at the cost of postponing standing or walking. However, this preoccupation with normalization of tone is not supported by evidence and there are several other approaches that combine early mobilization with active muscle tone management during rehabilitation (Pomeroy and Tallis, 2000b).

The management of abnormal tone and spasticity is difficult, as it depends on achieving the right balance between hypo- and hypertonia between different muscle groups. The problem is compounded by the fact that spasticity varies between different groups of muscles, times of day, emotional state of the patient, activity being undertaken, and posture of the limb. Inappropriate exercise can result in inappropriate tone patterns to the ultimate detriment of the patient. If not managed correctly, spasticity leads to bad gait patterns,

contractures, and loss of function. Management of spasticity should be undertaken jointly by doctors and physiotherapists. Spasticity should be considered in relation to other impairments and in the context of therapy goals because interventions directed solely at reduction of spasticity are unlikely to result in significant functional gains. Treatment of abnormal tone is initiated by physiotherapists, who can offer a range of interventions including physical therapy, attention to posture and seating and conventional orthoses. Drug therapy can be used in conjunction with physical maneuvers and adjusted to achieve optimal effects. Its main drawback is its lack of selectivity; since all muscle groups are affected equally, there may be undesirable hypotonia in some muscle groups (e.g. drugs for reducing spasticity in arm muscles may affect walking). Localized treatments such as botulinum toxin have been shown to be effective in reducing spasticity in small studies, but this effect was short-lived (up to 3 months) and not translated into functional improvements (Davis and Barnes, 2000). Electrical stimulation techniques are a useful adjunct to other treatments, particularly for treating spastic equinus deformities. In some cases, phenol nerve blocks can produce good results especially when standard treatments fail or botulinum toxin produces beneficial short-term effects. In patients refractory to medical treatments, surgical interventions such as ablation of peripheral nerves, tenotomies, or reconstruction of tendons and joints may be required.

The Hemiplegic Shoulder

Shoulder pain, restriction of movement, and subluxation of the shoulder joint are common problems in stroke patients. In hypotonic patients, the loss of muscle strength around the shoulder joint and the weight of the paralyzed arm may result in malalignment of the humeral head in the shallow glenoid cavity, predisposing to inferior subluxation of the shoulder. There is considerable variation in the reported incidence of subluxation in stroke patients, but it is estimated that one in every five patients is affected. Shoulder pain is more common and inconsistently related to subluxation. It is encountered in rehabilitation settings with disconcerting frequency and may be a result of spasticity in the shoulder muscles, glenohumeral subluxation, reflex sympathetic dystrophy (the shoulder-hand syndrome), or orthopedic causes such as rotator cuff injury, arthritis, or adhesive capsulitis made worse by immobility. Contributory factors include careless handling of patients and incorrect position of the hemiplegic arm. Management should be undertaken in collaboration with physiotherapists and include measures such as proper positioning of the arm during periods of inactivity, avoidance of abnormal arm movements that cause excessive strain on the shoulder joint or inappropriate pulling of the hemiplegic arm during transfers, and early passive exercise to prevent joint stiffness and contractures. Treatment with analgesics, strapping, nonsteroidal antiinflammatory drugs and steroid injections may help in some patients.

Depression

It is estimated that between 30 and 60% of stroke patients have clinically significant depression, the highest prevalence and severity occurring in the first 2 years after stroke (Rao, 2000). Diagnosis of mood disorders in patients with acute stroke is difficult because changes in appetite, sleep, or interest (all indicative of depression) may be a normal adjustment response to physical disability and changed roles. The diagnosis of depression in stroke is further hampered by the presence of dysphasia and impairments in attention or concentration, which make assessment difficult. It is commonly accepted that depression in stroke is frequently associated with left hemisphere lesions despite some studies suggesting no laterality (Carson *et al.*, 2000). Poststroke depression appears to be more common in patients with a personal premorbid history or a family history of depression. Poststroke depression may last for 7 to 8 months or more without treatment and is highly correlated with failure to resume premorbid social and physical activities. Depression also has a negative effect on functional and cognitive recovery, integration into the family environment, and caregiver stress in stroke patients (Robinson-Smith *et al.*, 2000). There is growing evidence suggesting that early recognition of depression in stroke and early treatment with appropriate antidepressants can facilitate recovery, although most series are small (Rigler, 1999).

Psychosocial Aspects (*see* Chapter 75, Clinical Psychology in Physical Rehabilitation)

Stroke is a major life event that presents major difficulties for patients, their spouses, and their families. It not only may result in physical dependency but also requires a wide range of emotional and social adjustments within families, often leading to role reversals and establishment of new hierarchies (Robinson *et al.*, 1999). The poststroke phase is a period of considerable turmoil during which patients and their families need to be supported in order to achieve good outcomes. The reaction to stroke is akin to bereavement; a phase of shock and despondency is followed by a period of positive thinking and optimism as patients' focus on the activities of the rehabilitation team. Many patients and caregivers harbor unrealistic hopes of recovery and it becomes important for the clinician to prevent unrealistic expectations and pave the way for more successful adaptation to the reality of residual disability. People who were very active and independent prior to stroke feel distressed when they need to rely on others for even the most basic personal tasks. This loss of esteem may lead to apathy and even depression and is more likely to happen in the paternalistic environment of hospitals. The attitude and approach of the medical team are crucial in enabling the patient to maintain dignity. Esteem plummets when patients are not given much attention on hospital rounds or are depersonalized by staff who refer to them as "CVAs" or "hemis" rather than considering them as unique individuals. Stroke patients may need counseling as well as

practical support to cope with the fears of disfigurement, loss of physical function, falls, poverty, and an uncertain future after returning home. Alterations in personality may occur after stroke and are a source of great distress to spouses and caregivers of stroke patients.

CONCLUSION

Stroke is a devastating illness and causes long-term disability that dramatically and irreversibly changes the lives of patients and their families. Although there is great optimism that improvements in preventive care and acute interventions will reduce the burden of stroke, their potential remains to be realized. Meanwhile, organized coordinated rehabilitation provided by specialists in partnership with patients and their caregivers offers the only realistic hope of reducing disability and handicap after stroke. Despite its proven effectiveness, specialist stroke rehabilitation is not available to the majority of stroke patients who stand to gain from this input (Royal College of Physicians, 2002). A part of the problem is the lack of infrastructure, resources, staff, and training to provide specialist care. This is compounded by the lack of awareness of the special needs of stroke patients and the benefits of dedicated rehabilitation among some professionals. Increased resources may be hard to achieve in the short term, but improving the level of awareness among health professionals may prove a quicker, simpler, and effective way of improving stroke outcome.

KEY POINTS

- Stroke is the leading cause of severe physical disability in adults.
- The brain is capable of significant recovery after stroke, provided that appropriate treatments are applied in adequate amounts and at the right time.
- Early and planned multidisciplinary rehabilitation remains the cornerstone of stroke management.
- Rehabilitation is a multidisciplinary problem-solving, educational process focusing on disability and intended to reduce handicap.
- Objectives of rehabilitation should include supporting and training caregivers in disability management.

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Clinical Psychology in Physical Rehabilitation

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INTRODUCTION

Clinical psychology is a relatively recent development within the area of mental health: its first practitioners only began to appear in the 1950s. In contrast, the medical profession has been involved in legally managing mental disorder for a century before that. The profession of clinical psychology has therefore emerged from an organizational context dominated by medicine. That dominance has had three major consequences: medicine has incorporated psychological theory (*see* **Chapter 4, Physiology of Aging**); it has monitored the autonomous development of nonmedical practice; and it has provoked the development of competing bodies of knowledge in clinical psychology (Pilgrim and Treacher, 1992). There is often some confusion between clinical psychology and psychiatry. The latter draws on a knowledge of psychology, but it is a branch of medicine concerned with the treatment of enduring psychological problems and chronic mental illness using drugs and psychotherapeutic techniques. Psychology is the scientific study of behavior: what we think, feel, say, and do. Clinical psychology is an applied discipline working professionally within the mental health context. It incorporates scientific methods involving observation, measurement, cognitive assessment, hypothesis testing, experimentation and logical inference, and the use of statistics to test the significance of research findings. It involves clinical therapeutic interventions to treat psychological and psychiatric disorders. The training is lengthy (minimum six years) in the United Kingdom, culminating in the practicing qualification of the Doctorate of Clinical Psychology.

Historically clinical psychologists have been primarily employed in mental health settings offering individual and group therapies based on a psychological understanding of mental health problems. Core areas of the service cover the developmental life span from child to older adult, including learning disabilities, as well as more specialized areas such as drug and alcohol abuse and sexual health. More recently, there has been considerable expansion of the profession of clinical psychology within medical settings, both in the number of individuals working in that milieu and in the number and range of clinical services provided. A joint report of the Royal College of Physicians and Psychiatrists (2003) emphasized the importance of psychological factors in the care of patients in general medical settings, reflecting an increasing awareness within the medical profession of psychological care for medical patients. The report recognizes that the delivery of effective health care is optimized when psychological principles underlying interpersonal interactions and communication are understood, and when there is an awareness of people's basic psychological needs as patients in health-care settings. The report discusses two dimensions of this issue: the need for psychological care and the need to develop psychiatric liaison services to identify and treat psychiatric illness in medical patients. Liaison psychiatry has developed from the medical psychiatric perspective to offer a service to psychiatrically ill patients in medical settings. In a recent survey on psychiatric services for older people in general hospitals (Holmes, 2002), it was found that most psychiatric illness in this setting is managed by general hospital staff, who have received little or no training to deal successfully with this comorbidity. The report goes on to suggest that liaison psychiatric services should be provided by a range of professions including clinical psychology and psychiatry and should involve ongoing training for general hospital staff in the core knowledge, skills, and attitudes related to the diagnosis, investigation, and management of common psychiatric illnesses in older people. It is the work of clinical psychologists and the psychological care relevant to all patients in medical and physical rehabilitation settings, which are the focus of this article.

In the United Kingdom, older adults comprise the largest subgroup of patients seen in general medical and

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rehabilitation settings (almost two-thirds). The proportion of people aged 65 and over is set to rise by 14% between 1998 and 2021 and those aged over 75 years by 29% (Holmes, 2002). Older people currently consume 40% of National Health Service (NHS) resources and this will invariably increase over time. The likelihood of suffering from a chronic or disabling medical condition increases rapidly with age. In 2000, 37% of those aged between 65 and 74, and 47% of those aged over 75 said that they had a long-standing illness that limited their lifestyle (General Household Survey, 2000). As well as increased rates of physical illness, older people have higher prevalence of mental illness, and, in particular, more dementia (Holmes, 2002). Dementia affects one person in 20 aged over 65 years and one person in five over 80 years of age. However, this needs to be counterbalanced by the fact that the majority of older people have reasonably intact cognition, and that professionals working within a hospital environment tend to see a skewed section of the older population both in terms of physical illness and disability, and cognitive function and psychiatric illness.

Indeed, in the United States, there appears to be substantial evidence of a decrease in chronic disease in old age, and recent analyses of projected mortality question much of current methodology (Manton, 1998). It has further been suggested that the cost-benefit of medical procedures in older age may be underestimated because life expectancy of individuals in later age and the amount of functional capacity that can be regained by medical intervention are underestimated (Manton, 1998) (*see* **Chapter 9, The Demography of Aging**).

Thus, many older people find that medical advances allow an extended life span, which, however, may be lived out in the context of chronic ill-health that limits lifestyle and independence. It is this dimension of limited lifestyle that rehabilitation directly targets as a means of optimizing independence and improving the quality of service-users' lives. The role of clinical psychologists within rehabilitation settings has recently been formally acknowledged as an essential professional discipline. In relation to stroke care, for example, the recently published UK Department of Health (DOH) "National Service Framework for Older People" (NSFOP, 2001) specifies (Standard Five) that multidisciplinary stroke rehabilitation teams should include clinical psychologists, a view echoed in the Royal College of Physicians' "National clinical guidelines for stroke" (Royal College of Physicians, 2004).

As essential members of rehabilitation teams, clinical psychologists offer a theoretically driven understanding of patients' needs to nonpsychologist colleagues; they provide in-depth neuropsychological and emotional assessment of individual patients, which enables individual tailoring of rehabilitation endeavors by all team members; and they offer direct psychological interventions to all those affected by illness and disability including family and carers. We will address this theoretical framework next, and then review psychological models and the role of the clinical psychologist in practice, using the typical rehabilitation of stroke as an illustrative context.

THEORETICAL FRAMEWORK

The World Health Organization (WHO) has refined its framework and classification of health and disability over successive publications in recent years, placing greater emphasis on the interaction between pathology, individuals' responses, and the social and physical contexts in which the person functions.

The WHO (2001) "International Classification of Functioning, Disability and Health" describes disability as a consequence of bodily *impairment* that arises from *pathology*. These are the first two dimensions of a model that also includes *activity* and *participation* as keys to the roles that the person values and wishes to maintain. The WHO model contrasts disability with handicap. The latter is defined as "*a disadvantage for a given individual, resulting from an impairment or disability that limits or prevents the fulfillment of a role (depending on age, sex and social and cultural factors) for the individual*". The handicapping impact of disability can thus be tackled through rehabilitation targeting participation and role fulfillment. One early but still salient definition of rehabilitation is thus: "*. . . a dynamic process of planned adaptive change in lifestyle in response to unplanned change imposed on the individual by disease or traumatic incident. The focus is not on cure, but on living with as much freedom and autonomy as possible at every stage and in whichever direction the disability progresses*" (McEachron, 1986).

The development and progress of rehabilitation can be contrasted with that of more highly technological and scientific advances in other areas of health care. In reality, no important advances in single treatments have occurred. There is, however, an increasing evidence-base for specific interventions, practical innovations, and organized, coordinated, multidisciplinary rehabilitation services based on a problem-oriented approach. Rehabilitation work has moved from a predominantly medical model to approaches and processes in which psychological and sociocultural aspects are given equal importance.

Fortunately, there is now a more sophisticated understanding of these psychological and sociocultural aspects of the human response to illness, disability, and rehabilitation. Furthermore, it is increasingly relevant to talk about rehabilitation as an understanding of living with chronic disease over the long term, that is, of disability services. Within the psychology literature, there is extensive work on models of health and illness behavior, allowing a conceptualization of adjustment, coping, and adaptation as arising from the interaction among disability, individual responses, family system, and care systems.

Early models draw on important constructs of *control, self-efficacy beliefs, health value, intention*, and *social and cultural normative expectations* to explain patient behavior in medical contexts, including concepts such as compliance with medication. Similarly, constructs of *control* and *self-efficacy* have been used to understand the role of patients and professionals in issues of communication, which is the core of good psychological care.

An important development in these models was Diefenbach and Leventhal (1996) *Common-Sense Model of Illness Representation* (earlier *termed* the *Self-regulation Model*). The model explains behavioral responses as being mediated by the person's efforts to make sense of their experience. Thus, the dimensions of the "objective" knowledge about the illness/disability constitute a person's cognitive representations of that illness. This understanding relates to the identity of the illness, likely course of the illness in time, cause, controllability, and consequences of the condition. In consequence of this framework of understanding that the individual develops, the person experiences an emotional response: in adjustment and coping, it is this emotional reaction that the individual is primarily dealing with, in addition to the physical challenges to everyday life posed by the illness/disability.

Johnson (1996) additionally drew on concepts of intention and environmental eliciting cues in her Integrative *Social Cognition Model.* In conjunction with factors of perceived behavioral control and internal representations of the illness, eliciting cues have strong cultural and social weight. These additional factors may explain discrepancies in independence behavior in the contexts of home or rehabilitation settings. For example, a physiotherapist may elicit more independence behavior than a family member (or vice versa for family member – nurse).

Similarly, existing family schemas or "scripts" of well-rehearsed patterns of interaction and roles within the family context may be a significant factor in illness/disability behavior within that family. Rolland (1994) *Psychosocial Typology of Illness* allows an understanding of the tasks facing families at different stages of illness. The typology of time phases, for example, allows an understanding of the transitions to be made. So that in an acute, crisis phase of illness, cooperative coping and support is helpful: it may become problematic overprotectiveness at a later stage, which requires a transition to greater independence, if the transition has not been successfully negotiated by the family (*see* **Chapter 152, Carers and the Role of the Family**).

Rolland's and Johnson's models, in particular, allow a framework for working in a systemic family therapy model when families experience significant adjustment and coping difficulties. The work of family therapists in health settings draws on the theoretical knowledge underlying psychotherapeutic work in offering family interventions. Altschuler (1997) has demonstrated the benefits of training of other professionals to achieve greater competence in working with families on the issues of the impact of illness on families.

Goal value and importance is hypothesized to be an important additional factor to self-efficacy constructs. The Goal Planning process – reviewed later in this article – highlights the clinical application of an understanding of the importance of personally relevant goals in rehabilitation.

In offering therapeutic interventions, clinical psychologists draw on other theoretical models. Space does not allow a full description of these: however, the most widely recognized is cognitive behavioral therapy (CBT) – which derives from models of the importance of cognitions and behaviors in mediating emotional and mood responses. Others include Motivational Interviewing, Brief Solution-Focused Therapy, Systemic Family Therapy, Person-Centered Counseling, Cognitive Analytic Therapy (CAT), and a range of other psychotherapies (see Rees *et al.*, 2002, for a fuller discussion of constructs, theories, and interventions).

PSYCHOLOGICAL KNOWLEDGE – INFLUENCE ON SERVICE MODELS

At a service design level, the significance of the personal experience in health-care delivery is acknowledged via the increasing clinical emphasis on understanding the individual's role in self-management, particularly of chronic disease. "The Expert Patient" (Department of Health, 2001), for example, reflects the UK DOH perspective of "*a fundamental shift in the way in which chronic diseases are managed – a shift which will encourage and enable patients to take an active role in their own care".*

A related paradigm shift has resulted from commissioned reports into the future funding and management of the UK NHS (Wanless, 2003) (*see* **Chapter 161, Health and Care for Older People in the United Kingdom**). These advocate alternatives to acute hospital admissions through focused coordinated strategies aimed at prevention and early intervention. These concepts make clear that living with chronic disabilities, which is a large cost to health services, need not drain acute hospital-based services. A range of new supports for chronic conditions is needed: one example given is the introduction of chronic obstructive pulmonary disease teams that have been shown in trials to result in avoidance of 30% of acute admissions (Wanless, 2003). The personal experience of patients with chronic illness also reflects a greater satisfaction with community rather than hospital care, which may often lead to the negative disempowering of patients through contact with numerous different staff who usually do not know the patient or his/her illness at all well.

Research by Michie *et al.* (2003) suggests that a critical issue in self-management is the clinician's ability to enable or empower the patient to take an active role in consultation and management of their illness – something relatively alien to many less-educated and elderly patients, and particularly difficult where cognitive impairment is present. Michie *et al.* undertook a meta-analysis of 30 studies of interventions in patients with chronic conditions (diabetes, chronic pain, heart failure, hypertension, and adults and children with asthma), which aimed to enhance patient-centeredness. Two classifications of such studies were revealed, the *patient perspective* approach – the ability to elicit and discuss patients' beliefs; and the *patient activation* approach – the ability "to activate the patient to take control not only in the consultation but also in the management of their illness". Both styles facilitated patient adherence, but the latter style was associated with better physical health outcomes than the former. The authors speculate that this "activation" style fosters patient's self-efficacy beliefs, enhances motivation and the ability to set their own goals, and plan how to

achieve them. Similarly, patients' beliefs about illness and treatment impact on their participation, particularly with respect to adherence to treatment. Health belief research illustrates the extent to which patients engage in cost-benefit analyses of adherence to treatment. For example, Horne and Weinman (1999) examined medication adherence in a group of patients with chronic illnesses who were asked about their understanding of the necessity of medication and their concerns regarding dependence or long-term effects. These self-reported beliefs about necessity and concern were more predictive of medication adherence than clinical or sociodemographic factors. An understanding of the power of such beliefs enables true partnership with patients as their own expert.

For medical clinicians and rehabilitation professionals, becoming a partner with their patients in managing their care will require extended skills and psychological understandings, building on existing communication skills. Such close working with the users of rehabilitation and chronic health provision is greatly enhanced by a practical understanding and application of the psychological knowledge of patient behavior. Clinical psychologists frequently become involved in this specialist training with all rehabilitation professionals.

STROKE

As outlined in the article introduction, stroke care provides a good example with which to illustrate the role of the clinical psychologist in rehabilitation, as it includes areas of physical disability, cognitive impairment, mood disorder, and life expectancy, as well as family and relationship issues. Reference will be made to other prevalent health conditions of the older adult, such as cardiovascular problems, the consequences of falls, Parkinson's disease, and dementia.

Stroke is a traumatic event that can have a major impact on people's lives. It is the third most common cause of death and the most common cause of disability in the United Kingdom. One man in four and one woman in five aged 45 or over can expect to have a stroke if they live to be 85 (*see* **Chapter 71, Acute Stroke** and **Chapter 134, Rehabilitation**). Approximately one-third of sufferers remain moderately to severely disabled. It is virtually impossible to estimate the true cost of stroke, be it to the health services, the sufferer and the family, or society as a whole, though it is estimated that 4–5% of the health budgets is spent on stroke services (British Psychological Society, 2002).

Stroke as a condition is gaining greater public and political awareness partly due to recent documentation such as the National Service Framework for Older People (NSFOP, 2001). The psychological impact of stroke and the effect this may have on rehabilitation outcome is also gaining in awareness. The NSFOP recommends that not only should every stroke patient be admitted to a specialized stroke unit, but that the unit should also be multidisciplinary, and that there should be a psychologist as part of that team. The rehabilitation of a stroke patient is a continual process from the time of onset of the infarct, through in-patient rehabilitation, to discharge and beyond (*see* **Chapter 74, Stroke Rehabilitation**).

The psychological impact of stroke and the issues surrounding rehabilitation can be viewed from several perspectives, namely, mood disorders, emotionalism, cognitive impairment, cognitive rehabilitation, sexual functioning, goal planning, and the rehabilitation environment. As stroke is a complex condition, there may be more than one aspect involved at any one time.

Mood Disorders

In the first year following stroke, mood disorders have been estimated to affect between 23 and 79% of patients, more than twice the proportion in the general elderly population or in populations matched for physical disability (BPS, 2002). Such large variability is attributed to methodological differences, such as the point at which patients are assessed relative to stroke onset and what instruments and criteria are used in assessment. As depression is thought to impede physical, functional, and cognitive recovery and can be effectively treated, early identification is clearly beneficial (BPS, 2002) (*see* **Chapter 100, Depression in Late Life: Etiology, Diagnosis and Treatment**).

Detection of mood disorder in medically ill patients is not easy, however. Schubert *et al.* (1992a) indicate that mood disorders are often underdiagnosed. Somatic complaints may be symptomatic of depression, but are prevalent in patients with and without concurrent depressive illness. Fatigue, loss of energy and appetite, and insomnia are common core symptoms of depression but are also common in hospitalized patients independent of depression and may be caused by comorbid conditions or medication. In addition, physically ill patients commonly experience somatic symptoms, withdrawal, fatigue, and lethargy without other evidence of depressed mood. Other specific factors may hinder the diagnosis of poststroke depression (PSD). Clinicians and family may judge the patient's mood on outward expression such as emotional lability, but this may be unreliable. The effects of stroke may mimic depression or impair emotional communication. Patients with aphasia may be depressed, but unable to report their feelings. Injury to the right hemisphere or frontal lobes may cause apathy or indifference, and such symptoms may be difficult to distinguish from depression.

In the United Kingdom, The Royal College of Physicians' *National Clinical Guidelines for Stroke* states that "Patients should be screened for depression and anxiety within the first month of stroke, and their mood kept under review. In those patients who can respond to it, a standardized questionnaire may be used for screening, but any clinical diagnosis should be confirmed by clinical interview" (Royal College of Physicians, 2004).

The choice of mood scale used must be carefully made. The majority of measures have been devised around a psychiatric population; others do not take into account the

physical limitations of an acquired disability, as they include items concerning activity and somatic or cognitive disorder. Therefore, the choice of assessment scale should not rely too heavily on somatic symptomatology of depression as these are clearly confounding features in a physically ill population.

The General Health Questionnaire (GHQ) (Goldberg and Williams, 1988) and the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) are among the most commonly used and best validated measures of psychiatric morbidity after stroke. The GHQ was designed as a screening instrument to identify psychiatric disorders. It does not aim to provide a diagnosis but rather to identify those in need of further psychiatric assessment. In a cross-sectional correlational study examining the relation between questionnaire measures of mood in 143 hospital and community stroke patients, the GHQ-28 showed closest correspondence with interview and sensitivity (Lincoln *et al.*, 2003). The HADS provides scores on the two subscales of anxiety and depression. It was specifically designed for use with hospitalized, medically ill patients to detect clinical cases of anxiety and depression. The scale attempts to reduce bias caused by somatic complaints. The Geriatric Depression Scale (GDS) (Yesavage *et al.*, 1983) was developed for use with older people and contains no somatic items. It has 30 questions with a yes/no format. Yesavage *et al.* found that the GDS differentiated depressed from nondepressed physically ill older patients. For patients with communication problems, the Visual Analogue Mood Scale (VAMS) (Nyenhuis *et al.*, 1997) and the Hospital Stroke Aphasic Depression Questionnaire (SADQ), (Lincoln *et al.*, 2000) could be used. Both are promising tools for use with aphasic patients, but further validation is required.

There has been a great deal of research on the psychological management of PSD. Kneebone and Dunmore (2000) identified that Cognitive Behavioral Therapy (CBT), in particular, is potentially effective. Future research should involve treatments for PSD appropriate for those with cognitive impairment and communication difficulties, younger versus older sufferers, and those in institutional settings. Studies should also consider the necessity of specialist assessment strategies and allow for possible subtypes of PSD for which psychological treatments might be differentially effective.

There is evidence that the prevalence of depression in stroke may be found in other chronic illnesses also, to varying degrees. For example, signs and symptoms of clinical depression, including fatigue, exhaustion, and dysphoric mood, are prevalent among patients with coronary heart disease (CHD). Studies have reported that nearly one in five cardiac patients can be diagnosed as having clinical depression (Frasure-Smith *et al.*, 1993). As in stroke, the presence of a major depressive episode in CHD patients is associated with poor psychosocial rehabilitation and increased medical morbidity. Psychological approaches to treatment are equally effective in a range of chronic conditions.

Emotionalism

One of the effects of stroke is reduced control of emotions or emotionalism. For some patients and family, such emotional reactions are the most distressing of the physical or psychological sequelae of stroke (Allman, 1991), and has been found to occur in 10–20% of a community sample. The incidence is likely to be higher in those admitted to hospital. Emotionalism is a heightened tendency to cry (or, rarely, laugh) such that crying occurs more frequently, more easily, more vigorously, or in circumstances that previously would have been out of character. Some attribute this to damage caused by the stroke, others view emotionalism as a mood disorder. A third opinion is that these changes can be understood as part of a psychological reaction to the fact of having had a stroke. Further investigation of these factors is needed in order to gain a better understanding of individual causality, as different cases may well require different treatment approaches. Simple education and advice is all that is required for the majority of patients suffering from emotionalism. Some patients feel they are going mad or are being stupid. Family members and carers also find the symptom distressing and may inadvertently promote the behavior by automatically consoling the patient. Most will benefit from the reassurance that the symptom is common and that it will generally improve with time. Low dose antidepressants have been found to be effective in some but not all cases of emotionalism (Allman, 1991).

Cognitive Impairment

The majority of stroke victims are disoriented and confused during the acute stage, but this confusion generally resolves over the first few days, leaving more selective cognitive problems. These can include impairment in the areas of memory, language, praxia (control of purposeful movement), and executive skills, such as reasoning, planning, self-monitoring, and judgment. Uninhibited, impulsive, or disorganized behavior (often termed *personality change*) can also be observed; when present, these changes are perplexing and upsetting for family members or carers.

It is estimated that at least 35% of those who survive stroke have significant intellectual impairment, and it is well established that the presence of cognitive impairment following stroke has a negative impact on rehabilitation outcome (Diller, 2000). As the incidence of organic cognitive impairment rises sharply with age, the issues relevant to cognitive screening in stroke are also applicable to the general rehabilitation of older adults.

Early assessment of cognition can help with tailoring rehabilitation programs, thereby increasing the likelihood of success. It can also reduce strain in carers (McKinney *et al.*, 2002). Although neuroimaging techniques are increasingly precise, there often remain discrepancies between observed cognitive difficulties as a result of neuropathology and imaging results (Bigler, 2000). Routine cognitive screening on admission to rehabilitation therefore offers insight into cognitive difficulties, allowing therapy sessions to be tailored

more appropriately to individual needs. Such screening tools include the MMSE (Mini-Mental State Examination), (Folstein *et al.*, 1975) – a quick but rather insensitive measure of general cognitive function; the MEAMS (Middlesex Elderly Assessment of Mental State), (Golding, 1989); or the cognitive assessment from the CAMDEX (The Cambridge Examination for Mental Disorders of the Elderly), (Roth *et al.*, 1998). Further detailed assessment of memory, executive functioning and perceptual disorders may be indicated from these screening measures.

For the assessment of complex cases, the use and interpretation solely of standardized screening assessments is inadequate. Clinical psychologists have an expertise in the more detailed assessment of such complex cases, drawing on published specialized neuropsychological tests developed and standardized under strict conditions of reliability and validation. A mapping of cognitive strengths and needs provides a basis for tailoring rehabilitation strategies for individual patients, which is especially valued by rehabilitation colleagues. Cognitive assessment can help the patient and their family understand some of the symptoms they may have been experiencing or witnessing, and greater understanding can lead to greater tolerance and possibly avert relationship difficulties (McKinney *et al.*, 2002). Repeated cognitive assessment can monitor change in cognitive level and so rehabilitation tasks can alter accordingly. This is particularly true if the patient is also suffering from a form of dementia, which generally implies a global and progressive impairment of cognitive function. It is also often necessary to assess cognitive function as part of a wider assessment-determining capacity to make a range of medico-legal decisions including consent to treatment and procedures, as discussed later.

An important element of the clinical psychologist's assessment is the evaluation of neuropsychological skills known to underlie driving competency (*see* **Chapter 13, Transportation, Driving, and Older Adults**). This applies to any form of neurological brain damage, whether from stroke, Parkinson's disease, dementia, or other. On-road assessment at an accredited driving assessment center remains a "gold standard" evaluation, particularly from the perspective of licensing agencies (*see* **Chapter 13, Transportation, Driving, and Older Adults**). However, within rehabilitation settings, it is important to make a clinical evaluation of the necessity for referral for on-road testing. The clinical relationship that develops during rehabilitation engenders a responsibility to offer informed advice to patients about the objective need for a further level of assessment, particularly for patients who may be highly likely to fail on-road evaluation. Rehabilitation units should be able to offer the first two of three stages of assessment of likely driving competence. At the first screening stage, a tool such as the Stroke Drivers Screening Assessment may be used. This has been developed by the Stroke Rehabilitation Unit at Nottingham University (Nouri and Lincoln, 1993) and has a high success in predicting who will pass or fail on-road evaluation. Clear success or marked failure on such a screening assessment may thus result in advice about driving safety without the need for more extensive on-road evaluation. Patients whose results on such screening fall into a "gray" midscore range may then undertake more extensive neuropsychological testing with a clinical psychologist, that is, progress to the second stage of assessment while still in rehabilitation services.

There is good evidence regarding what the important neuropsychological skills underlying driving competence are. Driving may be significantly compromised in the presence of impairment of the key skills of executive functioning, visuospatial perceptual skills, praxis, and language (McKenna, 1998). The key executive skills indicated to be related to driving skills include sustained attention, divided attention, self-monitoring, planning ahead, decision-making, and problem solving. Thus, this more detailed neuropsychological evaluation at the second stage can result in clear successes and failures, thus allowing feedback and informed advice for or against driving. Patients whose performance falls within the "gray" midrange on such detailed evaluation may then be referred on to the third stage of testing – on-road evaluation at a driving assessment center. Avoidance of a probable on-road failure experience by such prior screening and neuropsychological assessment can be seen as part of a humanistic approach to rehabilitation. It is a more appropriate clinical role to offer such patients realistic advice based on an evaluation of their known skills than to refer all patients for on-road testing regardless of their likelihood of success or failure. This is particularly appropriate for patients suffering dementia, who may lack insight into their declining powers, yet could be potentially grossly humiliated by on-road testing without prior advice.

Cognitive Rehabilitation

Cognitive rehabilitation, in particular, neuropsychological rehabilitation in functional tasks, can help people with stroke and other neurological disorders adjust to, and compensate for, cognitive impairment, thus minimizing disability (BPS, 2002). Evidence of the effectiveness of direct retraining of lost abilities is limited; however, there is some research that indicates that certain approaches to address memory and executive disorders can be effective. One approach involves errorless learning, a technique, which, as the name implies, involves learning without errors or mistakes. Most learning results from remembering mistakes. However, people without episodic memory cannot remember their mistakes, so fail to correct them. Furthermore, engaging in a behavior can strengthen or reinforce it even though that behavior is errorful. Consequently, for someone with severe memory impairment, it makes sense to ensure that any behavior that is going to be reinforced is correct rather than incorrect (Wilson and Clare, 2003). In 1994, Baddeley and Wilson published the first known study demonstrating that amnesic patients learn better when they are prevented from making mistakes during the learning process (Baddeley and Wilson, 1994). Additionally, it is well known that tasks and situations that depend upon implicit memory are more likely to benefit from errorless learning methods than tasks requiring explicit and conscious recall of new learning.

The functional problems that arise from the dysexecutive syndrome are multidimensional, and there is no single approach regarding rehabilitation. Some interventions are driven by cognitive models of executive functioning, while others attempt to train people to use external aids to act as cuing systems, thus circumventing underlying executive impairment. Yet others adopt a process-oriented approach in which the goal is to stimulate recovery of cognitive functioning and promote reorganization of cortical function (Sohlberg *et al.*, 1993). Interventions will differ in terms of what deficit or problem they are attempting to change. Problems can broadly be described in terms of difficulties with anticipation, goal selection, planning, organization, initiation, execution, and self-regulation of goal-directed activity. Interventions, therefore, can be designed to modify one or more of these problems. One such intervention involves goal management training, a theoretically derived protocol that addresses that subset of executive functions serving the maintenance of intentions in the self-regulation of behavior (Levine *et al.*, 2000). Burgess *et al.* (1998), however, suggest that the dysexecutive syndrome consists of a number of factors, such as inhibition, intentionality, executive memory, positive and negative affect. Conceptualizing difficulties using this schema could lead to a different categorization of interventions than those offered to date.

One particularly important aspect of rehabilitation of executive difficulties is the recognition of residual difficulties that may continue to impact greatly on behavior. Self-regulation of goal-directed behavior may never be successfully achieved, and family carers face a significant role in providing high levels of monitoring, regulation, supervision, and support on an ongoing basis. The challenges involved for family members are considerable and carers need thorough preparation by the rehabilitation team and ongoing advice and support when a patient returns to their family environment.

Patient-centered Goal Planning

As mentioned earlier in this article, Michie *et al.* (2003) stressed the importance of patient activation and involvement. One of the methods of promoting engagement is through the process of goal planning – a patient-centered approach of defining aims and targets throughout the period of rehabilitation.

Kennedy *et al.* (1986) have described the process as: "a behavioral intervention strategy which involves the multidisciplinary team and the patient in negotiating and establishing goals based on the individual's needs. During goal planning meetings, needs are identified, goals are set and targets clarified. An action plan is agreed specifying who will do what, under what conditions and to what degree of success".

Appropriate rehabilitation goals are improved mobility, increased participation in activities of daily living (ADL), improved cognitive function, or reduced duration or frequency of hospital stays. All these goals combine to allow the patient to optimize role fulfillment or renegotiate their valued role. McGrath and Adams (1999) have demonstrated that appropriate goal planning can also reduce anxiety, distress, and negative affect in both patients and family.

In addition, in an audit of 100 consecutive neurorehabilitation cases, McMillan and Sparkes (1999) found significant correlations between achievement of long-term goals and physical outcome. They argue that goal planning can be the core procedure for neurorehabilitation, which in addition provides audit information and a simple, if unsophisticated, measure of change. It can improve coordination and cooperation among all those involved in the rehabilitation of patients, whose aim is to reduce disability and increase quality of life.

Sexual Function

The consequences and fears following stroke or any other major illness (such as neurological disorder or cardiovascular problems) can result in changes in sexual feelings and opportunities for individuals and their partners; medication can have adverse effects on sexual function; and illnesses that result in disability such as stroke and dementia can lead to important changes in sexual behavior. In addition, factors such as loss of self-esteem, depression, reduced level of desire, fears of precipitating another medical incident, role shifts, concern about the partner's response, performance anxiety, limited mobility, communication difficulties, and cognitive deficits, may well have an impact on sexual function.

Yet, despite the high prevalence and incidence of sexual dysfunction, it is an area that is often not addressed by clinicians. This may be due to simple oversight, discomfort with the topic, or stereotypic notions about the asexuality of older people. Although sexual activity may well decline with age, this is not always necessarily the case, and the needs of each patient and his or her partner should be evaluated individually (*see* **Chapter 11, Sexuality and Aging**). Clinical psychologists in rehabilitation usually have a valued therapeutic relationship with patients, which allows them to create the opportunity for safe and open discussion of sexual difficulties. Advice, therapy, and support to patients and partners facing such difficulties draws on the psychotherapeutic skills that clinical psychologists offer, often in the context of a systemic family therapy model. They are also able to provide guidance and management interventions when inappropriate sexual behavior becomes challenging to staff, relatives, and other patients.

Environment

The impact of environmental factors on the behavior of older adults in rehabilitation settings is not well understood. We may speculate that important mediating constructs include control, social, and cultural expectations of the rehabilitation setting.

In a study by Maclean *et al.* (2000), patients reported how their attitude toward rehabilitation was influenced by a range of factors, such as the manner in which health-care

professionals communicated information; overprotection by family members and nurses; comparisons with other patients' performance; and the unstimulating hospital milieu. Patients with high and low motivation placed different emphases on how environmental factors influenced their attitude toward rehabilitation.

ETHICAL ISSUES

In any rehabilitation setting, there are many ethical dilemmas that are frequently difficult and complex (*see* **Chapter 141, Ethical Issues**). Clinical psychologists are often involved as part of the health-care team in addressing these difficulties. A common area of concern is the assessment of an individual's mental capacity to make decisions about their treatment regime. Adults with the capacity to take a particular decision are entitled to refuse the treatment being offered, even if this will clearly be detrimental to their health. The only exception to this rule is where treatment is being provided for mental disorder, under the terms of the mental health legislation. Detention under mental health legislation does not give a power to treat unrelated physical disorders without consent, however.

Within UK legislation, adults are always presumed to be capable of taking health-care decisions, unless the opposite has been demonstrated. This applies just as much to older people as to any other adult: age or frailty alone is not a reason for doubting a person's capacity. For people to have the capacity to make a particular decision, they must be able to comprehend and retain information relevant to the decision, especially as to the consequence of having or not having the interventions in question, and use and weigh up this information in the process of decision-making. Some people may have the capacity to consent to some interventions but not to others. People suffering from the early stages of dementia, for example, would probably still have the capacity to make many straightforward decisions about their own care (e.g. washing or bathing) but might lack capacity to take very complex decisions. A person's capacity may also fluctuate.

If a person lacks the capacity to make decisions about their own health care, it is still possible for treatment and care to be provided lawfully, provided the care is in the person's "best interests" as determined by responsible professional opinion, taking their known views into account. It is crucially important to optimize the patient's participation in discussions, and to address as far as possible overcoming communication difficulties. Care can be validly refused in advance in some form of "advanced directives", which vary from country to country.

Additionally, two further ethical issues that arise in rehabilitation are the patient's capacity to give informed consent to a treatment or procedure such as Percutaneous Endoscopic Gastrostomy (PEG) feeding, and whether a patient retains the capacity to make a decision about their future care, particularly if it is felt by the rehabilitation team that a return to previous living arrangements is considered inappropriate due to the individual's specific needs or the risks involved.

The clinical psychologist's involvement in assessing capacity can include in-depth awareness of neuropsychological strengths and needs (particularly in the assessment of the executive function that can impact on the individual's cognitive insight into their difficulties), an understanding of the person's mental health state at the time of the assessment, and, possibly, a more comprehensive knowledge of the patient, and their family's, wishes regarding treatment. They may thus be seen as acting as the patient's advocate where knowledge has been gained through neuropsychological assessment and clinical interview. Clinical psychologists are in a strong position to assist other health-care professionals to optimize individual patients' participation where there are difficulties in communication or where doubt exists about the individual's comprehension or retention of information.

CONCLUSION

This article has addressed the body of theoretical knowledge available to clinical psychologists working in health rehabilitation settings. The exploration of a number of models for understanding the human response to illness, disability, and rehabilitation has served to illustrate the ways in which rehabilitation efforts can be optimized. Patients' participation and active involvement in rehabilitation and self-management of chronic illness can be effectively elicited through attention to key constructs within these models, and clinical psychologists offer skills in working closely with patients, families, and clinical rehabilitation staff to enable better understanding of these psychological and psychosocial factors. Clinical psychologists' roles within rehabilitation settings can optimize the recognition, understanding, and treatment of neuropsychological impairments, mood disorder, difficult individual and family adaptation and adjustment, and important medico-legal dilemmas.

KEY POINTS

- Patients' responses to illness and disability can be better understood by reference to a range of models of health behavior.
- Key constructs in these models include *self-efficacy beliefs, control, health value, sociocultural and environmental eliciting cues*, and *goal value and importance.*
- Psychotherapeutic approaches offered by clinical psychologists include CBT, family therapy, motivational interviewing, solution-focused therapy, and cognitive rehabilitation.
- It is crucial to develop systems and processes to identify mood and neuropsychological impairment in

older people in rehabilitation settings. Clinical psychological approaches may contribute both individually and within the team system to support identification and treatment of these difficulties.
- A range of medico-legal-ethical issues are present in rehabilitation settings. Clinical psychologists' close relationships with patients and families, and their analytic skills and knowledge allow effective partnership with all colleagues to address these issues as sensitively as possible.

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Epilepsy

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INTRODUCTION

Epilepsy is the third commonest neurological diagnosis in old people after dementia and stroke. The peak ages of onset of epilepsy are in childhood and old age (Hauser, 1992) (Table 1 (Tallis *et al.*, 1991)). About 25% of newly diagnosed patients and 23% of people with epilepsy in the community are over the age of 60. However, little epilepsy research has been undertaken in elderly subjects (Crowley, 1994).

Epilepsy is defined as the tendency to recurrent seizures, excluding febrile convulsions. A single seizure is not considered as "epilepsy" though recent studies have suggested that up to 75% of people go on to have a second seizure (Hart *et al.*, 1990). A seizure results from a paroxysmal abnormal synchronous electrical discharge in the brain (Hopkins, 1995). A diagnosis of epilepsy is not an endpoint diagnosis – it should automatically lead to investigations for classifying the type of seizure (compare making a diagnosis of jaundice) as epilepsy is the result of many diverse neurochemical, neuropathological, and neurophysiological abnormalities.

Epilepsy is a clinical diagnosis based on an eyewitness description of an episode. About 10% of people with a diagnosis of "epilepsy" do not have the disorder. One of the commonest misdiagnoses is reflex anoxic seizures. These occur when someone feels faint and is kept upright, a few muscle jerks occur and a diagnosis of an "epileptic" seizure is made. As epilepsy has such serious consequences with regard to activities of daily living, in particular, driving, it is a diagnosis which should not be made lightly. If there is doubt, it is better to await clear evidence. An electroencephalogram (EEG) does not make the diagnosis of epilepsy as many trivial abnormalities are often overinterpreted. An EEG simply helps classify the kind of epilepsy – localization-related or generalized.

ETIOLOGY

In the majority of elderly patients developing epilepsy, it will be presumed to be secondary to cerebrovascular disease (Table 2) (Hildick-Smith, 1988). Although the majority of patients are worried that they have an underlying brain tumor, this is rare. Neurodegenerative diseases such as Alzheimer's disease account for a significant percentage of those developing epilepsy but with the advent of MRI scanning it is likely that in a higher proportion of patients an etiological factor will be found.

Dementia

Epileptic seizures are common in demented patients, especially in the later stages of the disease. A study in Dundee suggested that 9% of patients had had an epileptic seizure. Ninety-two percent of reported seizures were tonic clonic. As complex partial seizures are generally more common than tonic-clonic seizures, this would suggest probably many partial seizures go unrecognized. Patients developing epilepsy were significantly younger and more severely demented. On the whole, the epilepsy appeared to be reasonably well controlled (McAreavey *et al.*, 1992). Another study found that the mean onset of epilepsy was 6.5 years (range 2–15 years) after the onset of the dementia. There was a threefold increase in the incidence of epilepsy compared to a reference population (Hauser *et al.*, 1986).

A study of 446 autopsy-proven cases of Alzheimer's disease found that 17% were documented as having seizures during their lifetime. However, two-thirds of patients had less than three seizures, suggesting that on the whole the seizure disorder was mild (Mendez *et al.*, 1994).

Cerebrovascular Disease

Cerebrovascular disease is the commonest cause of seizures in the elderly. The overall incidence of seizures after a cerebrovascular accident varies between 4.4 and 12.5%, depending on the population studied and the methods used. Studies looking at the risk factors for the subsequent development of epilepsy have suggested that patients with hemorrhagic

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Table 1 Incidence of epilepsy at different ages

Age	Incidence
0–10	$60:10^5$
20–40	$40:10^5$
60–69	$101:10^5$
70–79	$150:10^5$
80–89	$190:10^5$

Source: Reproduced from Tallis R *et al.*, How common are epileptic seizures in old age, *Age and Ageing*, **20**, 442–448, by permission of Oxford University Press.

Table 2 Etiology of the seizure disorder in elderly people with epilepsy (Hildick-Smith, 1988)

Cerebrovascular disease	30–42%
Tumor	2–14%
Dementia	2–14%
Toxic/metabolic	6–12%
Other	22–58%

Source: Reproduced by permission of Royal Society of Medicine Press.

strokes, cortical lesions, or lesions involving more than one lobe are at greater risk of developing epilepsy. About 50% of patients have a seizure within a month of the "stroke". About a quarter will go on to have further seizures. There are no significant differences between those who develop late epilepsy and those who have seizures within 1 month of the "stroke" (Lancman *et al.*, 1993).

DIAGNOSIS

The diagnosis of epilepsy is the same in elderly as in younger patients. It is a clinical diagnosis based on eyewitness description of the episodes. One of the major problems in diagnosing epilepsy in the elderly is that they may be unable to give a description of what is actually happening to them before or after an attack and as they often live on their own, an episode may not have been witnessed. A classical tonic-clonic seizure is relatively easy to diagnose from eyewitness descriptions. Minor attacks such as absence or complex partial seizures are much more difficult to diagnose. Often they may consist of staring episodes where the person is not responsive for a few seconds. These can be followed by automatisms or confusion, often quite short lived.

An EEG is useful for the classification of seizure type. Only rarely can it be used to make a diagnosis, that is, if a seizure occurs whilst an EEG is being performed or specific diagnostic EEG changes occur.

DIFFERENTIAL DIAGNOSIS

Transient Ischemic Attacks

A TIA is a vascular event lasting less than 24 hours. It tends to be associated with negative phenomena such as weakness or sensory loss. Conversely, epilepsy tends to have positive phenomena such as paresthesiae or jerking of a limb. However, at times it is difficult to differentiate simple partial seizures from TIAs. If consciousness is lost, it is very unlikely to be a TIA. It also has to be remembered that cerebrovascular disease is an important etiological factor in the development of epilepsy (*see* **Chapter 45, Arrhythmias in the Elderly** and **Chapter 69, Epidemiology of Stroke**).

Transient Global Amnesia

This is not an uncommon disorder occurring in later life, when a person has no memory for a significant period of between a few hours and a day or so. Eyewitnesses say that the person appeared normal and was able to perform complex tasks. On closer questioning, the person often was repeating the same questions such as "what time is it?" A person tends to have only a single episode so if repeated the diagnosis needs to be reconsidered. The symptoms are due to a defect in memory for events of the present and recent past. During the episode, consciousness is retained and there is no impairment in intellectual functioning.

Although considered by some to be related to vascular disease, recent studies have suggested that there is no increase in risk factors for vascular disease and no subsequent increase in cerebrovascular disease. There is, however, an increased incidence of migraine.

Transient global amnesia is an important diagnosis to make in that, unlike epilepsy, people in the United Kingdom with this condition, after reporting to the Driving Vehicle Licensing Authority (DVLA), are allowed to continue driving.

Cardiac Arrthymias

These are very important in the differential diagnosis of epilepsy in the elderly. If the brain is starved of oxygen, for whatever reason, a tonic-clonic seizure will result. Both tachy- and bradyarrthymias can result in tonic-clonic seizures. Clues to the fact that the seizure may be a secondary phenomenon may be found in the prodrome. A history of feeling faint or preceding or a history of palpitations should make a clinician suspect a cardiac cause for the episodes of loss of consciousness.

A 24-hour EEG with an ECG lead can be useful in trying to differentiate between a cardiac and an epileptic episode. If the episode is cardiac in nature, the arrythmia will begin before the abnormal electrical activity in the brain by a significant time lapse. It has to be remembered that during a seizure, it is not uncommon for a cardiac arrythmia to occur but it will begin about the same time as the abnormal electrical activity in the brain.

Syncope

If a person is kept upright during a vasovagal attack, it is not uncommon for a few myoclonic jerks to occur and in

susceptible people, a tonic-clonic seizure can result. The events leading up to the episode of loss of consciousness as well as eyewitness descriptions are very important. The feeling of faintness, dizziness, the need to get fresh air preceding the episode make it likely that the episode was syncopal rather than epileptic in nature.

The person is usually upright during the episode. They feel dizzy, queasy, and giddy and often things recede or go black. Pallor is noted and often a cold perspiration. Nausea and vomiting occasionally accompanies these symptoms. After falling to the ground, consciousness is regained very fast and if the person lies down, often the episode can be aborted. A few myoclonic jerks can occur, as can incontinence if the bladder is full.

Micturition syncope, especially in men having to get up during the night, is a relatively common cause of loss of consciousness; so too is cough syncope.

The elderly are more prone to syncope as they may have impaired cardiovascular reflexes or be on vasodilating drugs such as glyceryl trinitrate (GTN) or have carotid sinus hypersensitivity.

Nonorganic Epileptic Attacks

Psychogenic seizures beginning *de novo* in the elderly are very rare but there have been occasional case reports (Fakhoury *et al.*, 1993).

Panic Attacks

It is rare for these to present *de novo* in the elderly as usually there is a life long history. The person feels that something is going to happen. He/she feels the need to take deep breaths, becomes dizzy and light-headed, develops paresthesiae in the limbs and around the mouth, and the legs become heavy. Symptoms can be reproduced by getting the person to hyperventilate. The initial precipitant was often a faint and panic attacks develop subsequently because of a fear of a further episode.

Drop Attacks

These are episodes of unknown etiology where a middle-aged or older person, usually a woman, will suddenly drop to the ground. There is no preceding warning and consciousness is not lost. There is often bruising to face, hands, and knees. After the episode, the person can get up immediately. The EEG is normal, even during a fall. There is no treatment (*see* **Chapter 83, Abnormalities of the Autonomic Nervous System** and **Chapter 112, Gait, Balance, and Falls**).

Hypoglycemia

Hypoglycemia is a rare cause of tonic-clonic seizures. It obviously needs excluding in diabetic patients on treatment. Rarely an insulinoma can produce tonic-clonic seizures. Other metabolic causes such as hypocalcemia can precipitate seizures.

Alcohol and Drugs

Alcohol abuse and withdrawal can precipitate seizures and it is important to take a alcohol history even in the elderly. Many drugs, particularly tricyclic antidepressants, antimalarials, phenothiazines, and butyrophenones lower the seizure threshold and can precipitate seizures. The withdrawal of benzodiazepines occasionally can produce seizures (*see* **Chapter 102, Drug Misuse and the Older Person: A Contradiction in Terms?** and **Chapter 15, Alcohol Use and Abuse**).

SEIZURE CLASSIFICATION

Epilepsy is classified in two ways. There is classification of the seizure itself (Commission on classification and terminology, 1981) (Table 3) and then there is syndromic classification (Commission on classification and terminology, 1989).

Epilepsy is divided into two main groups. The generalized epilepsies are when the abnormal electrical activity rises from both hemispheres together (generalized spike wave). Localization-related epilepsy is when the abnormal electrical activity arises in one place in the brain and then spreads.

Generalized Epilepsies

The generalized epilepsies are divided into two broad categories. *Primary generalized epilepsy* is a genetic disorder that manifests itself in various syndromes such as childhood absence epilepsy and juvenile myoclonic epilepsy. Various types of seizures can occur, such as absence seizures,

Table 3 Classification of seizures (Commission on Classification and Terminology, 1981)

I. *Partial seizures*
  A. Simple partial seizures
  B. Complex partial seizures
    1. With impairment of consciousness at onset
    2. Simple partial onset followed by impairment of consciousness
  C. Partial seizures evolving to generalized tonic-clonic convulsions
    1. Simple evolving to generalized tonic-clonic convulsion
    2. Complex evolving to generalized tonic-clonic convulsion (including those with simple partial onset)

II. *Generalized Seizures*
  A. 1. Absence seizures
    2. Atypical absence
  B. Myoclonic seizures
  C. Clonic seizures
  D. Tonic seizures
  E. Tonic-clonic seizures
  F. Atonic seizures

III. *Unclassified seizures*

myoclonic, and tonic-clonic seizures in association with generalized spike wave (3/second) on the EEG. These syndromes tend to occur in people of normal intelligence and begin in childhood or early adult life although occasionally new onset cases have been seen in the elderly (Grunewald and Panayiotopoulos, 1994). Minor seizures beginning for the first time in the elderly are not absence seizures or *petit mal*. They are likely to be complex partial seizures. Primary generalized epilepsy responds best to treatment with sodium valproate, or lamotrigine, or levetiracetam as second-line therapy. The outlook for total seizure control is excellent. The majority of children with childhood absence epilepsy will be seizure free and off treatment by adult life. Most patients with juvenile myoclonic epilepsy become seizure free but will relapse if treatment is stopped even if the patient is elderly.

The second category is symptomatic generalized epilepsy which is more commonly seen in people with learning disabilities.

Localization-related Epilepsy

In localization-related seizure disorders the abnormal electrical activity begins in one area of the brain and spreads. The seizure manifestations depend on the site of onset of the abnormal electrical activity and the rate of involvement and spread to other areas of the brain. For example, abnormal electrical activity arising in the temporal lobe may begin with a feeling of fear or *déjà vu* or an abnormal taste or smell. This is a simple partial seizure. As the abnormal electrical activity spreads, it involves more of the temporal lobe and consciousness is lost, a complex partial seizure. The person may be seen to stare or gulp or swallow or perform repetitive movements or automatisms. If the abnormal electrical activity spreads to the other side of the brain, a tonic-clonic seizure results. Therefore, tonic-clonic seizures occur in both generalized and localization-related epilepsies. This is the type of epilepsy that usually begins in late adult life.

INVESTIGATIONS (TABLE 4)

EEG (Table 5; Fish, 1995)

The diagnosis of epilepsy is based on an eyewitness description of a seizure, plus the exclusion of other causes. An EEG is useful in trying to classify the type of seizure disorder and occasionally in diagnosis if seizure activity is captured. Many patients without epilepsy will have minor abnormalities in the EEG particularly in the elderly because of cerebrovascular disease. In between seizures, a person with epilepsy can have a normal EEG; so an EEG is not an appropriate tool to diagnose epilepsy.

If an ordinary EEG is normal, a *sleep deprivation EEG*, performed after a night without sleep, can sometimes be helpful.

Table 4 Investigation of epilepsy in the elderly

EEG	Routine
	Sleep deprivation
	24-hour ambulatory
	Video telemetry
ECG	Routine
	24-hour ambulatory
Basic hematology	
Urea and electrolytes	
Blood sugar	
Calcium	
CXR	
CT scan/MRI	

Table 5 Types of EEG and their principal use in epilepsy

Type of EEG study	Principal indications
Routine EEG	Help confirm the diagnosis of epilepsy Classify the seizure disorder Look for photosensitivity Look for specific syndromes
Sleep/sleep deprived	In patients with normal EEGs to help classify the seizure disorder
Ambulatory EEG	Detection/quantification of generalized spike wave discharges Diagnostic screening test in patients with paroxysmal attacks of unknown cause
Video-EEG telemetry	Diagnosis of paroxysmal attacks Seizure classification/quantification

Source: Reproduced from Fish D. The role of electroencephalography. In Epilepsy Second Edition, 1995, pp 123–142. With kind permission of Springer Science and Business Media.

Ambulatory EEGs and *videotelemetry* can be useful in the diagnosis of odd episodes of loss of consciousness. A 24-hour ambulatory EEG is portable but only records from a few scalp electrodes. An ECG lead should be recorded at the same time. When the person feels an event coming on or has happened, an event button is pressed. The episode can be reviewed for both the cardiac rhythm preceding and during the event and the EEG activity. However, it must be realized that epileptic episodes may be missed or misinterpreted because of the placement of electrodes or movement artifact. Videotelemetry is a more sophisticated monitoring technique that is only available at specialist neurological centers. A standard EEG and ECG are recorded at the same time as the patient is videoed. This means that the episode can be observed as well as looking at the EEG. Neither of these investigations is likely to be of value unless the patient is having at least weekly episodes.

ECG

A routine ECG can either demonstrate a cardiac arrhythmia or suggest that a patient may be prone to a brady- or tachyarrhythmia, for example, heart block or an supra ventricular tachycardia (SVT). If cardiac causes are suspected, a 24-hour ECG is mandatory.

CT Scan/MRI

A form of imaging is valuable in trying to determine the etiology of the seizure disorder especially as neurosurgeons will consider operations on older patients. If seizures are focal in origin, an MRI scan is the most sensitive investigation to look for underlying pathological changes. A normal CT scan will exclude any major underlying pathology, although a small low-grade glioma may not be visible. A change in seizure frequency or the development of neurological signs is an indication for rescanning.

Other investigations such as basic hematology, biochemistry, and an ECG are usually performed. Various other investigations may be indicated, depending on the likely etiology of the seizures.

TREATMENTS

The aim of treatment is to suppress seizures totally with the lowest possible dose of one antiepileptic drug. This can be achieved in about 70% of people developing epilepsy. The choice of drug depends on the type of seizure disorder and various factors such as other medical conditions and therapies (Crawford, 1994; Shorvon, 1995a). The elderly are also more prone to antiepileptic drug side effects and interactions partly because of concomitant diseases and medications. Long-term antiepileptic treatment also predisposes toward osteoporosis. It is estimated that antiepileptic drug treatment for over 5 years doubles the risk of osteoporotic fractures in the elderly (Sheth, 2002).

In primary and symptomatic generalized epilepsy, the drug treatment of choice is sodium valproate or lamotrigine.

In people with localization-related epilepsy, all the first-line drugs are equally effective; they just differ in side effects. It is therefore advisable to choose a drug with a low side effect profile such as carbamazepine, sodium valproate, or lamotrigine. Barbiturates (phenobarbitone, mysoline) have little place in today's treatment of epilepsy. Phenytoin, although an effective drug, is difficult to use (Table 6). Second-line therapies include gabapentin, levetiracetam, topiramate, and tiagabine. Clobazam can be useful for predictable seizures or when they occur in clusters.

Table 7 Elimination half-life of antiepileptic drugs

	Half-life (hours)	
	Adult	Elderly
Carbamazepine	5–26	35–36
Phenytoin	20–40	Not established
Sodium valproate	9–15	13–19

Source: Reprinted from Leppik IE, Metabolism of antiepileptic medication: newborn to elderly, *Epilepsia*, **33**(suppl 4) S32–S40, with permission from Blackwell Publishing Ltd.

A study looking at antiepileptic drug usage in the elderly showed that the mean dose of antiepileptic drug was lower than in younger patients. Even so 27% of these patients felt that they had side effects from their medication (Cameron and Macphee, 1995).

Several studies show that a greater proportion of drugs such as phenytoin, sodium valproate, and benzodiazepines are present in the free state in plasma in the elderly, which implies a higher brain concentration. There is an alteration in the half-life (Table 7) and clearance of the commonly used antiepileptic drugs, suggesting reduced dosage requirements (Leppik, 1992).

ANTIEPILEPTIC DRUGS (TABLE 7)

Phenobarbitone

Phenobarbitone is an effective antiepileptic drug but its use is accompanied by an unacceptably high incidence of behavioral problems and sedation. There are many new drugs that are just as effective, but produce a much lower incidence of side effects.

Primidone

Primidone is a compound that is converted in the body to phenobarbitone. It has an even higher incidence of side effects than phenobarbitone and should no longer be used (Mattson *et al.*, 1985).

Table 6 Titration schedule for commonly used antiepileptic drugs

Drug	Starting dose	Dosage schedule increments fortnightly	Maximum dose/day	Frequency
Carbamazepine	100 mg BD	100 mg	800–1000 mg	BD
Sodium valproate	200 mg BD	200 mg	2500 mg	BD
Phenytoin	100 mg BD	50 mg	400 mg	ID
Lamotrigine	50 mg ID	50 mg	200–300 mg	BD
With enzyme inducers	50 mg ID	50 mg	400 mg	BD
With sodium valproate	25 mg alternate nights	25 mg	100–150 mg	BD
Gabapentin	400 mg TDS	400 mg over 1 week	2400 mg	TDS
Topiramate	50 mg	50 mg	400–600 mg	BD
Levetiracetam	250 mg	250 mg	2000–3000 mg	BD

Phenytoin

Phenytoin is an effective antiepileptic drug but appears to have a higher side effect profile (Table 8) than some of the newer agents. It is a difficult drug to use because of its many interactions and saturable metabolism. Phenytoin has a narrow therapeutic range and nonlinear pharmacokinetics, so small increases in dosage can precipitate toxicity. A comparative study of phenytoin and sodium valproate suggests that they are both equally effective in controlling seizures in the elderly, while having similar effects on cognitive function (Craig and Tallis, 1994; Tallis *et al.*, 1994).

Carbamazepine

Carbamazepine is one of the first-line drugs for the treatment of partial seizures. It can have a positive effect on behavior. It is a hepatic microsomal enzyme inducer and therefore speeds up the metabolism of other drugs such as warfarin, phenytoin, phenobarbitone, and lamotrigine as well as inducing its own metabolism. Its main side effect is a rash which occurs in about 10% of people (Table 9). If it is given in high dosages people are likely to complain of double vision and drowsiness. If this occurs after a dosage increase, it is worth waiting a week to see if symptoms resolve as hepatic enzyme induction occurs and blood levels fall. Maximum tolerated monotherapy dosages tend to be between 800 and 1200 mg day^{-1}. The retard formulation tends to be associated with a lower incidence of peak dose side effects.

Sodium Valproate

Sodium valproate is the other first-line drug for localization-related epilepsies and the treatment of choice for the generalized epilepsies. A recent American study suggested that sodium valproate was less effective than carbamazepine against complex partial seizures but other studies have not found this.

The main side effects of sodium valproate are weight gain, tremor, and hair loss at higher doses (Table 10). About 60 cases of acute fatal hepatic failure have been reported with valproate therapy, the majority were children under the age of 2 with developmental delay. These problems should be differentiated from the benign elevation in liver enzymes that occurs in about 30% of patients treated with valproate.

Table 8 Side effects of phenytoin

CNS	Drowsiness	
	Dizziness	
	Incoordination	
	Ataxia	
	Involuntary movements	
	Mental slowing	
	Sedation	
	Confusion	
	Cerebellar degeneration	
	Peripheral neuropathy	
Skin	Gum hypertrophy	
	Coarsening of facial features	
	Hirsutism	
	Acne	
Hematological	Red blood cell aplasia	
	Thrombocytopenia	
	Agranulocytosis	
	Pseudolymphoma reaction	
Others	Hepatic failure	Vitamin D deficiency
	Low Ig A levels	Folate deficiency
	Myasthenia gravishyposexuality	
	Lupuslike reaction	Decreased fertility

Table 9 Side effects of carbamazepine

Dose dependant	Drowsiness
	Dizziness
	Ataxia
	Double vision
	Nausea
Idiosyncratic	Behavioral changes
	Rash
	Stevens Johnson syndrome
	Leucopenia
	Inappropriate ADH syndrome

ADH, anti diuretic hormone

Table 10 Side effects of sodium valproate

Dose related	Tremor
	Weight gain
	Anorexia
	Nausea and vomiting
	Dizziness
	Drowsiness
	Alopecia/hair loss/curly hair
	Encephalopathy
Idiosyncratic	Thrombocytopenia
	Hemorrhagic pancreatitis
	Acute hepatic failure
	Bone marrow aplasia

Gabapentin

Gabapentin is an antiepileptic drug that is structurally related to GABA. It is an effective antiepileptic drug in partial seizures but does not appear to work in absence seizures and may exacerbate some symptomatic generalized seizure disorders. It is also licensed for chronic pain. It has a low side effect profile. The main side effects reported are dizziness, drowsiness, and light-headedness. Its benefits are its ease of use and lack of interaction with drugs including other antiepileptic drugs apart from a minor interaction with cimetidine. Gabapentin is excreted unchanged in the urine; therefore, doses do need to be reduced in renal failure. It has been evaluated after stroke in the elderly (Alvarez-Sabin *et al.*, 2002; Crawford, 1996).

Pregabalin

Pregabalin is structurally related to Gabapentin. Clinical studies have shown it to be effective as add-on therapy in

resistant partial seizures. It has not been evaluated in the elderly.

Lamotrigine

Lamotrigine is a broad-spectrum antiepileptic drug like sodium valproate and is active against both generalized and partial epilepsies. It is well tolerated with a low side effect profile. Its main problems are those of rash and interactions with other antiepileptic drugs. This has meant that differing dosage schedules and maximum doses are used according to concomitant antiepileptic drugs. Its half-life varies from 15 hours, when used in combination with enzyme inducers such as phenytoin or carbamazepine, to 30 hours when used as monotherapy, and 72 hours when combined with sodium valproate. Lamotrigine is now licensed in the United Kingdom as first-line monotherapy medication. It appears to reduce interictal seizure activity and many people appear much brighter and more alert between seizures even though seizure frequency may not alter. Studies in elderly patients suggest it is well tolerated (Georgi *et al.*, 2001; Johnson and Johnson, 1994).

Topiramate

Topiramate appears to be an effective antiepileptic drug but does have a high side effect profile including mental slowing and difficulties in concentration.

Clobazam

Clobazam is a 1,5 benzodiazapine specifically licensed for the treatment of epilepsy. It is used in a dose of between 10 and 30 mg at night. Its main problem is that, if used daily, tolerance tends to develop in 30–70% of people. It is very useful for predictable seizures or if seizures cluster. It can be used to terminate episodes of minor status.

Clonazepam

Clonazepam tends to be used for generalized epilepsies. Again it has the problem of tolerance and appears to be more sedative than clobazam.

Diazepam

Rectal diazepam is of considerable value in terminating episodes of convulsive and nonconvulsive status epilepticus. It can be used in the community and the need for hospital admission may be avoided. There is a video available from the manufacturers to teach carers in the use of rectal diazepam.

Ethosuximide

Ethosuximide decreases absence and atypical absence seizures. It is of no value in complex partial seizures so has little use in the elderly.

Levetiracetam

Levetiracetam is a new broad-spectrum antiepileptic drug (AED). Subanalyses of studies have suggested that it is effective and well tolerated in the elderly (Cramer *et al.*, 2003; Ferendelli *et al.*, 2003).

Tiagabine

Tiagabine is a GABA re-uptake inhibitor that appears effective in people with complex partial seizures, particularly those who have responded to vigabatrin. At present it appears from clinical trials to have a lower side effect profile than vigabatrin and may provide a useful alternative to vigabatrin. It has not been evaluated in the elderly.

Oxcarbazepine

Oxcarbazepine is an analog of carbamazepine. It has advantages over the parent compound in that it appears less sedative with a significant lower incidence of side effects including rash. Its main drawback is that there is an increased incidence of hyponatremia compared to carbamazepine so it may be of limited use in the elderly (Kutluay *et al.*, 2003). Oxcarbazepine is effective against partial seizures.

ANTIEPILEPTIC DRUG LEVEL MONITORING

Antiepileptic drug levels only need to be monitored in those patients who have continuing seizures in order to check compliance, which is one of the commonest reasons for therapy failure. Levels are much more difficult to interpret in the elderly because of an increase in the free state and the lack of a "therapeutic" range in this age-group. People are their own *in vivo* drug assays. If someone is seizure free they are receiving the correct dosage of antiepileptic drug and no alterations in dose are indicated. If seizures continue without side effects then the dose can be increased. If dose-related side effects occur, the dosage is too high. There is no bottom limit to the so-called therapeutic range and many people are able to tolerate plasma levels in excess of the "upper limit" (Crawford, 1995).

Anticonvulsant levels occasionally are helpful for drugs such as phenytoin which have difficult pharmacokinetics and can give an idea of the scope for dose increments in someone with continuing seizures. Sodium valproate levels

are of little value as there are wide fluctuations in measured concentrations throughout the day. Blood level monitoring is not needed for any of the recently licensed antiepileptic drugs.

A study in elderly patients suggested that the majority of samples taken for antiepileptic drug concentrations were for no specific reasons and there was a limited response to the results obtained (Burns and McAlpine, 1992).

MANAGEMENT OF DRUG RESISTANT EPILEPSIES

If seizures have failed to respond to a first-line antiepileptic drug, various questions need to be asked.

1. Is this epilepsy?
2. Is this the best antiepileptic drug for the seizure type?
3. Is it being given in an adequate dosage?
4. Is the person actually taking the drug?

If someone has genuinely failed to respond, alternative therapies need to be considered. If seizures are predictable, intermittent clobazam is a useful adjunctive therapy. If not, another drug needs to be added, and the dosage increased until a response is obtained or side effects develop. If the second drug is ineffective, then it should be stopped before another therapy is considered. If it is effective, then the first drug gradually needs to be withdrawn, as the aim of treatment is someone seizure free on monotherapy (Crawford, 1994).

ANTICONVULSANT WITHDRAWAL

The Medical Research Council (MRC) antiepileptic drug withdrawal study showed that in patients who have been seizure free, at least 40% were able successfully to withdraw from therapy. The longer the seizure-free period, the greater the likelihood of success. Successful withdrawal was also associated with few seizures before becoming seizure free and the use of a single antiepileptic drug. Patients who had juvenile myoclonic have a greater than 95% chance of relapse even if they had been seizure free for many years. This is the only group of people that needs to be on treatment for life (MRC Antiepileptic Drug Withdrawal Study, 1991). Many elderly people would be able to satisfactorily stop AED therapy but are reluctant to decrease therapy because of the driving regulations. The DVLA in the United Kingdom suggests that a person does not drive whilst treatment is being reduced nor for 6 months after stopping treatment. If a person has a seizure on trying to come off therapy or afterwards, they need to inform the DVLA and may not drive for 1 year.

STATUS EPILEPTICUS

Status epilepticus is a major neurological and medical emergency associated with a high morbidity and mortality. It is defined as a condition in which epileptic activity persists for 30 minutes or more, this covers a wide spectrum of clinical symptoms and with a highly variable pathophysiological, anatomical, and etiological basis. The elderly give rise to the largest number of status epilepticus cases per annum even though the incidence is higher in childhood (DeLorenzo *et al.*, 1995; DeLorenzo *et al.*, 1992; Shorvon, 1995b).

In patients with established epilepsy, tonic-clonic status epilepticus rarely occurs without warning. It is usually preceded by a phase in which seizures become increasingly frequent and severe. Urgent treatment with a benzodiazepine (such as clobazam, diazepam, midazolam) or paraldehyde will often prevent the evolution into true status epilepticus. Once status epilepticus has developed the patient needs to be admitted to hospital and IV lorazepam (4 mg bolus IV) or diazepam (10 mg at a rate of 2–5 mg minute^{-1}) needs administering. If intravenous access is not possible, intramuscular (IM) or rectal paraldehyde is a useful alternative. If seizures continue, then an infusion of phenytoin (18 mg kg^{-1} at a rate of 50 mg minute^{-1}, e.g. 1000 mg in about 20 minutes) with diazepam 10–20 mg over 5–10 minutes if not already given, or phenobarbitone (10 mg kg^{-1} at a rate of 10 mg minute^{-1} e.g. 700 mg over 7 minutes) should be administered (Shorvon, 1995b).

If seizures continue for longer than 30–60 minutes, admission to an ITU is indicated, as treatment with a general anesthetic using either propofol or thiopentone is needed. Anesthesia should continue for 12–24 hours after the last clinical or electrical seizure and then the dose tapered down/off.

The clinical features of complex partial status are highly variable reflecting the diverse underlying pathophysiology. Episodes frequently last for many hours. It is characterized by confusion that can fluctuate. It can often be precipitated by a tonic-clonic seizure. It can vary from a profound stupor to mild mental slowing. Characteristically, language may be sparse and answers to questions, although appropriate are often delayed. There can also be motor manifestations and psychotic symptoms can occur. An EEG will be diagnostic (Shorvon, 1995b).

DRIVING

People who have been free of all types of seizures for 12 months or more may reapply for their licence. For those who continue to experience their seizures only during sleep, they may drive if that has been the only manifestation of their epilepsy for over 3 years.

KEY POINTS

- Epilepsy is the third commonest neurological disorder in the elderly.
- It is important to make an accurate definite diagnosis.

- Epilepsy in the elderly is usually easy to treat.
- Use an appropriate AED (taking into consideration preexisting disorders and medication) in the lowest possible dose.
- Long-term AED therapy predisposes toward osteoporosis.

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Syncope and Nonepileptic Attacks

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INTRODUCTION

Presentation with a "collapse", "blackout", or "funny turn", with or without impairment of awareness and responsiveness is common in older people and there is a wide differential diagnosis (Table 1). The commonest etiologies are epileptic seizures, the various types of syncope and cerebral vascular disease. Epileptic seizures and cerebral vascular disease are discussed in other chapters; this chapter deals with syncope and some of the less common etiologies, such as psychogenic nonepileptic attacks.

The information required to reach the correct diagnosis is usually contained within the history from the patient and from witnesses, and an adequate history will often obviate the need for extensive investigations. Difficulties arise most commonly when no witness account is available. When an attack has been witnessed, attempts should be made to contact a witness, even if he/she was a bystander not previously known to the patient. If a witness has not accompanied the patient to the consultation, a witness account can usually be obtained by making use of that important investigative tool, the telephone, and ringing the relative, friend, care assistant, shop assistant, and so on, involved. General practitioners or ambulance personnel called to attend a patient who has collapsed can provide crucial diagnostic evidence, as they are in a position to interview witnesses while the features of the episode are fresh in their minds.

Diagnosis can sometimes be difficult. Pending clarification by the occurrence of further attacks, diagnostic uncertainties may persist even after specialist referral and investigation. It is usually better to accept this diagnostic uncertainty, explaining it to the patient and relatives, than to plunge for a specific diagnosis which may be incorrect and lead to inappropriate treatment and management. In particular, problems arise when nonepileptic attacks are labelled as epileptic. The patient then has to come to terms with an erroneous diagnosis to which significant stigma is still attached, and receives unnecessary antiepileptic drug treatment, possibly with adverse effects.

SYNCOPE

Syncope can be defined as loss of consciousness due to transient impairment in blood flow to the brain. The term "presyncope" can be used to describe symptoms of impending syncope. It is impaired flow to the brainstem and thalamus that is most likely to result in loss of consciousness, and thus adequacy of flow in the posterior (vertebrobasilar) circulation usually determines whether syncope will occur. The impairment in blood flow can occur for a variety of reasons, and it is important to recognize this since the different causes of syncope have differing symptoms and signs. A classification of syncope is given in Table 2. The incidence of the different causes of syncope changes with age. In the older patients, areflexic syncope, cardiac syncope, and carotid sinus syndrome become increasingly frequent. It is a common problem accounting for 0.77% of A&E department attendances, with admission rates increasing with age (Sun *et al.*, 2004). A specialist syncope and falls service will improve the diagnosis and outcome (Kenny *et al.*, 2002).

Mechanisms Underlying Syncope

A sudden fall in blood pressure and syncope can occur due to the following:

1. "Reflex syncope", when there is a reflex response of an intact autonomic nervous system to a trigger (e.g. vasovagal syncope, carotid sinus syndrome).
2. "Areflexic (paralytic) syncope", when an erect posture is adopted and there is postural hypotension due to a dysfunctional autonomic nervous system (e.g. autonomic neuropathy).

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Table 1 Differential diagnosis of blackouts and funny turns

Syncope
Epilepsy
Transient ischemic attacks
Panic attacks
Hyperventilation attacks
Other psychogenic nonepileptic attacks ("nonepileptic attack disorder")
Sleep phenomena
Hypoglycemia
Migraine
Transient global amnesia
Cataplexy
Paroxysmal movement disorders
Paroxysmal symptoms in multiple sclerosis

Table 2 Classification of syncope

	Type of syncope	Triggers
Reflex	Vasovagal	Psychological (fear, trauma, pain)
		Low venous pressure (standing, hemorrhage)
		Anoxia
	Carotid sinus	Neck pressure
	Micturition	Micturition
	IX^{th} and X^{th} cranial nerve disease	Glossopharyngeal neuralgia
		Neck tumors
	Oculocardiac	Ocular pressure (children)
Areflexic	Autonomic neuropathy	Upright posture
	Spinal cord disease	Upright posture
	Drugs	Upright posture
	Old age	Upright posture
Cardiac	Dysrhythmias	
	Ventricular outflow obstruction	Exertion
Respiratory		Coughing
		Trumpeting
		Weight lifting
		Hyperventilation
Cerebrovascular	Vertebrobasilar TIAs	

3. "Cardiac syncope", when there is a sudden reduction in cardiac output due to a cardiac disorder (e.g. bradyarrhythmia, tachyarrhythmia).

Syncope can also occur due to transiently reduced perfusion of the brain in "respiratory syncope", when there is a transient increase in intrathoracic and intracranial pressure (e.g. cough syncope). Finally, a transient reduction in perfusion of the brainstem may also occur in cerebrovascular disease and occasionally present as syncope, for example, vertebrobasilar transient ischemic attacks (TIAs). In elderly patients, there may be a combination of these mechanisms.

In reflex syncope a fall in blood pressure occurs due to (1) bradycardia and a reduced cardiac output (cardioinhibitory response), (2) vasodilatation in muscle and a reduced peripheral resistance (vasodepressor response), or (3) a combination of these mechanisms (mixed response) (Barcroft *et al.*, 1944; Brigden *et al.*, 1950). In vasovagal syncope, these responses can be distinguished by tilt testing, and in the elderly vasodepressor responses are much more frequent than in younger patients (Galetta *et al.*, 2004). Recognition of this is important as insertion of a cardiac pacemaker is not likely to prevent attacks in patients with vasodepressor responses. In vasovagal syncope there is also reflex vasoconstriction in skin, causing pallor and reflex sweating. The trigger for these reflex responses is usually either "psychological" (e.g. a response to fear, sight of trauma, pain) (Roddie, 1977) or low venous pressure detected by mechanoreceptors in the great veins and heart (e.g. prolonged standing, hemorrhage) (Abboud, 1989). Anoxia can be a trigger, and it is important in the context of anesthesia and air travel (Sharpey-Schafer, 1956; Bourne, 1957). Nonmassive pulmonary embolism may present as syncope, probably by triggering a vasovagal reflex (Castelli *et al.*, 2003). In the carotid sinus syndrome syncope is thought to be triggered by activation of a "hypersensitive" carotid sinus, and can be provoked by carotid sinus massage; again cardioinhibitory, vasodepressor, and mixed responses occur. In micturition syncope, the trigger is the sudden loss of the pressor stimulus of a distended bladder (Taylor, 1963), occurring usually when the patient has got up to micturate at night, the skin is vasodilated, and the upright posture has just been assumed (contrary to common belief, "straining" is not an important factor).

In areflexic syncope, the loss of the baroreceptor reflexes that normally keep the blood pressure stable despite changes in posture can occur for a wide variety of causes. These include autonomic neuropathy (in diabetes, Shy–Drager syndrome, Guillain–Barré syndrome, etc.) and spinal cord disease (in particular, traumatic cervical cord lesions) (Bannister, 1988). The baroreceptor responses tend to become more "sluggish" in the elderly, causing an increased tendency to postural syncope with age. This can be exacerbated by a large range of medications, by dehydration, and by some conditions affecting the central nervous system (e.g. Parkinson's disease). Caird *et al.* (1973) found a postural fall in blood pressure of more than 20 mmHg in about 30% of a large elderly population, and a fall of more than 40 mmHg in 10%. Drugs implicated included ganglion blockers, diuretics, phenothiazines, antihistamines, antidepressants, benzodiazepines, barbiturates, and antiparkinsonian drugs. Davidson *et al.* (1989) emphasized the role of drugs given for cardiovascular disease in causing syncope, in particular, nitrates, β-blockers, and nifedipine. Donepezil may increase the risk of syncope. Orthostatic hypotension and syncope are common in the elderly following hemodialysis.

Cardiac syncope occurs in association with complete heart block (Stokes–Adams attacks), but also with other severe bradyarrhythmias, asystole, and paroxysmal tachyarrhythmias (e.g. ventricular tachycardia). The commonest underlying condition is sinoatrial node dysfunction (sick sinus syndrome), with intermittent sinus arrest or sinus node exit block. If it is associated with atrioventricular block, paroxysmal tachycardia may also occur (tachy–brady syndrome). In the older patient, the arrhythmias will occur most commonly in the context of ischemic heart disease. Cardiac syncope also occurs with ventricular outflow tract obstruction due to

aortic stenosis or hypertrophic cardiomyopathy and may be associated with exertion.

A number of different mechanisms contribute to respiratory syncope (Sharpey-Schafer, 1953; McIntosh *et al.*, 1956; De Maria *et al.*, 1984). The rise in intrathoracic pressure associated with coughing, playing a wind instrument, weight lifting, or performing the Valsalva maneuver will be associated with a decrease in venous return to the heart, reduced cardiac output and fall in blood pressure. With cough syncope, which can occur after just one or several paroxysms of coughing, this will be only a brief response. Two additional mechanisms are of probable importance. First, the very high intrathoracic pressure transient is transmitted via the carotid artery to the baroreceptors, causing a more prolonged reflex fall in blood pressure. Second, the very high pressure transients are also transmitted via the venous system to the intracranial cavity, reducing cerebral perfusion pressure. Yet another mechanism is likely to contribute to syncope associated with hyperventilation; the fall in carbon dioxide partial pressure causes vasodilatation in muscle and reduced peripheral resistance.

Vertebrobasilar ischemia may occasionally present as syncope, but there will usually be additional neurological symptoms. The underlying etiology might either be embolic or related to critical changes in flow distal to atheromatous disease. With the latter the symptoms may be related to changes in posture.

Clinical Manifestations of Syncope

The usual image of a syncopal attack is of a subject feeling dizzy, going pale, falling with loss of awareness and then recovering rapidly within about 30 seconds. This sequence of events certainly occurs, but the variety of other manifestations of syncope of different types needs to be emphasized. The motor manifestations are particularly prone to cause diagnostic error and will be discussed first, followed by the other clinical features. In the elderly, presentation may be with a history of falls or drop attacks with no recall of loss of consciousness (Kenny *et al.*, 2001).

Motor Manifestations

A detailed study of vasovagal syncope in normal young volunteers led to important insights into the variety of clinical manifestations of syncope, which is relevant to the differential diagnosis of blackouts at any age. Lempert *et al.* (1994) induced vasovagal syncope in 56 of 59 volunteer medical students, by asking them to hyperventilate while squatting, and then to stand up performing the Valsalva maneuver. They carefully documented the manifestations with video recording. It was only a minority of subjects that lay still after falling, 90% having some asynchronous myoclonic jerks of the limbs. In a few, the jerks were quite vigorous for several seconds, such that the attack might be mistaken for a generalized clonic seizure. Some displayed other motor activity, such as limb-posturing, head-turning, complex movements, eye deviation, and eyelid flicker that might be misinterpreted as manifestations of partial epileptic seizures. Vocalization was frequent.

Similar findings of a very high frequency of myoclonic movements in syncope have also been reported in cardiac syncope (Aminoff *et al.*, 1988). The opportunity to make these observations of the features of cardiac syncope has arisen with patients with recurrent ventricular arrhythmias treated with implantation of an automatic defibrillator, in whom syncope has been deliberately induced by induction of the arrhythmia to test the defibrillator. Simultaneous electroencephalogram (EEG) recording has shown no evidence of associated epileptiform activity. The variety of clinical manifestations of syncopal attacks has also been documented in attacks induced by use of a tilt table (Passman *et al.*, 2003).

In vasovagal and cardiac syncope, therefore, the classic image of the patient falling, lying still for some seconds and then coming round is unusual, and much more often there are jerks and other motor manifestations. In these types of syncope it can be argued that the fall in blood pressure was very sudden and marked, and that this may have predisposed to the myoclonus. There is anecdotal evidence that the patient who faints, and who is propped up on falling rather than falling flat on the ground, is more likely to have myoclonic movements, presumably associated with a more prolonged and severe fall in blood pressure, and rarely the hypoxia may provoke an epileptic seizure. It may be that myoclonic movements are less common in patients with areflexic syncope and postural hypotension, in whom the presyncopal symptoms will often permit preventive measures, the fall in blood pressure is less catastrophic, and the blood pressure will be immediately restored once they have fallen.

Other Clinical Features

The various trigger factors for the different types of syncope have been described in the preceeding text, and their importance will be discussed further in the section on diagnosis.

Warning symptoms, before loss of awareness, are common with reflex and areflexic syncope, but are absent in some patients (or not recalled). The symptoms of light-headedness, dizziness, and blurring of vision are familiar to most people on standing up from a hot bath too suddenly. Additionally, there may be nausea, "hot and cold" feelings, feelings of depersonalization or distance from the surroundings, and buzzing in the ears. In the Lempert *et al.* (1994) study, described earlier, the students often described having had visual and auditory disturbances. Palpitations, dyspnoea, and chest pain may occur (Graham and Kenny, 2001). Warning symptoms in cardiac syncope are less frequent and can consist just of a brief premonition as well as better-defined dizziness. A history of palpitations is usually sought, but positive responses are often difficult to interpret and negative responses are not diagnostically useful.

Marked pallor and clamminess are prominent features of vasovagal syncope due to the reflex vasoconstriction in skin and reflex sweating. In contrast, patients with areflexic

syncope and postural hypotension may have relatively little color change in association with their attacks, there is no sweating and the skin remains warm. Patients with cardiac syncope become pale owing to the marked reduction in cardiac output, and sometimes there is subsequent flushing when the output is restored (but this sequence is not sufficiently consistent or specific to be diagnostically very helpful).

If the opportunity arises to feel the pulse early in vasovagal and other causes of reflex syncope, it will be weak and there will be a reflex bradycardia. In contrast, in areflexic syncope there will be no change in heart rate. In cardiac syncope the heart rhythm changes could, of course, be diagnostic, but it is rare for a chance to arise to feel the pulse in an attack.

Not all syncopal attacks are associated with complete loss of either responsiveness or awareness. In the Lempert *et al.* (1994) study, 13 of the 56 subjects had a fall associated with only partial loss of awareness, and sometimes with confused behavior that might be mistaken for a partial epileptic seizure. These phenomena are also well recognized in patients with postural hypotension and areflexic syncope.

Incontinence may occur with syncope of any type, and is not useful in differential diagnosis. Tongue biting is extremely rare, but has been reported as a consequence of the fall.

Syncopal attacks of any type are necessarily brief, with responsiveness returning in less than a minute and often much sooner. Marked reduction of cerebral perfusion for significantly longer periods would clearly result in ischemic brain damage or death. Patients with reflex and with areflexic syncope usually recover very rapidly without confusion once supine, unless there has been a complicating factor such as head injury. Even patients with cardiac syncope and a transient severe reduction in cerebral perfusion recover rapidly. Following ventricular tachycardia or ventricular fibrillation Aminoff *et al.* (1988) described recovery of consciousness within 20 seconds of restoration of the circulation, and subsequent confusion lasted no more than 30 seconds.

Diagnosis and Investigation of Syncope

The diagnosis of "blackouts" is critically dependent on adequate patient and witness accounts of the attacks. In diagnosing syncope correctly, emphasis should be placed on potential trigger factors and the short duration of attacks. Thus, areflexic syncope is likely when there has been a clear relationship between the attacks and changes in posture, irrespective of a description of "some jerking", other motor features, incontinence, and injury in some attacks. Vasovagal attacks and other causes of reflex syncope are likely when potentially syncopal attacks have been associated with characteristic trigger factors and much less likely if they have not, in which case cardiac syncope should be seriously considered. The presence of underlying cardiac disease increases the probability of a cardiac cause. Cough syncope should be considered in patients with chronic obstructive pulmonary disease, emphysema, and chronic cough, and an adequate witness account should be obtained, since some patients fail to recall the bout of coughing that triggers an attack. Syncope as a manifestation of cerebral vascular disease is unlikely in the absence of additional symptoms suggestive of posterior circulation transient ischemic attacks.

In the last 15 years, increasing use has been made of tilt testing to obtain evidence to support a suspected diagnosis of vasovagal syncope and to investigate the underlying mechanisms (Grubb *et al.*, 1991; Smith *et al.*, 1994; Patel *et al.*, 1993; Sutton *et al.*, 1992). It has proved to be safe in the elderly (Gieroba *et al.*, 2004; Galetta *et al.*, 2004). The proportion of positive tilt tests is increased following the administration of glyceryl trinitrate. One of the difficulties in interpretation of the results, however, is the occurrence of positive tests in a significant minority of control subjects, which limits the positive predictive value. Nevertheless, provocation of a habitual attack is diagnostically very suggestive.

The work of Kenny has suggested that carotid sinus syndrome is a common cause of syncope in the elderly, and is not just confined to those with a history of fainting, following neck movement when wearing a collar (Kenny *et al.*, 2001). Other groups have also reported a high incidence of syncope provoked by carotid sinus massage in patients with otherwise unexplained syncope (Freitas *et al.*, 2004; Kumar *et al.*, 2003). Carotid sinus massage appears to carry a very low risk of complications, despite potential underlying atheroma, but should not be carried out if there is a carotid bruit unless ultrasound examination has excluded severe carotid stenosis (Richardson *et al.*, 2002).

When cardiac syncope is suspected, routine 12 lead electrocardiogram (ECG) recording will occasionally demonstrate an arrhythmia, or abnormalities that predispose to arrhythmias. Twenty-four-hour ECG tapes can be diagnostic if an attack is recorded, but the yield of diagnostic recordings is very small unless the attacks are very frequent. Moreover, interpretation of the significance of asymptomatic rhythm disturbances can be difficult. In an older population, minor asymptomatic cardiac dysrhythmias are common and may be an incidental finding unrelated to a patient's attacks. When cardiac syncope is suspected, specialist cardiac referral will usually be indicated for further assessment, noninvasive investigation, and intracardiac electrophysiology in selected cases. In the last few years, implantable loop recorders have emerged as important tools in the diagnosis of cardiac syncope, permitting recordings of cardiac rhythm during attacks, even when the attacks are infrequent (Solano *et al.*, 2004; Armstrong *et al.*, 2003). The yield of positive recordings is greater in an elderly population (Brignole *et al.*, 2005). Although the recorders are expensive, they can be cost-effective as there is a relatively high chance of capturing an attack and answering the clinical question (Krahn *et al.*, 2003).

In areflexic syncope, the diagnosis is likely to be supported by finding a postural fall in blood pressure on examination that may or may not be symptomatic. The size of fall that

is clinically significant varies between patients. A fall of at least 20 mmHg is usually defined as abnormal, but in some patients a fall of 10 mmHg is symptomatic, whereas in others with a higher supine blood pressure a fall of 40 mmHg might be asymptomatic. The blood pressure should be measured supine, immediately after standing and after standing for 1–2 minutes. Failure of the baroreceptor reflex responses can be confirmed by observing the heart rate changes in response to the Valsalva maneuver, standing, and deep breathing.

There are a number of features of syncope that can cause diagnostic confusion with epileptic seizures. The jerky myoclonic movements might be interpreted as a generalized tonic clonic seizure, but in the context of syncope these movements are brief, usually lasting only a few seconds and no more than 10 seconds. Other motor manifestations, a warning feeling of depersonalization, auditory and visual hallucinations, and confused behavior, risk being misinterpreted as features of partial epileptic seizures. Pallor and clamminess are important features of vasovagal syncope but are not specific and such autonomic manifestations can occur in some partial epileptic seizures. Misdiagnosis of syncopal attacks as epilepsy can have tragic consequences when they are due to potentially fatal, but treatable cardiac arrhythmias. Although most patients will have one type of attack, epilepsy and syncope can coexist. Rarely, patients have been described in whom an epileptic seizure has been triggered by a syncopal event and, conversely, significant cardiac arrhythmias (and potentially syncope) can occasionally be induced by epileptic seizures.

When a confident clinical diagnosis of syncope has been made, the temptation to request an EEG "just in case it's epilepsy" must be resisted. If EEGs are done in a population of patients in which the prevalence of epilepsy is very low, then they have a very low positive predictive value (Scottish Intercollegiate Guidelines Network, 2003). Even if epileptiform abnormalities are found, the patient may still be more likely to have had a syncopal than epileptic attack. A request for EEG should be reserved for cases in which there is diagnostic uncertainty, and in which it is felt that epilepsy is a reasonably likely diagnostic possibility. It should be remembered that note should only be taken of definite epileptiform features and that nonspecific slow-wave abnormalities are not diagnostically helpful.

Although the differentiation of syncope and epilepsy can be difficult, syncope is less likely to be confused with the other attack disorders listed in Table 1, which have characteristic clinical features or tend to cause attacks that are more prolonged.

Management of Syncope

Vasovagal syncope is usually managed by avoiding provocative factors, and only a small proportion of patients need other interventions; many pharmacological treatments have been advocated, but are of no or uncertain efficacy, and pacemaker insertion may be ineffective (Brignole, 2003; Kaufmann and Freeman 2004; Connolly *et al.*, 2003). Tilt training has been suggested, but is poorly tolerated and of uncertain benefit. In carotid sinus syncope the role of drug treatment is again uncertain; insertion of a cardiac pacemaker may need to be considered, if there is a significant cardioinhibitory component to the response to carotid sinus massage (Brignole, 2003; Healey *et al.*, 2004). Surgical denervation of the carotid sinus is a possibility in severe cases. Micturition syncope can usually be avoided by micturating sitting down. Cardiac syncope requires appropriate specialist treatment with antiarrhythmic medication, pacing, or insertion of an implantable defibrillator as appropriate; timely and effective treatment may be life saving. In cough syncope, treatment has to be directed at the underlying chest condition.

In older patients with syncope, areflexic syncope with postural hypotension is a common management challenge. Attention should first be directed to factors that may be causing or exacerbating the problem. The patient's medication should be reviewed, but it is not always possible to discontinue relevant drugs. For instance, in Parkinson's disease the effect of dopaminergic drugs in aggravating a postural fall in blood pressure may have to be balanced against their beneficial therapeutic effects. Treatable conditions such as Addison's disease should be excluded. Factors causing vasodilatation should be avoided, such as high temperatures, marked exertion, and alcohol. Small, frequent meals should be eaten rather than large meals. Dehydration should be avoided. When sitting up or standing, the changes in posture should be made slowly and reversed temporarily if postural symptoms supervene. Crossing the legs, tensing the calf muscles, and abdominal compression can sometimes transiently ameliorate postural symptoms (Wieling *et al.*, 1993).

Elastic compression stockings can make a significant contribution, although patients may need help in putting them on and they are difficult to tolerate in the summer. Sleeping with slight head-up tilt may help, possibly by expanding plasma volume, but a tilt of more than about 10° is difficult to tolerate. Chronic exposure to low blood pressure seems to improve cerebral autoregulation, so patients should be encouraged to remain as active as possible.

If these measures are not adequate in controlling symptoms of postural hypotension, drug treatment may be commenced. Most drugs are used without their license and benefits may be limited. Fludrocortisone 100–200 μg at night is usually commenced first and causes salt and water retention (and potentially hypokalemia). Ephedrine, a sympathomimetic, can be added (15 mg tid, increasing if necessary to 30 mg tid). Higher doses may cause tremor, tachycardia, and agitation. A number of other drugs, including midodrine, have been used (Jankovic *et al.*, 1993; Hoeldtke and Streeten, 1993; Mathias *et al.*, 1986). With drug treatment supine hypertension is a risk. Pacing does not help (Sahul *et al.*, 2004).

In an elderly population, the risks of serious injury and complications from falls are very high. It is important that the patient with syncope recognizes these risks, and understands

the need to take precautions to avoid syncopal attacks, if at all possible.

OTHER NONEPILEPTIC ATTACK DISORDERS

Panic Attacks and Hyperventilation Attacks

The clinical diagnosis of panic attacks in the context of an anxiety syndrome is usually straightforward, but fear and anxiety can of course be features of partial epileptic seizures. Treatment is directed toward the underlying anxiety disorder.

Hyperventilation may or may not be a component of panic attacks and, conversely, hyperventilation attacks may or may not be associated with panic. Classically, hyperventilation is associated with dizziness, paresthesia in the hands and around the mouth and a paradoxical feeling of breathlessness. Feelings of unreality or depersonalization can occur, and may lead to a misdiagnosis of partial epileptic seizures, particularly when there is impaired consciousness, tetany, or tremor. The hyperventilation can be subtle and not always obvious, even to an experienced witness. The paresthesia and tetany are probably related to a reduction of extracellular ionized calcium induced by the respiratory alkalosis. The cerebral symptoms are ascribed to reduction of cerebral blood flow, and are associated with EEG slowing (Gotoh *et al.*, 1965). Occasionally, loss of consciousness occurs in hyperventilation attacks, and this may be due to syncope caused by vasodilatation in muscle. It has been reported, however, that loss of consciousness can also occur without a fall in blood pressure, and it has been suggested that this is due to the severity of cerebral vasoconstriction (Naschitz *et al.*, 1997). In the diagnosis of hyperventilation attacks, an attempt to induce symptoms by hyperventilation in the clinic or laboratory can be useful. Attacks may be aborted by rebreathing ("paper bag treatment"). Training in breath control and anxiety management by physiotherapists and/or clinical psychologists is indicated when the attacks are troublesome.

Psychogenic Nonepileptic Attacks

Psychogenic nonepileptic attacks ("nonepileptic attack disorder", pseudoseizures, functional seizures) present for the first time most frequently in teenage or young adult females, but there is increasing recognition that they also present in elderly patients. They are a common diagnosis in elderly patients undergoing assessment with long-term EEG and video monitoring in specialist epilepsy units (Kellinghaus *et al.*, 2004). A significant number of patients with psychogenic nonepileptic seizures are misdiagnosed, in particular, as having epilepsy, and are treated inappropriately. Between 6 and 15% of patients investigated for apparently uncontrolled epileptic seizures have psychogenic nonepileptic seizures. When attacks persist despite treatment, a diagnosis of epilepsy should always be reviewed, and some patients with misdiagnosed psychogenic nonepileptic attacks will be identified. The correct identification of pseudostatus epilepticus is also very important.

A wide range of psychiatric labels has been attached to different patients with psychogenic nonepileptic attacks, in particular, conversion disorder and somatization disorder, but also anxiety, depression, posttraumatic stress disorder, episodic dyscontrol, and malingering. This suggests a variety of often ill-understood underlying mechanisms. With the exception of malingering, which is a very rare cause of an attack disorder, the attacks appear to occur without the conscious mediation of the patient. Often the attacks occur without any apparent trigger. One exception is episodic dyscontrol, in which rage attacks are triggered by irksome events and control of temper is inappropriately lost. In making a diagnosis of psychogenic attacks, it is usually important to take into account the "whole picture" and not just one aspect of the patient's problems. As with other attack disorders, the diagnosis is critically dependent on adequate descriptions of the attacks but even with video recording, this may not, by itself, provide adequate information. In a study in which neurologists attempted to make a diagnosis of epileptic or nonepileptic attacks on the basis of video recordings alone, they were correct in only 71% of epileptic seizures and in 73% of psychogenic nonepileptic seizures (King *et al.*, 1982). In addition, account needs to be taken of the timing and circumstances of attacks, the detailed past medical and psychiatric history, current psychiatric, neurological, and other symptoms and examination findings, bearing in mind that psychiatric symptoms are common in patients with epilepsy as well as in those with nonepileptic attacks. Other factors may be interictal and ictal EEG, the relationship of attacks to medication, and measurements of serum prolactin.

The attacks tend to fall clinically into two main groups, those in which the patient collapses with impaired or absent responsiveness and little movement, and those with prominent motor activity (Meierkord *et al.*, 1991). Betts and Boden (1992a) suggested an additional category of "abreactive" attacks with hyperventilation, stiffening, breath-holding, gasping, incoordinate jerking, and pelvic thrusting, and sometimes screaming, spitting, and retching. In nonepileptic seizures, injury and incontinence are not uncommon, but tongue biting and cyanosis are very rare. In generalized tonic–clonic epileptic seizures, limb movements are in phase, whereas in nonepileptic seizures with generalized limb movements they are usually out of phase (Gates *et al.*, 1985). Some frontal lobe epileptic seizures can, however, also be associated with brief prominent out-of-phase limb movements (e.g. bicycling movements). Some attacks are easy to diagnose. For instance, episodes of collapse and unresponsiveness that are prolonged (e.g. 30 minutes) are most unlikely to be epileptic. Attacks with wild movements of all limbs and some degree of retained responsiveness are also unlikely to be epileptic. However, other attacks can be difficult to classify and require specialist referral.

Long-term video and EEG monitoring and the recording of attacks will usually, but not always, lead to a diagnosis. It is expensive. Even when attacks are relatively infrequent it can be worthwhile, as patients with psychogenic nonepileptic seizures tend to have more attacks than expected during monitoring. Indeed, short-term video EEG recordings on outpatients have been shown to have a high diagnostic yield when combined with suggestion that an attack will be provoked by hyperventilation or photic stimulation (McGonigal *et al.*, 2004). The absence of epileptiform abnormalities during an attack does not exclude epilepsy, as many simple partial and rare complex partial seizures are not associated with scalp EEG changes. Prolactin level measurements have only a limited role. About 20 minutes after a generalized tonic–clonic seizure there is usually a marked rise in serum prolactin above 1000 mU/l, which is not seen in psychogenic nonepileptic seizures, but can occur following syncope (Trimble, 1978). The rise should be confirmed by measuring a baseline level or the level at least 1 hour after the seizure. In practice, however, it is unusual to have much diagnostic difficulty with attacks that might be generalized tonic–clonic epileptic seizures and, with the more difficult diagnosis of attacks that might be partial seizures, the rise in serum prolactin is less marked and reliable. A rise above 500 mU/l is often seen after complex partial seizures, but not after simple partial seizures (Dana-Haeri *et al.*, 1983; Laxer *et al.*, 1985). However, such rises have also been reported following psychogenic nonepileptic seizures (Alving, 1998).

Between 10 and 30% of patients with psychogenic nonepileptic seizures also have epilepsy, and sometimes there is an inverse relationship between the frequency of the epileptic and nonepileptic attacks. In managing such patients, it is obviously necessary to distinguish clearly between the types of attack.

The first step in the management of psychogenic nonepileptic seizures is to explain the diagnosis clearly to the patient and his/her family. If the label of epilepsy has previously been attached, it is made clear that this is being removed (except in those with both types of attack). It is explained that a diagnosis of nonepileptic attack disorder is a positive diagnosis, that it is quite common and that the mechanisms underlying the attacks are sometimes not well understood. It is important that there is no hint of a suggestion that the attacks are being "put on", and it should be made clear that this is not the case (except in the very rare malingerer). Further management will involve withdrawal of antiepileptic drugs, counseling from informed clinicians, nurse specialists, or clinical psychologists, and treatment of any associated depression or anxiety. It will usually be important to involve the whole family in the treatment program. If the attacks are diagnosed early and any precipitating issues are dealt with, then the prognosis is good (Betts and Boden, 1992b). In the older patient with a long history of attacks, however, the prognosis for cessation of the attacks will be poor, and management will be aimed at helping the patient cope with them.

Sleep Phenomena, Hypoglycemia, Migraine, Transient Global Amnesia, Cataplexy, Paroxysmal Movement Disorders, and Paroxysmal Symptoms in Multiple Sclerosis

It is beyond the scope of this chapter to describe these remaining disorders in detail.

Episodic events during sleep can be due to normal physiological phenomena (e.g. hypnic jerks, periodic movements) and sleep disorders (e.g. myoclonus, restless legs syndrome, non-REM and REM parasomnias, sleep apnea) as well as due to partial or generalized epileptic seizures. Periodic movements become increasingly frequent with age and are very common in an elderly population. They may disturb the sleep of the patient as well as that of the partner. They occur at a regular interval of 10–60 seconds and usually consist of transient flexion movements of one or both legs lasting a few seconds. The restless legs syndrome also becomes more frequent with age and is associated with periodic movements of sleep. REM parasomnias occur characteristically in elderly males, last up to a few minutes and involve thrashing about and calling out in response to vivid dreams. Injury to a partner in the same bed is a risk. They can be confused with frontal lobe seizures and may respond to clonazepam.

Hypoglycemia can cause a variety of manifestations. Attacks usually begin with autonomic disturbances such as sweating, palpitations, nausea, and hunger. Symptoms related to cerebral dysfunction may then ensue, including paresthesia, visual disturbance, weakness, tremor, dizziness, confusion and aphasia, as well as coma and epileptic seizures. Sometimes there are bizarre prolonged episodes of altered behavior that might suggest a fugue state or partial status epilepticus. Most attacks occur in the context of diabetes, liver disease, alcohol abuse, or in clear relationship to meals (reactive hypoglycemia). Insulin-secreting tumors are very rare, and often diagnosed late.

The focal sensory, motor, and psychic symptoms that can occur in migraine attacks may be mistaken as epileptic phenomena or ascribed to transient ischemic attacks. The duration of migrainous symptoms tends to be longer (usually between 5 and 60 minutes) than the duration of epileptic symptoms (usually between a few seconds and 2 minutes). Associated headache, photophobia, nausea, and vomiting will usually make a diagnosis of migraine clear. The loss of consciousness that can occur in vertebrobasilar migraine can cause diagnostic difficulty.

The diagnosis of transient global amnesia is usually immediately apparent from the history if a witness account is available to describe the profound amnesia (retrograde and anterograde) lasting usually between one and a few hours. There is often repetitive questioning with failure to recall the replies. The cause of the attacks remains uncertain and there is no specific treatment. It is important to distinguish them from prolonged postictal confusional states with amnesia that may follow partial epileptic seizures, and from ictal amnesia.

Cataplexy, paroxysmal movement disorders, and paroxysmal symptoms in multiple sclerosis are unlikely to present for the first time in older patients. In all these conditions

there is no impairment of consciousness, and responsiveness is only transiently impaired in cataplexy due to the transient weakness.

KEY POINTS

- In attack disorders a detailed account from the patient and witnesses is often crucial in reaching an accurate diagnosis.
- Motor manifestations lasting a few seconds (jerks, twitches, posturing) are common in syncopal attacks.
- Cardiac syncope, carotid sinus syndrome and areflexic syncope (with postural hypotension) become increasingly common in the elderly.
- Carotid sinus massage, tilt testing, and cardiac loop recorders are playing an increasing role in the differential diagnosis of syncope.
- Psychogenic nonepileptic (functional) seizures can occur in older as well as younger patients, and are commonly misdiagnosed.

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Peripheral Neuropathy

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INTRODUCTION

Inherent in any discussion of peripheral neuropathy in the elderly is the issue of what is considered "normal" for age. While the process of normal aging involves some structural and functional changes in the peripheral nervous system, the key is to separate the normal changes from those that are due to pathological processes. Dyck *et al.* (1995) showed a positive correlation between vibration threshold and age. In the same study, ankle areflexia or hyporeflexia was present in more than 5% of healthy individuals older than 50 years, rising to almost 30% after age 70. By the seventh decade, diminished distal foot vibratory sensation, absent Achilles reflexes, and changes in nerve conduction measurements may occur but are considered a part of normal aging, whereas diminished vibratory sensation in the hands is generally considered pathologic. Alterations in temperature and pain modalities are less clearly a part of the aging process. These age-related changes are often referred to as the "nonspecific neuropathy of late life" (Thomas, 1999). Over the years, the etiology of these changes has been attributed to a wide variety of causes including trauma or ischemia of the peripheral nerves and structural alterations to myelin, axons, or peripheral receptors.

Several authors have suggested that certain "abnormalities" observed in electrophysiological studies may be associated with increasing age. Buchthal *et al.* (1975) demonstrated that the amplitude of sensory nerve action potentials at age 70 may be 50% of that at age 20. Compound muscle action potentials also may be reduced. Conduction velocities decline progressively after age 40, and by age 60 they are reduced by as much as $10\,m\,s^{-1}$, when compared to 30-year-old individuals (Kimura, 2001).

Peripheral neuropathies are common in the elderly and often present with similar signs and symptoms despite diverse etiologies, including metabolic dysfunction, toxins, neoplasms, vitamin deficiencies, malnutrition, immune-mediated, and hereditary causes. Presenting complaints often include numbness in the feet and fingers, a sensation that the limbs are "wooden-like" uncomfortable (particularly burning) dysesthesias, clumsiness or imbalance, and generalizes weakness. Atrophy of muscles is rarely noticed until a neuropathy is advanced.

The evaluation of the patient with peripheral neuropathy should include a thorough history to identify precise symptoms, their duration, and the course of the illness. Underlying illnesses associated with peripheral neuropathy, such as diabetes, endocrine disturbances, connective tissue disorders, and renal or liver failure, need to be identified. Information about medications, alcohol and tobacco use, and potential work-related exposures are essential. Relevant family history is important because heritable neuropathies such as Hereditary Motor Sensory Neuropathy (HMSN) Type II and Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) may present late in life. In the physical examination, blood pressure (supine and upright), cardiac rhythm, and dermatological changes (see Table 1) should be evaluated. Careful attention is paid to the distribution of motor and sensory disturbances, the sensory fiber types that are affected, the autonomic nervous system, and the deep tendon reflexes.

If the precise diagnosis cannot be determined on the basis of the history and physical examination, further evaluation is necessary. Electrodiagnostic studies are performed to determine whether the neuropathy is axonal or demyelinating, symmetric or asymmetric, and predominantly distal or proximal (see Figure 1).

The information gathered from the history, physical, and electrodiagnostic studies should be used to classify the neuropathy in one of the following categories:

Course: acute, subacute, or chronic
Fiber-type involvement: sensory, motor, autonomic, or mixed
Functional class: small and/or large fiber
Distribution: distal versus proximal.

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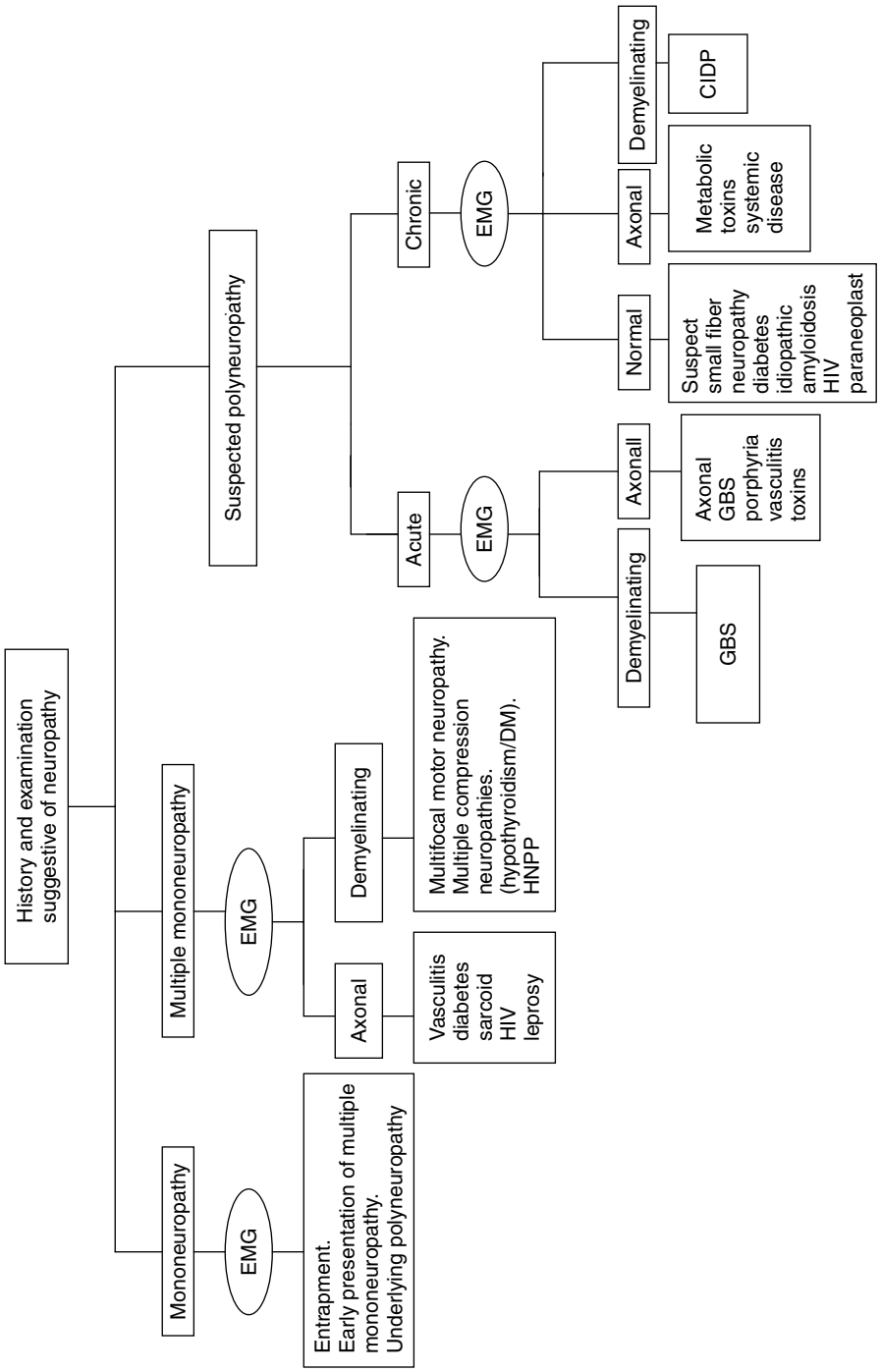

Figure 1 Algorithm for evaluating patients with suspected peripheral neuropathy

Table 1 Dermatological clues to the neuropathy type

Dermatological changes	Neuropathy
Purpura	Vasculitis
Livedoreticularis	Vasculitis
Hypopigmentation	Sarcoid/Leprosy
Ulceration	Diabetes
Alopecia	Hypothyroid/Thalium/Lupus
Mees' lines	Arsenic or Thalium toxicity
Target rash	Lyme's disease

Table 2 Causes of neuropathies with prominent motor involvement

Proximal and distal
Guillain-Barré Syndrome (GBS)
Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
Neuropathy of osteosclerotic myeloma
Porphyria
Distal predominant
Multifocal Motor Neuropathy
Hereditary Motor Sensory Neuropathy (HSMN)
Lead toxicity

Table 3 Causes of neuropathies with prominent sensory involvement

Proximal (Asymmetric)
Paraneoplastic
Sjögren's
Idiopathic
Distal (Symmetric)
Metabolic/Diabetes[a]
Toxins
Amyloidosis[a]
HIV[a]
Idiopathic[a]

[a]Neuropathies associated with severe pain.

Table 4 Causes of neuropathies with prominent autonomic involvement

Diabetes
Amyloidosis
Paraneoplastic
Vinca alkaloids
Porphyria
GBS
HIV
Idiopathic

Classification of the neuropathy (see Tables 2–4) should enable the physician to perform a directed laboratory evaluation, which *might* include hematological and biochemical screening, fasting blood glucose, glucose tolerance test (GTT), fluorescent treponemal antibody (FTA), serum immunofixation, and serum vitamin B12 and E levels. The use of panels of autoantibodies (see Table 5) is strongly discouraged; it is expensive and provides little direction in the diagnosis or therapy of most neuropathies. In some patients, specific antibody testing is warranted. For example, detecting Anti-Hu antibodies in patients with recent onset idiopathic sensory ataxic neuropathy not only supports the diagnosis but also prompts an immediate search for cancer (lung, ovarian, breast). Anti-GM1 antibodies in patients with clinical suspicion of multifocal motor neuropathy in whom conduction block could not be found might justify treatment trial with intravenous immunoglobulin (Kissel, 2001). The yield of heavy metal screening is low and should be considered only when exposure is suspected (see Table 1). Autonomic reflex testing to detect, quantify, and describe the distribution of autonomic failure is helpful in patients with peripheral autonomic neuropathies. Skin biopsy for analysis of intraepidermal nerve fibers is helpful in patients with suspected distal small fiber neuropathy. Biopsy of a cutaneous nerve such as the sural or superficial peroneal should be considered if the etiology remains unclear or if the possibility of vasculitis, amyloidosis, or a treatable demyelinating neuropathy is raised (Mendell *et al.*, 2001b).

Table 5 Neuropathies associated with autoantibodies

Neuropathy	Antibody
Multifocal motor neuropathy	Anti-GM1
Guillain-Barré Syndrome	Anti-GM1, Anti-GD1a
Anti-MAG (Myelin Associated Glycoprotein) neuropathy	Anti-MAG
Paraneoplastic/subacute sensory neuronopathy	Anti-Hu

Diabetes Mellitus (*see* Chapter 122, Type 2 Diabetes Mellitus in Senior Citizens)

A frequent cause of neuropathy in the elderly is diabetes mellitus. This occurs because diabetes is more common in the elderly and the incidence of neuropathy increases with the duration of diabetes (Pirart, 1978). Neuropathy associated with diabetes is quite varied and may be acute or subacute, systemic or focal, and may involve one or more parts of the peripheral nervous system (see Table 6).

Diabetic neuropathies have been divided empirically into two broad categories: the symmetrical polyneuropathies and the asymmetrical (focal and multifocal) neuropathies (Taylor and Dyck 1999).

Table 6 Neuropathies commonly associated with diabetes

Focal and multifocal diabetic neuropathies
Cranial neuropathies (most common are CN 111 and V1)
Mononeuropathies
• Median nerve entrapment at the wrist (Carpal Tunnel Syndrome)
• Ulnar nerve entrapment at the elbow
• Common peroneal nerve entrapment at the fibular head
• Lateral femoral cutaneous nerve entrapment (Meralgia Paraesthetica)
Diabetic truncal radiculoneuropathy
Diabetic lumbosacral radiculoplexus neuropathy
Diabetic polyneuropathy
Sensory
Sensory motor
Sensory-motor autonomic
Predominately autonomic

The most common type of diabetic neuropathy is a mixed sensory, motor, and autonomic polyneuropathy. This neuropathy evolves over time and usually presents with distal sensory symptoms. Distal vibratory thresholds are mildly elevated and there is a symmetric stocking-glove distribution loss to pain, light touch, and temperature sensation. In the early stages, weakness and muscle wasting are minimal except in the intrinsic foot muscles. Although subtle, autonomic symptoms are usually present. Sensory and motor nerve conduction studies are abnormal with reductions in amplitudes, prolonged distal and F-wave latencies, and mildly reduced conduction velocities. Better glucose control has been associated with slight improvement in nerve conduction velocities (DCCT Research Group, 1995).

While sensory symptoms are often the first manifestation of a more generalized polyneuropathy, a pure sensory polyneuropathy may be seen in diabetes. These sensory symptoms may occur in the "nondiabetic" patient, that is, the diabetes is discovered during the evaluation of the patient's symptoms. Although some patients may be asymptomatic, numbness and tingling in the feet are the most common presenting complaints. Pain is overemphasized as a component in the usual diabetic patient; burning and aching in the soles of the feet or even lancinating pain in the legs are less frequent complaints, often, more severe at night. Usually, the initial findings are impairment of vibratory sensation in the feet and reduced or absent ankle reflexes. The signs are length dependent in that the longer, more distal nerves are involved first. As symptoms advance proximally to include the calf and lower thigh, the hands may be affected as well. With time, as the sensory loss extends as proximal as the elbow, there may be a "tear drop" pattern of sensory loss over the anterior trunk. Complications of sensory neuropathies include chronic foot ulcers due to loss of pain fibers complicated by ischemia from diabetic vascular disease. More serious problems including Charcot joints and osteomyelitis may develop.

Autonomic manifestations often accompany the distal sensory-motor polyneuropathy of diabetes. They correlate with the severity of the somatic nerve abnormality. Abnormalities of the cardiovascular, genitourinary, gastrointestinal, and/or thermoregulatory systems may occur. The presence of diabetic autonomic neuropathy has been associated with an increased mortality rate, presumably due to cardiac arrhythmias (McLeod and Tuck, 1987a,b).

Postural hypotension is the most common manifestation of autonomic dysfunction (*see* **Chapter 83, Abnormalities of the Autonomic Nervous System**). Postural (or orthostatic) hypotension is defined as a decrease in systolic (>30 mmHg) and/or diastolic (15 mmHg) blood pressure without an associated rise in pulse rate upon the assumption of an upright posture. Mild symptoms include dizziness, lightheadedness, or visual changes. Antihypertensive agents, diuretics, and even insulin may aggravate symptoms. At times, the cardiovascular symptoms can be quite debilitating, causing syncopal episodes or even the inability to maintain an upright posture. Orthostatic hypotension is thought to be due to damaged vasoconstrictor fibers in the splanchnic bed, muscle, and skin (McLeod and Tuck, 1987a).

Other cardiovascular abnormalities include resting tachy- or bradycardia, loss of sinus arrhythmia, and silent myocardial infarctions. Simple tests to assess autonomic function can be performed in most electrophysiologic laboratories or at bedside, measuring variability in R-R intervals, and heart rate and blood pressure changes in response to upright posture (preferably using a tilt table).

Symptomatic orthostasis is treated first by providing the patient with a tight-fitting garment (such as Jobst stockings) that reduces the volume of venous beds in the legs and abdomen. Often, patients are reluctant to wear these garments because of the difficulty of putting them on or general discomfort while wearing them. The head of the bed should be elevated while sleeping in order to decrease renal artery pressures and thereby increase renin secretion. Help may also be obtained from simple physical countermaneuvers, such as, squatting, leg crossing, knee flexion, and toe raises. If symptoms do not improve with these conservative measures, sodium intake may be increased unless contraindicated by a history of congestive heart failure. Pharmacologic treatment include use of Fludrocortisone that depends on sodium retention to increase blood volume; however, supine hypertension, edema, congestive heart failure, and hypokalemia may complicate its use. Midodrine is a prodrug that acts as a potent alpha one receptor agonist; side effects include chills, scalp paresthesia, and pruritus related to piloerection, urine retention, chest pain, and the most important side effect is supine hypertension. Patients should be instructed to take their final dose at least 4 hours before bedtime. Recombinant human erythropoietin (Epoetin alpha) has a limited use in some patients with severe autonomic failure who have failed other agents.

Other organ systems affected by autonomic neuropathy include dysfunction of the genitourinary system as manifested by erectile dysfunction and/or bladder atony. Gastrointestinal manifestations include gastroparesis and nocturnal diarrhea. Other autonomic changes include abnormal sweating patterns and reduced pupillary light responses.

Diabetic mononeuropathies may affect either cranial or peripheral nerves. The relationship of mononeuropathies to the duration of diabetes, the control of the serum glucose and the age of the patient are uncertain. Cranial mononeuropathies are more frequent over the age 50. The most common cranial nerve (CN) involved is CN III (oculomotor nerve) followed by CN VI (abducens nerve) and CN IV (trochlear nerve). Though it is suggested that CN VII is often affected in diabetes, the common occurrence of Bell's palsy makes it difficult to substantiate the association. The presenting sign of oculomotor nerve palsy is often abrupt retro-orbital pain followed within a few days by diplopia secondary to partial ophthalmoplegia; 50% of the cases occur without pain. Usually, diabetic CN III palsies are "pupil sparing". The symptoms commonly resolve over several months to a year.

Because diabetic nerves are more susceptible to compression neuropathies, peripheral mononeuropathies are generally seen at common sites of entrapment in the median, ulnar, peroneal, and lateral femoral cutaneous nerves. The increased susceptibility of the diabetic nerve to compression is multifactorial. Both metabolic changes, which may lead to endoneurial edema, and vascular changes in the vasa nervorum, which may compromise blood supply to the nerve, have been thought to increase this risk. A more complete discussion of individual entrapment syndromes can be found below.

There has been much disagreement about the clinical presentation and pathogenesis of proximal diabetic neuropathy or, as it is often referred to as *diabetic amyotrophy*. The most descriptive term based on autopsy and electromyography (EMG) studies is diabetic lumbosacral radiculoplexus neuropathy (Taylor and Dyck, 1999).

It occurs mostly in Type 2 diabetes, after age 50. There is no correlation between the neuropathy and the duration of the diabetes. Pain is a major feature. Weakness follows pain and may progress over weeks or even months. Both proximal and distal muscles are affected. Frequently, the other leg is affected after a latency of days to months. On clinical observation, there is marked atrophy of thigh muscles; patellar reflexes may be reduced or absent, whereas Achilles tendon reflexes may be present. EMG of proximal leg and lumbar paraspinal muscles demonstrates denervation potentials and evidence of chronic partial denervation and reinnervation. Cerebrospinal fluid (CSF) examination reveals an elevation, often marked, of protein content. Though the etiology is uncertain, it has been suggested that it is ischemic in origin. Treatment consists of institution of tight control of the diabetes; aggressive treatment of pain, and physical and rehabilitation services. Patients often recover within weeks to months. The pain, which can be quite disabling, may be responsive to a brief course of intravenous methylprednisolone; however, this should be done cautiously.

Another syndrome associated with diabetes is thoracic or thoracoabdominal radiculopathy which most commonly occurs after age 50; patients present with complaints of pain, either acute or gradual in onset, in one or more thoracic or lumbar dermatomes. The pain may be unilateral or bilateral in a belt-like distribution and may be burning, stabbing, or dull in nature. This symptom complex often results in extensive and unrewarding investigations for abdominal disease. EMG confirms the clinical diagnosis, demonstrating denervation potentials in affected thoracic and lumbar myotomes. Eventually, this syndrome resolves with time, though pain may persist for a long time.

The typical symmetric distal sensory, motor, and autonomic polyneuropathy is likely to be caused by chronic hyperglycemia. While the precise pathophysiologic events are not clear, the predominant theory is related to activation of the polyol pathway in nerve tissue resulting in an excess of sorbitol production in the nerve. Excess sorbitol causes changes in phosphoinositide metabolism and inhibition of myo-inositol uptake in the nerve. These metabolic changes are felt to cause structural changes, especially at the axoglial junction. Another possible cause of diabetic neuropathy is the formation of advanced glycosylation end products, which have been shown to accumulate in the diabetic nerve (Ryle and Donaghy, 1995). It has also been suggested that ischemia may play a major role in the pathogenesis of diabetic neuropathy. Diabetics are predisposed to vascular changes affecting the vasa nervorum with basement membrane thickening and reduplication, and pericyte degeneration (Giannini and Dyck, 1995).

The mainstay of treatment of diabetic neuropathies is a "tight" control of serum glucose, and treatment of symptoms. Diabetic control may be improved by frequent monitoring of blood glucose and glycated hemoglobin. Recent studies have demonstrated that control of glucose is associated with improved nerve conduction velocities (DCCT Research Group, 1995). Treatment of established diabetic neuropathy with aldose reductase inhibitors in several trails showed little, if any clinical improvement (Nicolucci *et al.*, 1996). Trials of treatment with Myo-inositol were disappointing. Trials using nerve growth factors showed only minimal measurable clinical benefit. The role of pancreatic transplantation is controversial.

Patients with diabetic and other neuropathies should be educated to avoid painless injuries that may be associated with decreased sensation, particularly in the feet. This instruction should include regular foot inspection, rotation of well-fitting shoes, skin and nail care, and wearing shoes whenever ambulating.

Many pharmacologic agents, including some anticonvulsants and antidepressants, have been tried with varying success. Often, the limiting factor has been the side-effect profile of each drug, particularly the central nervous system effects to which the elderly may be particularly susceptible. Starting with low doses of each drug and raising the dose slowly is sometimes effective. Occupational and physical therapy consultations are helpful in providing rehabilitation and assistive devices.

Uremia (*see* Chapter 127, Renal Diseases)

At least 60% of patients with end-stage renal failure develop polyneuropathy (Asbury, 1993). It occurs irrespective of the underlying disease causing the renal failure. Though the neuropathy may be subclinical, symptomatic patients often complain of paresthesias, dysesthesias, and muscle cramps. The neuropathy is usually a mild, distal, symmetric, sensory-motor polyneuropathy with features of both axonal degeneration and demyelination. Occasionally, patients may be more severely affected, presenting with marked weakness and sensory deficits.

Dialysis may prevent further progression of uremic neuropathy; however, its institution does not result in improvement of symptoms. On the other hand, 6–12 months after successful kidney transplant, there is evidence that nerve function may improve (Bolton and Young, 1990).

Nutritional/Alcohol (*see* Chapter 15, Alcohol Use and Abuse; Chapter 29, Vitamins and Minerals in the Elderly)

Alcohol is one of the most common toxins associated with the development of peripheral neuropathy. Its affects are compounded by many years of abuse. In one study, it accounted for as many as 15% of the neuropathies occurring in the elderly (Huang, 1981). The neuropathy, sensory and motor with features of distal axonal degeneration, is insidious. Complaints of burning dysesthesias and cramps are common presentations. Distal sensory loss, absent Achilles tendon reflexes, and atrophy of intrinsic foot muscles are prominent features of the examination. With time, weakness and/or autonomic dysfunction may develop. The etiology of alcohol-related polyneuropathy is uncertain. It has long been thought to be secondary to nutritional deprivation, particularly of thiamine and other B-complex vitamins. However, neuropathy has been recognized in "well-nourished" alcoholics as well, suggesting that alcohol may have a direct neurotoxic effect. Therapy includes abstinence from alcohol, vitamin B supplementation, and maintenance of a nutritionally well-balanced diet. Alcoholic neuropathy may be arrested in the early stages with abstinence. However, in the more advanced stages of neuropathy, there will be little, if any, improvement in symptoms with cessation of alcohol (Hillbom and Wennberg, 1984).

Vitamin B12 and vitamin E deficiency are the most important in relation to peripheral nerve diseases. Although human neuropathy has been attributed to deficiencies of specific B-complex vitamins, there is little evidence to support these claims (Schaumburg *et al.*, 1992) except with vitamin B12 deficiency. Vitamin B12 deficiency is due to malabsorption either because of diminished secretion of intrinsic factor or surgery of the stomach or the small intestine. The prevalence of B12 deficiency ranges from 7 to 16% of the elderly population (Green and Kinsella, 1995). Patients may present with paresthesias in their hands and feet, stiffness and cramps in the legs, and complaints of unsteadiness. Examination reveals absent or diminished Achilles reflexes, hyper- or normoactive patellar reflexes, bilateral Babinski signs, and loss of vibratory and position sense. Though there is some disagreement about the extent to which these symptoms may be attributed to peripheral neuropathy rather than myelopathy (Schaumburg *et al.*, 1992), electrophysiologic studies may demonstrate distal axonal degeneration. The diagnosis is suggested by a low or normal serum B12 level, elevated methylmalonic acid and homocysteine levels, and confirmed by a two-stage Shilling test (Green and Kinsella, 1995). Parenteral B12 replacement is given for life, usually with stabilization of the neuropathy.

Vitamin E deficiency is commonly a result of disorders interfering with fat absorption. Patients mainly present with progressive gait ataxia. Examination demonstrates areflexia, posterior column loss with a Romberg's sign, and extensor plantar responses. In some patients, ophthalmoplegia, dysarthria, and intention tremor may be seen. A low plasma vitamin E level establishes the diagnosis. Vitamin E supplements are essential to prevent progression.

Toxins

In the elderly population, many of whom are subject to polypharmacy, the differential diagnosis for neuropathy should include iatrogenic causes. Multiple pharmacologic products have been implicated as etiologic agents in neuropathies, including drugs used in the treatment of malignancies, infections, and rheumatologic disorders. A few examples will be presented in Table 7.

Several antibiotics including isoniazid (INH), metronidazole, and nitrofurantoin have been associated with neuropathy. INH, a common agent for treating tuberculosis, may cause a sensory-motor neuropathy. Individuals who are slow acetylators (acetylation is the route of INH metabolism) are particularly prone to neuropathy. The first symptoms are often distal paresthesias, mild weakness, or gait unsteadiness. With the cessation of the drug, symptoms may lessen. The basis for the neuropathy is due to inhibition of pyridoxine action by INH. Therefore, pyridoxine, 50 mg daily, is administered along with INH to prevent the development of neuropathy in most patients (Schaumburg *et al.*, 1992). Metronidazole, used for certain bacterial infections and Crohn's disease, has been associated with a predominantly large fiber sensory neuropathy, thought to be reversible with cessation of therapy. Nitrofurantoin, used in the treatment of urinary tract infections, has been shown to cause a motor-sensory neuropathy. Patients with renal insufficiency are at the greatest risk.

Patients with chronic renal insufficiency are susceptible to a neuromyopathy when treated with colchicine for gout. The neuropathy is generally a mild sensory-motor axonal process. Cessation of the drug or reduction in dose may halt the progression of the neuropathy.

Pyridoxine, occasionally used for aches and cramps or in overzealous use of multivitamins, has been linked to a subacute sensory neuronopathy in doses as low as 200 mg/day. Patients may present with numb feet, gait ataxia, and dysesthesias in the feet.

Amiodarone, a drug used in ventricular and supraventricular arrhythmia, is associated with peripheral neuropathy in 6–10% of the patients. It starts with distal sensory symptoms followed by both proximal and distal weakness. Improvement occurs after stopping the medicine.

Many antineoplastic agents including cis-Platinum, vincristine, thalidomide, Taxol, cytosine arabinoside (Ara-C),

Table 7 Medications associated with neuropathy

Amiodarone	Metronidazole
Cis-platinum	Nitrofurantoin
Colchicine	Paclitaxel (Taxol)
Cytosine arabinoside (Ara-C)	Procarbazine
Dapsone	Pyridoxine toxicity
Isoniazid (INH)	Thalidomide
L-Tryptophan	Vincristine

suramin, and procarbazine have been associated with neuropathy. The symptoms may range from mild paresthesias to disabling sensorimotor axonal neuropathies. Usually, the neuropathies associated with these agents are dose related and may be more severe in individuals with underlying neuropathy from other etiologies. Unfortunately, the neuropathy may constitute a dose-limiting side effect to otherwise successful cancer chemotherapy. The neuropathy usually stabilizes after discontinuing the drug.

Inflammatory Demyelinating Polyneuropathies

Guillain-Barré Syndrome (GBS) or acute inflammatory demyelinating polyneuropathy (AIDP) may occur at any age. There are two main peaks of occurrence, one in the second and third decades and a larger one between the fifth and eighth decades. With advancing age both the severity of the disease and the prognosis appear to worsen (McKhann *et al.*, 1988). Most patients have suffered from a "viral" respiratory illness in the preceding 1–3 weeks. However, GBS has also been linked to infection with *Campylobacter jejuni*, vaccination, and surgery. The disease typically presents with symmetric weakness and paresthesias in the hands or feet or both, progressing rapidly in an ascending manner over a relatively short time. Low back pain is a common complaint. Hyporeflexia or areflexia is present. Autonomic dysfunction, marked by hypo- or hypertension or cardiac arrhythmias, may accompany the disease. The diagnosis is made by the clinical picture and is supported by CSF examination and electrodiagnostic findings. Corticosteroids are ineffective in altering the natural history of the disease, and may actually increase its rate of relapse. Plasmapheresis and human immunoglobulin have been shown to provide effective therapy, shortening the time on a ventilator and the time to independent walking (The Guillain-Barré Study Group, 1985; van der Meché and Schmitz, 1992). The decision to use one therapy over the other is usually determined by whether there are relative contraindications to either therapy. Supportive measures, including good pulmonary toilet, nutrition, and prevention of deep venous thrombosis and infection, are essential.

Chronic inflammatory demyelinating polyneuropathy (CIDP) may occur at any age, but the peak incidence is in the fifth and sixth decades. The chronic progressive form tends to occur at an older age (McCombe *et al.*, 1987). Most patients present with both sensory and motor symptoms. Examination usually demonstrated symmetric proximal and distal weakness. Neck flexors weakness is common. Reflexes are diminished or absent. Diagnosis depends on clinical recognition of the disease supported by CSF evaluation, electrodiagnostic studies, and nerve pathology (Cornblath *et al.*, 1991). Nerve biopsy is not necessary for the diagnosis in most patients. Less than 10% of patients will have a spontaneous remission. Therapy is directed toward modulation of the immune system with plasmapheresis, prednisone, and/or human immunoglobulin (Dyck *et al.*, 1982; Mendell *et al.*, 2001a). Underlying medical problems such as heart disease, hypertension, renal insufficiency, and osteoporosis may complicate the use of some, if not all, of these therapies. Their use should be closely monitored, particularly in the elderly.

Multifocal motor neuropathy is a rare syndrome occasionally mistaken for amyotrophic lateral sclerosis. Patients present with slowly progressive asymmetrical weakness without sensory loss. The diagnosis relies on careful electrodiagnostic evaluation, which may demonstrate multifocal motor demyelination with partial motor conduction block and normal conduction studies (Chaudhry *et al.*, 1994). Treatment with human immunoglobulin has been promising (Chaudhry *et al.*, 1993; van den Berg *et al.*, 1998).

Herpes Zoster (*see* Chapter 145, Infectious Diseases)

Herpes zoster, or shingles as it is commonly known, may occur at any age. However, it is usually considered a disease of the elderly or the immunocompromised. At least 50% of the population will have had at least one episode by the age 80. A result of reactivation of the varicella zoster virus, it usually occurs in the trigeminal or thoracic dermatomes. Pain and paresthesias may appear in the affected dermatome several weeks before the appearance of vesicles. Herpes zoster is usually self-limiting; however, there is an increased risk of developing postherpetic pain or neuralgia with increasing age. In most patients, the pain resolves in several months. A few will have pain that persists for up to 1 year. Many patients respond to tricyclic antidepressants, carbamazepine, or phenytoin. Also, gabapentin is now approved for treatment of postherpetic pain. While treatment of the acute infection with steroids or oral acyclovir does not prevent the occurrence of postherpetic pain, famciclovir has been reported to reduce the duration of an acute attack and that of postherpetic neuralgia (Tyring *et al.*, 1995).

Sensory Neuropathies

Patients who present with pure or predominantly sensory neuropathies deserve special attention. These neuropathies may be distinguished from each other by their clinical presentation. Those with features associated with small fiber involvement, often have prominent loss of pain and light touch, yet a significant component of spontaneous pain. The differential diagnosis of this group includes the diabetic polyneuropathies, amyloid neuropathy, some forms of vasculitic neuropathy, as well as idiopathic disorders. These neuropathies have been or will be discussed in other portions of this chapter.

Acquired sensory neuropathies with ataxic features have been associated with both Sjogren's syndrome and neoplasms (Griffin *et al.*, 1990). The neuropathy associated with Sjogren's has been described as loss of kinesthetic sense, with gait ataxia and pseudoathetosis. This pattern is strikingly similar to the presentation of tabes dorsalis. Patients may also

complain of sensory loss or paresthesias proximally over the face, scalp, or trunk. The majority of the patients are women. There is no proven therapy; however, some patients may improve without any intervention. Carcinomatous sensory neuropathies will be discussed in more detail in the following text.

Malignancy

While many oncology patients receive neurotoxic chemotherapeutic agents and suffer from nutritional deficits that may contribute to the pathogenesis of neuropathy, several distinct syndromes associated with malignancy can be identified.

It has long been recognized that there is an association between plasma cell dyscrasias, benign and malignant, and peripheral neuropathies. The advent of immunoelectropheresis and immunofixation techniques has facilitated the identification of plasma cell dyscrasias and therefore, the neuropathies related to them. The type of neuropathy ranges from a pure sensory disorder with areflexia and large fiber loss to a polyradiculoneuropathy similar to CIDP (Kelly, 1987).

While most patients with benign monoclonal gammopathies do not have neuropathy, those with progressive sensorimotor symptoms should undergo electrophysiologic testing and careful laboratory screening, including bone surveys and urine protein studies, to rule out an underlying malignancy. Plasmapheresis is beneficial, particularly in treating the neuropathy associated with IgG and IgA gammopathy (Dyck *et al.*, 1991).

About half of patients with osteosclerotic myeloma will eventually develop a peripheral neuropathy. The neuropathy is slowly progressive and symmetric, involving motor more than sensory function. CSF protein is usually elevated, and conduction velocities are markedly reduced. The neuropathy may improve in response to local radiation therapy and immunosuppression directed at the primary sclerotic lesion.

Peripheral neuropathy may occur in about 20% of patients with amyloid associated with paraproteinemia. In 10% of these patients, the neuropathy may be the presenting feature. Early on, sensory features such as dysesthesias and aching pain are prominent as is autonomic dysfunction. As the neuropathy progresses, mild to moderate weakness develops. Occasionally, nerve entrapment (especially carpal tunnel syndrome) may be the presenting feature (Schaumburg *et al.*, 1992). In general, there is no successful treatment for amyloid. The brachial plexus and the lumbar plexus are common sites of metastatic disease or radiation injury. Lesions to the brachial plexus, usually due to spread of lung or breast tumor, typically present with pain. Symptoms include weakness and/or numbness in a median and ulnar nerve distribution. Nerve conduction studies and electromyography may localize the lesion to the lower trunk of the plexus, with occasional spread to the roots.

On the other hand, radiation fibrosis tends to involve the upper trunk of the brachial plexus. Pain is a less prominent feature and weakness tends to involve the proximal muscles of the shoulder girdle. Swelling of the hand and arm is common.

Seventy percent of patients with lumbar plexopathy secondary to metastatic disease will present with severe and unremitting pain. Numbness or weakness may be delayed by months. The pain is often worse while the patient is supine, and may be either radicular or local. Incontinence or impotence occurs in less than 10% of the patients (Stubgen, 1995). Sensory loss, reflex asymmetry, sacral or sciatic notch tenderness, leg edema, and a positive straight leg-raising test are prominent features of the examination. Evaluation should include pelvic and lumbosacral spine imaging. Nerve conductions and EMG may be helpful to further localize the lesion. Radiation-induced lumbosacral plexopathies are often insidious and may be pain-free. Diagnosis is suggested by the presence of myokymic discharges in proximal muscles by EMG (Stubgen, 1995).

A carcinomatous sensory neuronopathy has been described most frequently in the setting of oat cell carcinoma and also in patients with breast, ovarian, prostrate, and rarely GI tract tumors. Pain and dysesthesias are often severe, frequently beginning in the arm or face in an asymmetric distribution. The most striking feature of the neurologic exam is proprioceptive loss and a resultant severe sensory ataxia. A serologic marker has been described, anti-Hu, that may be present in either the serum or CSF of these patients. The CSF may otherwise be normal or may show a mild pleocytosis and/or elevated protein. Nerve conduction studies demonstrate marked reduction in sensory nerve amplitudes, often asymmetrically, with normal or near normal motor nerve responses. An aggressive search for malignancy should be performed; however, the neuropathy may precede the diagnosis of a tumor by several months to years, necessitating repeated screenings for malignancy.

Entrapment Neuropathies

The three most susceptible nerves to entrapment are the median, ulnar, and peroneal nerves. The incidence of compression neuropathies increases with age, due in part to repeated trauma, loss of protective subcutaneous tissue, prolonged periods of immobility, and the coexistence of metabolic disorders such as diabetes, renal insufficiency, and thyroid disease which predispose to entrapment neuropathy. The most common entrapment syndrome, carpal tunnel syndrome, consists of compression of the median nerve as it courses through the carpal tunnel at the wrist. Stiffness or pain in the wrist, arm, or shoulder is a frequent complaint. Paresthesias and numbness in the tips of the fingers may awaken the patient at night. Repetitive actions throughout the day or excessive extension or flexion may exacerbate symptoms. Tinel's or Phalen's sign at the wrist, decreased 2-point discrimination in median-innervated fingers, and/or weakness of thumb abduction and opposition are frequent findings by examination. Wasting of the thenar eminence may be seen in severe cases. Diagnosis is confirmed by nerve conduction studies, which demonstrate reduction of sensory nerve

conduction velocity across the carpal tunnel and prolonged distal motor latency of the median nerve. Conservative treatment is tried first, unless there is marked denervation, loss of function, or atrophy. The arm should be placed in a custom-made, neutral position wrist splint and underlying metabolic diseases should be treated. If the patient does not have relief from symptoms after several months, then surgical decompression should be considered.

The ulnar nerve may be compressed at the elbow near the medial epicondyle or as it passes through the cubital tunnel. Pain is usually in the medial aspect of the forearm but may also radiate to the shoulder. Frequently, there is associated numbness of the fourth and fifth digits and mild weakness of the interosseous muscles. The flexor carpi ulnaris and flexor digitorum profundus muscles are usually spared unless the entrapment is severe. Diagnosis is confirmed by nerve conduction studies, which show reduction of the ulnar conduction velocity across the affected segment. Initial therapy is conservative and consists of the patient wearing elbow pads and avoiding activities that precipitate symptoms such as flexion or direct compression of the nerve. Surgical decompression may be necessary in severe cases.

The peroneal nerve may be compressed at the fibular head. Sitting for prolonged periods of time with legs crossed or having been immobilized in bed for an extended time may precipitate this entrapment. Clinically, there is weakness of ankle and toe dorsiflexion and foot eversion. Sensory loss is quite variable, depending upon which portion of the peroneal nerve, deep or common, has been affected. Diagnosis is confirmed by nerve conduction studies. Treatment is conservative; avoidance of pressure on the nerve is recommended. If there is significant motor dysfunction an ankle foot orthosis may be necessary.

Idiopathic Neuropathies

In spite of extensive evaluation up to 25% of neuropathies remain "idiopathic" in that the etiology remains undiagnosed. One large group that has gained recognition in the last decade is the idiopathic small fiber painful sensory neuropathy. It is the most common cause of painful sensory neuropathy in patients older than 50 years of age. Patients present with painful feet usually characterized by burning sensation. Examination demonstrates distal loss of pain and temperature modalities with preserved deep tendon reflexes. Electrodiagnostic studies are normal. Quantitative sudomotor axon reflex test (QSART) to evaluate the function of postganglionic sympathetic sudomotor axons and quantitative sensory testing (QST) are helpful in establishing the diagnosis. Skin biopsy to determine intraepidermal nerve fiber density is the most sensitive test for the diagnosis (Periquet *et al.*, 1999). Though many of these neuropathies remain "idiopathic", several recent studies have established an increased prevalence of impaired glucose tolerance (fasting serum glucose between 110 and 126 mg/dl or a serum glucose between 140 and 200 mg dl^{-1} in a 2-hour GTT) in patients with painful small fiber neuropathy. GTT appears to be more sensitive than other measures of glucose in screening these patients (Singleton *et al.*, 2001). The possibility of late-onset HMSN II as the etiology for some of these neuropathies has been raised. The rapid advances in genetic screening may help reduce the number of undiagnosed neuropathies even further in the future.

KEY POINTS

- Neuropathy of "late life" is not well defined.
- Evaluation of the patient with neuropathy should be guided by the time course and physical examination.
- Electrodiagnostic studies play an essential role in the work-up of elderly patients with peripheral neuropathy.
- Diabetes is the single most common cause of neuropathy in the elderly in the industrialized countries.
- The most common explanation of painful sensory neuropathy is idiopathic after excluding metabolic and nutritional abnormalities.

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Disorders of the Neuromuscular Junction

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INTRODUCTION

The commonest adult-onset disorders of neuromuscular transmission are myasthenia gravis (MG) and the Lambert-Eaton myasthenic syndrome (LEMS). Both conditions are antibody mediated and are arguably the best understood of all neurological autoimmune diseases. The membrane ion channels and receptors at the neuromuscular junction (NMJ) seem particularly vulnerable to attack from circulating autoantibodies. The main target antigen in MG is the postsynaptic muscle nicotinic acetylcholine receptor (AChR) and in LEMS the targets are presynaptic neurone calcium channels. In addition, antibodies to nerve potassium channels are the commonest cause of the neuromyotonia clinical variant of peripheral nerve hyperexcitability (PNH).

MYASTHENIA GRAVIS

Almost all cases with myasthenia presenting after infancy are autoimmune. We will not consider in detail here either transient neonatal MG caused by placental transfer of maternal AChR antibodies or the rare genetic (congenital) forms of myasthenia. There are at least 20 of these inherited syndromes, which are caused by genetic defects in functional or structural proteins and can be autosomal dominant or recessive. They usually present at birth or in infancy, are nonprogressive and do not respond to immunotherapy. Only some forms improve with symptomatic treatment (Newsom-Davis and Beeson, 2001).

Clinical Features

The overall incidence of MG is between 2–10/100 000 people. It affects all races and can begin at any age after the first year of life. However, the incidence of MG increases with age: about half of all patients present after the age of 40 and it is seriously underdiagnosed in people over the age of 75 (Vincent *et al.*, 2003b). Onset in nonthymoma patients peaks at 10–30 years and rises again over the age of about 60 years, whereas onset of MG with thymoma is commonest between the ages of 40–60 years. Men predominate in the over 60 age-group and women outnumber men by 3 to 1 under the age of 40.

Symptoms and Signs

The hallmark of MG is painless fluctuating skeletal muscle weakness that worsens with exercise and improves with rest. Power in the affected muscles varies characteristically throughout the day and gradually decreases toward the evening. Any skeletal muscle may be involved but certain muscles and muscle groups are especially susceptible, notably those supplied by the motor cranial nerves.

In more than 90% of patients, the peri and extraocular muscles are affected and ptosis and diplopia are common. Typically, there is asymmetrical weakness of several muscles of both eyes accompanied by weakness of eye closure. Patients often attempt to correct ptosis by contracting the frontalis muscle causing a characteristic wrinkled brow appearance. In 15–20% of patients, the weakness is confined to the ocular muscles – ocular MG – while the others present with or will develop the generalized form.

The muscles of facial expression, mastication, swallowing, and speech are the next most commonly involved. Relatives may notice that a lack of facial movement makes the patient look depressed and that the smile has a snarling quality. Jaw weakness can interfere with chewing. In severe cases, the jaw hangs open and is supported by the patient's hand. Palatal weakness can result in nasal speech and reflux of liquids while drinking. Dysphagia and choking reflecting involvement of the pharyngeal muscles and tongue, and hoarseness and dysphonia caused by laryngeal weakness are frequently seen.

Neck muscle weakness is common and the head droops forward in severe cases. In generalized disease, the proximal

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Table 1 Drugs that may worsen myasthenia gravis

Neuromuscular blockers	Including d-tubocurarine, pancuronium, curare, and succinylcholine
Aminoglycosides	Including gentamicin, streptomycin, kanamycin, neomycin, and viomycin
Polymixins	Including polymixin B and colistin
β-blockers	
Calcium channel antagonists	
Quinine, quinidine, and procainamide	
Chloroquine and hydroxychloroquine	

limb muscles are typically most affected. Reflexes are normal or brisk. On examination particular attention should be given to shoulder abduction, elbow extension, wrist and finger extension, finger abduction, and hip extension, as these are frequently weaker and fatigue quicker than their antagonistic limb movements. In severe cases, all muscles can be involved, including the diaphragm and intercostal muscles causing dyspnoea and hypoventilation. Chronic poorly controlled disease can in some patients lead to muscle wasting. Muscle strength should be quantified as serial assessment may give objective early warning of deterioration, as well as help to monitor treatment. Measurements should include vital capacity (VC), timed elevation of the eyes and eyelids and forward abduction of the arms. A rapid decline in VC or a reading below 1 l are signs of imminent respiratory failure.

Muscle weakness can be worsened by a wide range of conditions including intercurrent diseases especially infections, fever, extremes of temperature, and emotional upset. In addition, many drugs may adversely affect myasthenia and should be used with caution in poorly controlled patients (Table 1). If possible, neuromuscular blocking agents should not be used during general anaesthesia. Sufficient muscle relaxation can usually be provided by inhalation anaesthetics alone. Many other drugs may increase weakness and it is a useful rule to monitor carefully all MG patients starting a drug new to them.

Clinical Classification

The progression of MG is variable and it is difficult to predict the outcome in an individual patient. However, the classification shown in Table 2 serves both as an aid to prognosis and to planning of treatment. Based on this, studies have established several useful clinical guidelines. Only 10–15% of patients with myasthenia limited to the ocular muscles for 2 years will progress to develop generalized disease. In generalized MG, the rate of progression is more variable. However, maximum severity is reached within the first year in two-thirds of patients and respiratory crises are more likely to develop with increasing age of onset. Typically, MG follows a chronic course. Spontaneous remissions occur in less than half of all patients and are usually temporary.

Table 2 Clinical classification of myasthenia gravis

Group 1	Ocular myasthenia
Group 2A	Mild generalized myasthenia with slow progression
Group 2B	Moderate generalized myasthenia with prominent bulbar involvement
Group 3	Acute fulminating myasthenia with rapid progression and respiratory crises
Group 4	Late severe myasthenia similar to group 3, but starting as group 1 and progressing in less than 2 years to become generalized

Table 3 Immune disorders reported in association with myasthenia gravis

Thyroid disease: both hyper- and hypothyroidism
Rheumatoid arthritis
Systemic lupus erythematosus
Acquired peripheral nerve hyperexcitability (neuromyotonia)
Sjögren's syndrome
Polymyositis
Selective or pan-hypogammaglobulinaemia
Lambert-Eaton myasthenic syndrome
Dermatological diseases Pemphigus, lichen planus, vitiligo, alopecia
Haematological disease Pernicious anemia, red cell aplasia, neutropenia, aplastic anemia, idiopathic thrombocytopenic purpura

Associated Immune Diseases

Autoimmune diseases tend to cluster both in individuals and families. Hyperthyroidism, rheumatoid arthritis, PNH, and systemic lupus erythematosus are the diseases reported most consistently in association with MG (Table 3).

Pathogenesis

MG is caused by an antibody-mediated reduction in the number of AChR available at the skeletal NMJ, typically to about one-third of normal. Neuromuscular transmission involves the release of packets (quanta) of ACh from the nerve terminal. ACh diffuses across the junctional gap and binds to muscle AChRs. This reaction opens ion channels allowing influx of cations through the muscle fiber membrane and results in depolarization of the endplate (endplate potential). When this depolarization reaches a certain threshold, an action potential is generated that travels along the muscle cell membrane initiating contraction. In MG there are fewer AChRs and this reduces the amplitude of the endplate potential and, thus, decreases the likelihood of a muscle action potential being triggered.

Acetylcholine Receptor Antibodies

Serum AChR IgG antibodies can be detected in 85–90% of patients with generalized MG and in 50–60% of those with weakness restricted to the ocular muscles (Vincent and Newsom-Davis, 1985). The evidence that

Table 4 Evidence that myasthenia gravis is an antibody-mediated autoimmune disease

- Antibody can be demonstrated in the majority of patients with the disease: AChR antibodies are detected in 85% of patients with generalized MG
- Passive transfer of the antibody to experimental animals reproduces the disease: IgG from myasthenics injected into mice induces the clinical and electrophysiological features of MG
- Antibody interacts with the target antigen: Electron microscope immunohistochemistry has shown that AChR antibodies, as well as complement, localize to postsynaptic structures in a pattern appropriate to affect AChRs in a destructive autoimmune process
- Immunization with antigen produces a model of the disease: animals immunized with purified AChR develop myasthenia
- Lowering serum antibodies improves the disease: removal of circulating antibodies by plasma exchange results in marked, but transient, improvement in the disease in most myasthenics. After treatment, the antibody titer rises and the weakness returns

these antibodies are pathogenic in MG fulfils the five criteria that establish a causal relationship between an autoantibody and any suspected immune-mediated disease (Table 4).

Mechanisms of AChR Antibody Action

AChR antibodies reduce the number of available junctional AChRs in three ways. MG IgG cross-links AChRs and increases receptor turnover up to threefold by accelerating receptor endocytosis. Antibodies from up to 90% of myasthenics can also block the ligand-binding site of the AChR, making it unavailable to ACh. Furthermore, in severe MG the NMJ gap is widened and postsynaptic structures are damaged. Complement has been identified in association with IgG on postsynaptic membranes, implying that complement-mediated damage contributes to the loss of endplate morphology (Engel and Arahata, 1987).

Heterogeneity of AChR Antibodies

In an individual MG patient serial AChR titers correlate positively with disease severity, for example, before compared with after plasma exchange. However, between individuals, there is poor correlation of absolute antibody concentration with the degree of muscle weakness. This may be, at least in part, caused by the phenomenon of antibody heterogeneity. For example, IgG from some MG patients preferentially produce an acute block of AChRs whereas IgG from other patients have more effect on AChR turnover. In addition, there is evidence from individual MG patients that the antibodies are heterogeneous in their fine specificities (Tzartos *et al.*, 1991; Lindstrom *et al.*, 1978). An adult AChR is made up of five subunits (α_2, β, γ, ε). Most AChR antibodies bind to an α-subunit, in particular, to a sequence of 10 amino acids in the extracellular domain known as *the main immunogenic region* (Tzartos *et al.*, 1991). However, other antibodies from the same patient may bind to other sites not only on the α-subunits but also on each of the other three receptor subunits. Some AChR antibodies, therefore, are more disease inducing than others and it is likely that disease severity is related in part to the target specificities of the antibodies rather than exclusively to the total concentration.

AChR Antibody Negative (Seronegative) Myasthenia Gravis

About 15% of MG patients never have AChR antibodies detectable by standard assays (Vincent and Newsom-Davis, 1985). The condition is, nevertheless, antibody mediated, the antigen being some other non-AChR target on the muscle cell. These AChR antibody negative patients rarely have thymomas and have a lower incidence of thymic hyperplasia than those with AChR antibodies (Willcox *et al.*, 1991). Otherwise they have similar clinical, electrophysiological, and NMJ histological findings to antibody positive patients. They also usually respond to treatment with anticholinesterases and immunotherapy, and their sera contain an Ig that decreases neuromuscular transmission when injected into mice. Moreover, an Ig fraction from some seronegative patient plasma, which copurifies with IgM, caused an acute block of AChR function in a human rhabdomyosarcoma cell line (Yamamoto *et al.*, 1991). More recently, 10–50% of AChR antibody negative generalized MG patients were found to have antibodies to muscle specific tyrosine kinase (MuSK) – a protein that helps cluster AChRs at the muscle endplate (Vincent *et al.*, 2003a). Although the action of MuSK antibodies is not yet known, they are useful in the diagnosis of AChR antibody negative MG.

Striated Muscle Antibodies

These are a group of antibodies that bind to components of striated muscle (Romi *et al.*, 2000). Using immunofluorescence, antibodies to the muscle cell membrane are found in 30% of all MG patients and in 70–90% of those with thymoma. Therefore, these antibodies are used as a serum marker for this tumor. In addition, subgroups of these antibodies to titin or ryanodine receptors are particularly associated with severe MG as well as with thymoma (Romi *et al.*, 2000).

Penicillamine-induced Myasthenia Gravis

Unlike the drugs that may temporarily worsen myasthenia (Table 2), D-penicillamine may induce immune-mediated MG. Typically, patients develop AChR antibodies and clinical features that are often indistinguishable from spontaneous MG (Vincent and Newsom-Davis, 1982). The disease resolves within 1 year of stopping the drug in 70% of patients. Weakness is typically mild, often restricted to the ocular muscles, and usually responds to anticholinesterases alone.

Thymus

The normal thymus reaches it full size at birth, begins to involute at puberty, and is replaced by fatty tissue by the third decade. About 75% of MG patients have thymic abnormalities. Hyperplasia characterized by lymphoid follicles with medullary germinal centers accounts for up to 85% of these cases, typically in those patients who develop AChR antibody positive MG before the age of 40. Thymoma will develop in the other 15%. These are epithelial cell tumors that metastasize rarely, but may invade locally in up to 30% of cases. Thymoma may be found without MG, although many of these patients will develop myasthenia, even after the tumor has been treated.

As in all autoimmune diseases, the mechanisms responsible for the origin and maintenance of the abnormal immune response in MG are not known. Research has focused on the role of the thymus, T cells, and immunogenetic factors, and suggests that multiple processes are involved. Myoid (muscle-like) cells from hyperplastic thymus express AChRs which may suggest that these cells are important in the initiation of the disease in some patients (Kornstein *et al.*, 1995). In MG, the AChR antibody response is T cell dependent. T cells from both the thymus and peripheral blood of myasthenics show several differences from those from control subjects. For example, MG T cells have a different distribution of CD phenotypes and *in vitro* have increased reactivity to AChR. (Sommer *et al.*, 1990). This T-cell reactivity is heterogenous: cells from one myasthenic react to multiple AChR epitopes and, furthermore, cells from each individual recognize a different set of epitopes (Melms *et al.*, 1992). There is also heterogeneity in the genetic factors that predispose to MG. There is moderate association with certain human-leukocyte-associated antigen phenotypes that varies according to both the subtype of the disease and race.

Therefore, the striking clinical, immunological, and genetic heterogeneity seen in MG makes it unlikely that there is a single underlying etiologic factor. While this diversity complicates efforts to understand the mechanisms involved in the pathogenesis of MG, it may provide opportunities to design immunotherapy specific for individual patients.

Diagnosis

Diagnostic confusion arises most often when MG is mild or when one of the clinical features dominates the presentation. Patients may not volunteer a history of fluctuating weakness and it is useful to ask about this in anyone presenting with tiredness, ptosis, diplopia, dysphagia, or hoarseness. Examination should include assessment of muscle power and fatigability. Even when symptoms are restricted to one area it is sometimes possible to demonstrate weakness in the typical pattern described above. It is essential to confirm the diagnosis by laboratory tests, as treatment may involve surgery and drug therapy with potentially serious side effects.

Acetylcholine Receptor Antibodies

The most specific routine test for MG is the presence of serum AChR IgG antibodies detected by an radioimmunoprecipitation assay (RIA). This uses AChRs labeled with an iodinated toxin, which binds specifically to these receptors (^{125}I-α-bungarotoxin) (Vincent and Newsom-Davis, 1985). False positives are rare in the healthy British population, including the elderly, although 7% of a group of patients over the age of 65 selected for their predisposition to autoimmune disease (assessed by raised antithyroid antibody titers) had raised levels. This assay does not detect AChR antibodies in patients with "seronegative" MG. However, 10–50% of these patients with AChR antibody negative generalized MG will have antibodies to MuSK.

Electomyographic Techniques

The most commonly used tests are repetitive nerve stimulation (RNS) and single-fiber electromyography (SF-EMG) (Sanders, 1993). The results may be misleading in patients who have been on chronic high dose anticholinesterase treatment because of drug-induced downregulation of AChRs. If there is any doubt about the EMG findings, it is better – when possible – to stop these drugs for a week and repeat the tests.

In RNS, a train of electric shocks at 3–5 Hz is given to a nerve and action potentials are recorded from the relevant muscle. A decline in the amplitude of the fifth compared with the first potential of more than 10% is judged positive (decrementing response). This is found in about 50% of mild MG patients and 80% of those with more severe weakness.

During SF-EMG, recordings are made from two or three different muscle fibers within a single motor unit. The finding of increased jitter (breakdown in the timing relationship of activation between the muscle fibers), often accompanied by blocking of successive muscle discharges, is abnormal. When recordings are made from a range of muscles, abnormal responses are seen in up to 99% of generalized MG patients and 84% of those with pure ocular disease. This test, therefore, is highly sensitive. However, these findings are not specific for MG. Jitter and blocking can occur in LEMS and in conditions where there is reduced muscle fiber density, such as motor neurone disease. Furthermore, SF-EMGs can be difficult to interpret in elderly patients as jitter increases with age, and normal values were established using individuals under the age of 60.

Anticholinesterase Test

This is the least specific of the standard tests for MG. Positive responses may occur in a wide range of conditions including LEMS, motor neurone disease, neuropathies, myopathies, and psychogenic weakness. It is probably best reserved for when there are strong clinical reasons for suspecting MG and the results of antibody tests are negative, or not yet available, and EMG awaited.

Edrophonium chloride (Tensilon) is a short-acting acetylcholinesterase inhibitor. A test dose of 1–2 mg is given

intravenously (IV). If there is no adverse reaction, another 5–8 mg are injected. The test is positive if muscle strength improves within 1 minute. Assessment should be as objective as possible and include VC and timed forward elevation of the arms, as well as monitoring ptosis and diplopia. Increased muscle power lasts about 5 minutes. Some patients may develop severe bradycardia, and occasionally ventricular fibrillation. Thus, pretreatment with IV atropine (0.6 mg) is probably advisable and the test is best carried out under ECG monitoring with resuscitation equipment nearby.

Other Tests

A contrast enhanced CT or MRI scan of the mediastinum should be obtained to look for thymoma (Figure 1). In those at high risk of thymoma – with raised AChR and striated muscle antibody titers – a negative scan should be repeated at 2–3 years. In all patients it is useful to look for evidence of other autoimmune, especially thyroid, diseases (Table 3).

In difficult cases specialist techniques are available, including muscle biopsy for quantification of endplate AChRs and immunohistological and electrophysiological studies.

Differential Diagnosis

LEMS, certain restricted myopathies, mitochondrial cytopathies especially progressive external ophthalmoplegia, motor neurone disease, peripheral neuropathies, hyperthyroidism, psychogenic weakness, and intracranial mass lesions causing cranial nerve palsies, are some of the conditions that can mimic myasthenia and cause diagnostic confusion if appropriate tests are not carried out.

Management

The management of MG varies with type and severity of the disease, individual disability, concurrent illness, and age of the patient. Anticholinesterases, immunosuppressive drugs, thymectomy, plasma exchange, and intravenous immunoglobulin (IVIg) are the most frequently used therapies (Figure 2) (Skeie *et al.*, 2005). With current treatment regimens, remission or substantial improvement leading to a good quality of life can be expected in at least 90% of patients, regardless of age.

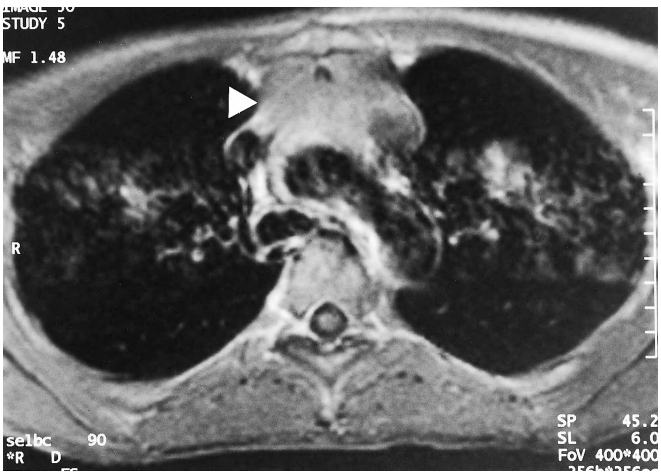

Figure 1 Thymoma. T2-weighted axial MRI of the mediastinum, after intravenous gadolinium-DTPA contrast, at the level of the aortic arch shows a large enhancing tumor (arrow)

Anticholinesterase Inhibitors

These are the first-line drugs for all MG patients. They inhibit ACh breakdown at the NMJ. Their main uses are to provide long-term symptomatic improvement in mild disease, especially ocular, and as a temporary adjunctive therapy for patients embarking on definitive treatment. These drugs act quickly (within 10–30 mins) but have a short half-life: their effect is maximal at 2 hours and lasts about 4 hours. Therefore, the starting dose of pyridostigmine (the most widely used drug) should be 30 mg two to four times per day. The dose can then be gradually increased according to response. However, the maximum useful dose is rarely greater than 60 mg five times per day. High doses may mask progressive disease and overdose can worsen weakness and precipitate a cholinergic crisis.

High doses will also produce more adverse effects caused by the action of the drug on smooth muscle muscarinic AChRs. These include nausea, abdominal cramps, diarrhea, and increased bronchial and oral secretions. Propantheline can alleviate these problems, but may mask the signs of overdose. Chronic high doses may, in addition, increase weakness owing to downregulation of AChRs. The aim should be slowly to withdraw pyridostigmine after thymectomy or when immunosuppressive treatment has been established.

Prednisolone

Steroids may be used in all forms of acquired MG (Evoli *et al.*, 1992). They are indicated in any patient who fails to respond adequately to pyridostigmine, and where the benefits of treatment for the individual outweigh the possible side effects. Prednisolone is usually started at a low dose and gradually increased because initiation of steroid therapy can be associated with a temporary worsening of MG (up to and including bulbar and respiratory failure) occurring 4–10 days after treatment has begun. Alternate day dosing minimizes suppression of the hypothalamic-pituitary axis. In selected patients with mild or localized disease, treatment may be started as an outpatient at a dose of 10 mg on alternate days and gradually increased by 10 mg per week. In most patients, however, treatment should be started as an inpatient, when the initial alternate day dose of 10 mg can be increased by 10 mg per dose under close supervision. The dose is increased until symptoms are controlled or a dose of 1–1.5 mg kg^{-1} body weight on alternate days is reached, whichever is sooner. Improvement is usually seen within 1–4 weeks but can take longer. Maximum benefit may not occur for 3–6 months. Initiating treatment at a high daily

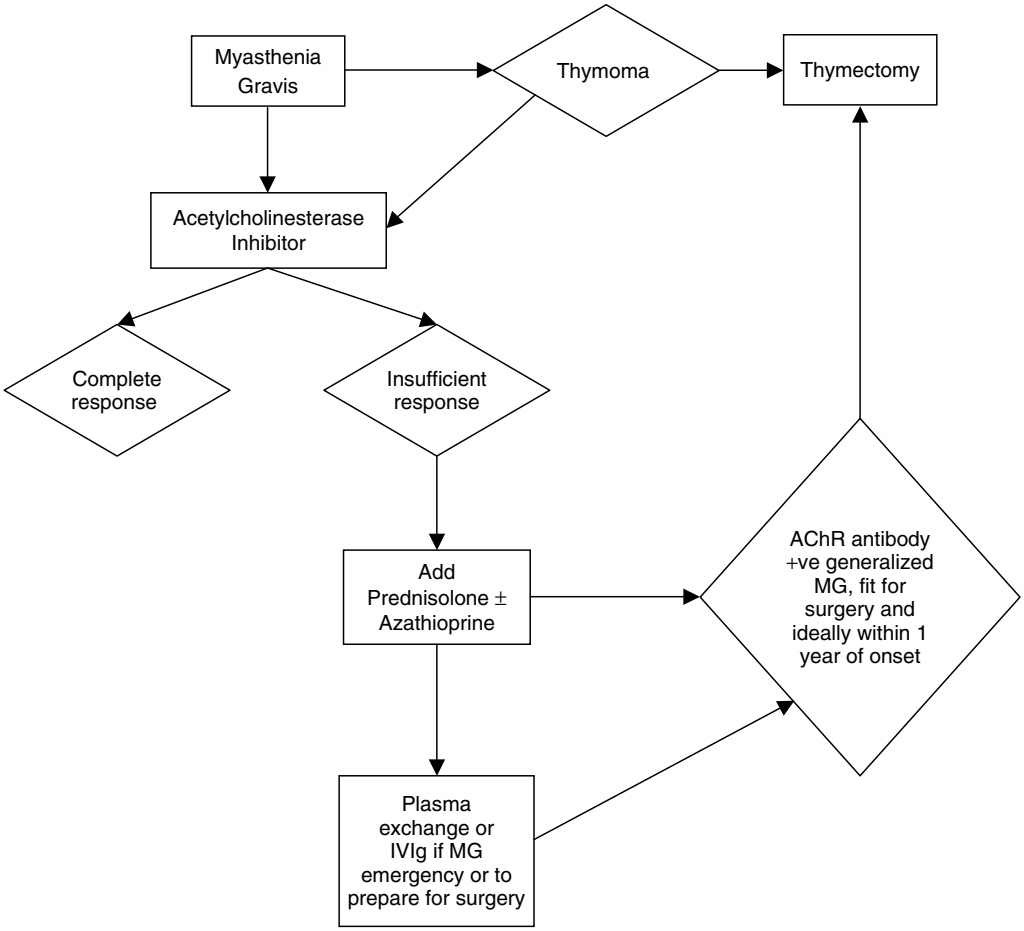

Figure 2 An algorithm for the management of myasthenia gravis

dose to achieve a faster response is usually reserved for those patients already in ITU.

The dose that has induced remission should be continued for 1–2 months. Sudden decreases may precipitate a severe relapse and should be avoided. The aim is to taper the dose slowly by 10 mg per month to find the lowest dose that fully controls symptoms. It may take many months to find this minimum effective dose. The often formidable problems of steroid side effects are well recognized and patients must be closely monitored. If present, hypokalaemia should be corrected by potassium supplements. It is also worth highlighting the problem of vertebral crush fractures caused by steroid-induced osteoporosis. It is now routine to cover steroid therapy from the onset with a bisphosphonate.

Azathioprine and Combination Treatment

Azathioprine may be used as initial immunosuppressive therapy in patients with mild to moderate MG or who have failed to respond to thymectomy, or when steroids are contraindicated (Palace *et al.*, 1998). However, it has the disadvantage that treatment must be continued for 6 months to 1 year before clinical improvement is seen and the maximum effect may be delayed for up to 3 years. Therefore, it tends to be used along with prednisolone in severe myasthenia. In addition, azathioprine allows the steroid dose to be reduced earlier and to lower levels. Experience suggests that this combination of drugs is the most effective immunosuppressive regimen for MG.

Azathioprine is typically started at 50 mg per day and the dose increased by 50 mg per week until a maintenance dose of 2.5 mg kg^{-1} day^{-1} is reached. After remission, the dose is slowly reduced by about 25–50 mg/month provided full control of symptoms is maintained. When used in combination with prednisolone, the steroid is withdrawn first. Up to 10% of patients develop an idiosyncratic reaction to azathioprine including fever, diarrhea, nausea, vomiting, and muscle pains. Bone marrow suppression and abnormalities of liver function can occur especially in those with thiopurine methyltransferase deficiency and this enzyme can be assayed before starting therapy. However, most patients tolerate the drug well and mild but stable haematological or liver abnormalities without symptoms are not usually reasons for stopping treatment. Full blood count (FBC), platelets, and liver function tests (LFTs) must be monitored weekly for the first 8 weeks of therapy and 3-monthly thereafter. If there are progressive blood test abnormalities the drug must be stopped, although it is often possible to restart

treatment at a lower dose after the blood tests have returned to normal. Azathioprine has also been associated with teratogenic effects and in renal transplant patients with malignancies, notably B cell lymphoma. The risk is usually low in MG (probably <1 in 3500), and in some cases it appears that the tumor may regress after azathioprine is withdrawn.

Methotrexate can be useful in patients who do not tolerate azathioprine. Ciclosporin can also be effective, either alone or in combination with prednisolone, and should be tried if other drugs fail. The combination of prednisolone and mycophenolate mofetil has been effective in many patients (Meriggioli *et al.*, 2003). The potentially severe toxic effects of cyclophosphamide have limited its use to rare cases of intractable MG.

Thymectomy

This is the treatment of choice for thymoma. A transsternal approach is preferred as this allows most complete removal of the tumor. If the patient is unfit, or the tumor is too widespread for operation, radiotherapy or chemotherapy may be indicated. Also, radiotherapy may be given if tumor removal is incomplete. MG often does not improve after treatment of thymoma, although weakness may improve with steroids (Skeie *et al.*, 2005).

In nonthymoma patients, surveys suggest that thymectomy is of most benefit to patients under the age of about 45–50 with AChR antibody positive generalized MG and is probably most effective when performed within 1 year of onset (Skeie *et al.*, 2005). It is not routinely indicated in older patients, AChR antibody negative MG, or in ocular myasthenia.

Plasma Exchange

In most MG patients, weakness improves after plasma exchange (Skeie *et al.*, 2005). It acts mainly by depleting circulating immunoglobulins. A standard protocol is five exchanges each of $50\,\mathrm{ml\,kg^{-1}}$ body weight over a period of 5–7 days. Typically, improvement begins within 1–2 days and is maximal at 1–2 weeks. However, the effects are temporary lasting about 2–6 weeks. It is mainly used to treat myasthenic crises and for rapid stabilization of patients undergoing thymectomy. Less often, several courses are given to control severe weakness in patients slow to respond to thymectomy or immunosuppression. With optimum treatment, repeated exchanges are rarely indicated as a chronic form of therapy.

Intravenous Human Immunoglobulin

The indications for IVIg in MG are the same as those for plasma exchange (Skeie *et al.*, 2005). Improvement is seen in the majority of patients, beginning within 4–5 days and lasting from weeks to months. Typically, $0.4\,\mathrm{g\,kg^{-1}}$ body weight is given daily for 5 days. The mechanism of action is likely to be complex. The most important adverse effects are the risk of transmitting viral infection and occasional anaphalactic responses.

Management in Special circumstances

Ocular myasthenia Many patients do not respond adequately to pyridostigmine alone and prednisolone is needed. This is generally started at a low, alternate day dose and gradually increased as described above. Maximum doses of 20–40 mg on alternate days are usually adequate.

Myasthenic and cholinergic crises A crisis is weakness severe enough for the patient to need ventilation. Myasthenic crisis is usually caused by infection or other intercurrent disease, surgery, or too rapid a reduction in the dose of immunotherapy. Excessive treatment with anticholinesterases underlies the rarer cases of cholinergic crisis. These are both medical emergencies and require ITU management. Much has been written on how to distinguish between these two conditions. In practice, if there is any doubt about the cause of the crisis it is safer to stop the anticholinesterase once the patient is on a ventilator. Infection is aggressively sought and treated. In myasthenic crisis, IVIg or plasma exchange is usually indicated and the doses of immunosuppressant drugs increased as appropriate. If anticholinesterases have been stopped, they are reintroduced gradually up to the maximum recommended dose (60 mg five times per day for pyridostigmine).

Anaesthesia Local or spinal anaesthesia is preferred if possible. If a general anaesthetic is needed, a nasotracheal tube inserted at operation allows ventilation to be assisted postoperatively if required. The tube is kept in place usually for 1–2 days, by which time the VC has usually recovered enough to allow extubation. Anticholinesterases increase bronchial secretions and it is usually best to withhold these drugs on the morning of the operation and for 24 hours afterwards. Reintroduction is guided by clinical assessment. Immunosuppresant drugs are continued.

LAMBERT-EATON MYASTHENIC SYNDROME

The experimental approaches first used in MG, focusing on the criteria listed in Table 4, have established LEMS as the second antibody-mediated autoimmune disorder of neuromuscular transmission. Presynaptic motor nerve terminal voltage-gated calcium channels (VGCC) are the main antigenic targets (Motomura *et al.*, 1995).

LEMS is divided into two types: paraneoplastic (occurring as a remote effect of neoplasm) and spontaneous. Two-thirds of patients, mainly older male smokers, develop LEMS in association with a tumor, most commonly small cell lung carcinoma (SCLC) or more rarely lymphoma, certain adenocarcinomas, and thymoma (O'Neill *et al.*, 1988). It is thought that VGCCs on tumor cells trigger the production of antibodies that crossreact with antigenically similar nerve

channels and that this leads to channel downregulation and a reduction in transmitter release. Spontaneous cases tend to be younger, have no smoking history, and are usually women. Three percent of those with SCLC develop LEMS and overall incidence is about 4/million.

LEMS presents most often as a subacute onset, ascending weakness of the proximal limb muscles, typically affecting first the lower limbs causing a characteristic rolling gait. Ptosis and diplopia can occur. Bulbar and respiratory muscle weaknesses are much less common than in MG (Wirtz *et al.*, 2002). Features of autonomic dysfunction including dry mouth, constipation, urinary hesitancy, and impotence, are frequently found. Some patients also have paraesthesias and muscle aches. On examination, the strength of the affected muscles can increase during the first few seconds of a maximal voluntary contraction, a phenomenon known as *augmentation*. Reflexes are reduced or absent, although are often transiently restored to normal after 15 seconds of sustained muscle contraction (posttetanic potentiation). The course is variably progressive.

The syndrome, most frequently the spontaneous form, is associated with other autoimmune diseases including vitiligo, thyroid disorders, diabetes, and pernicious anemia (O'Neill *et al.*, 1988). Paraneoplastic LEMS may coexist with other paraneoplastic neurological syndromes including subacute cerebellar degeneration and encephalomyelitis.

Serum VGCC IgG antibodies to the P/Q subtype of channels are detected in up to 90% of patients with paraneoplastic LEMS and 76% of those with the spontaneous disease by a RIA using ^{125}I-ω-conotoxin MVIIC, which binds specifically to these channels (Motomura *et al.*, 1995). On EMG, typically, there is a marked reduction in the amplitude of the compound muscle action potential (CMAP) following supramaximal nerve stimulation, that increases following maximal voluntary contraction for 15 seconds (Sanders, 1993). A 25% increase in amplitude is suggestive of LEMS and a 100% increase is diagnostic. On single-fiber recordings, increased jitter with frequent blocking are often found as in MG. Nerve conduction studies are normal. Patients may respond to edrophonium, but not as dramatically as those with MG. Repeated screening tests for tumors should be carried out particularly in those patients with a high risk of malignancy, such as smokers, as a SCLC may not be obvious for up to 5 years after the onset of LEMS.

The definitive management of paraneoplastic LEMS is treatment of the tumor. This often leads to neurological improvement (Skeie *et al.*, 2005). In those cases of LEMS with tumor, or at high risk of developing one, the first-line drug treatment is 3,4 diaminopyridine (10–20 mg up to five times per day), a potassium channel inhibitor that increases ACh release from neurones. Side effects include perioral and other paraesthesias. Sometimes the addition of pyridostigmine produces a further small improvement in muscle strength.

Mild cases of spontaneous LEMS are also treated with these drugs. Severe weakness requires the addition of immunosuppressive agents. The combination of prednisolone (1–1.5 mg kg^{-1} body weight) and azathioprine (2.5 mg kg^{-1} body weight) seems to be the most effective and the treatment plan generally follows that for MG. However, the response is slower, improvement can be delayed for 6 months, and after stabilization immunosuppressive drugs can rarely be withdrawn completely. Prednisolone may be useful in paraneoplastic LEMS when weakness fails to respond well to treatment of the tumor.

Patients may improve temporarily after plasma exchange and this can be used to supplement other treatments. Similarly, IVIg can increase muscle strength, mirrored by a decline in anti-VGCC antibody titers (Bain *et al.*, 1994). Improvement lasts from 4–6 weeks and this work has led to trials of regular IVIg in patients who are still disabled despite oral immunosuppression.

PERIPHERAL NERVE HYPEREXCITABILITY (NEUROMYOTONIA (ISAACS' SYNDROME)

The commonest acquired clinical variant of generalized PNH is neuromyotonia that is caused by antibodies to nerve voltage-gated potassium channels (VGKC) (Newsom-Davis and Mills, 1993). Neuromyotonia is paraneoplastic in up to 25% of patients and can predate the detection of tumor, usually thymus or lung, by up to 4 years.

The characteristic presentation is with muscle overactivity causing various combinations of muscle twitching, cramps, and stiffness. In severe cases, there is additional weakness, pseudomyotonia (delayed muscle relaxation after contraction), pseudotetany, and increased sweating (Hart *et al.*, 2002). Symptoms are often triggered by muscle contraction and disability can be severe. About a third of patients have some sensory features such as paraesthesias. Central nervous system features can occur (Morvan's syndrome). The electrophysiological hallmark is the spontaneous firing of single motor units as doublet, triplet, or multiplet discharges that have a high intraburst frequency (40–300/second) and occur at irregular intervals (Hart *et al.*, 2002). Their persistence after proximal nerve block by local anaesthetic proved their peripheral nerve origin, and suggested that in such cases the discharges were arising in the terminal arborization of motor nerves.

There is no autoantibody that indicates whether PNH is paraneoplastic. VGKC antibodies are found in about 35% of all PNH patients, although this rises to 80% in those with thymoma. VGKC antibodies can also be associated with limbic encephalitis and thymoma without PNH, or with nonparaneoplastic limbic encephalitis. Thymoma-associated cases are likely also to have striated muscle antibodies (Vedeler *et al.*, 2005).

All forms of neuromyotonia usually improve with symptomatic treatment. Carbamazepine, phenytoin, lamotrigine, and sodium valproate can be used, if necessary in combination. Paraneoplastic neuromyotonia often improves and can remit after treatment of the underlying cancer (Hart *et al.*, 2002).

Immunomodulatory therapies should be considered in patients with likely autoimmune variants of PNH whose symptoms are debilitating and refractory to symptomatic treatment. Plasma exchange often produces useful clinical improvement lasting about 6 weeks accompanied by a reduction in EMG activity and a fall in VGKC antibody titers (Hart *et al.*, 2002; Vedeler *et al.*, 2005). Single case studies suggest that IVIg can also help. By analogy with LEMS, selected patients with severe neuromyotonia refractory to other treatments may benefit from serial immunomodulatory therapy every 6–8 weeks.

There are no good trials of long-term oral immunosuppression. However, prednisolone, with or without azathioprine or methotrexate, has been useful in selected patients (Skeie *et al.*, 2005; Vedeler *et al.*, 2005).

KEY POINTS

- MG, LEMS and PNH are all antibody-mediated NMJ disorders.
- MG incidence rises with age.
- MG is seriously underdiagnosed in the elderly.
- MG is treatable – more than 90% of patients can return to normal function.
- MG should be considered in anyone presenting with ptosis, diplopia, dysphagia, or limb or respiratory muscle weakness.

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Sarcopenia and Sarcopenic-Obesity

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INTRODUCTION

Sarcopenia is the age-related loss of muscle mass, strength, and function. The term derives from the Greek "sarx" for flesh and "penia" for loss, and was first used by Rosenberg at a symposium on nutritional status and body composition held in New Mexico in 1988 with the intent of drawing increased attention of the scientific community to this important, but understudied problem of aging (Rosenberg, 1989, 1997). The strategy worked, and interest in sarcopenia solidified and accelerated with several workshops and symposia (Dutta, 1997; Dutta and Hadley, 1995; Marcell, 2003), as well as the issuance of two program announcements by the National Institutes of Health (PA-96-038; PA-97-060). Sarcopenia is now a major line of aging research as evidence has accumulated for its epidemiology, causes and consequences, and health-care costs. Much, however, remains to be elucidated. Debate continues as to the best measures and quantitative definitions for screening and diagnosis, and the public health burden posed by sarcopenia (Dutta, 1997). The pathophysiology of sarcopenia has been linked to oxidative stress, muscle fiber denervation, decreases in growth and sex steroid hormones, increases in circulating proinflammatory cytokines, physical inactivity, and malnutrition. But the complex interactions of these factors and others to sarcopenia, as well as the independent contributions of each, remain to be clarified. Sarcopenia has been shown to be associated with a spectrum of consequences including functional limitation, disability, falls and bone fractures, immunodeficiency, and impaired thermoregulation. It is unclear as to what extent these associations are confounded by underlying disease. The interaction of sarcopenia with obesity, or "sarcopenic obesity", has only recently been recognized (Baumgartner, 2000; Roubenoff, 2000b). Many issues remain to be clarified with regard to treatment, such as optimal exercise regimens with or without nutritional supplementation and type of supplement, dosage and side effects of hormone replacement and other anabolic stimulants, and the safety and efficacy of anti-inflammatory and other pharmacologic treatments (Kamel, 2003). There are almost no data for preventive interventions, especially at the community level. However, to quote Roubenoff, it is clear that, "as the number of elderly persons increases exponentially in the new century, a public health approach to prevention and treatment of sarcopenia … will be crucial to avoiding an epidemic of disability in the future" (Roubenoff, 2000a).

This chapter provides a comprehensive overview of the current literature on sarcopenia, as well as sarcopenic obesity, in aging.

DEFINITIONS

The most common definition of sarcopenia is the gradual loss of skeletal muscle mass and quality that occurs with increasing old age. It is a complex question as to how much of this process is age-related or due to underlying disease. Roubenoff *et al.* (1997b) attempted to distinguish sarcopenia from other processes resulting in skeletal muscle loss, specifically wasting and cachexia. They defined wasting as *unintentional loss of weight, including both fat and fat-free compartments*, and typically the result of inadequate dietary energy intake. Cachexia, on the other hand, they defined as *loss of fat-free mass … with little or no weight loss*, as a result of cytokine-mediated hypermetabolism and hypercatabolism. In contrast, sarcopenia was considered more of an "intrinsic age-related process", which suggests that it would occur even in the absence of malnutrition or disease. The distinction among these three conditions is less useful than it appears, however, as evidence has accumulated that the loss of muscle mass in old age likely involves a combination of mechanisms common to both wasting and cachexia that may or may not be secondary to disease, as well as primary, or "intrinsic", age-related ones, that may result in disease.

An effort has also been made to fit sarcopenia into other "syndromes" of aging, including "frailty", "failure-to-thrive", "homeostatic balance failure", and "inflammaging" (Kinney,

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2004; Roubenoff and Harris, 1997; Fried and Lipsitz, 2002; Bortz, 2002; Franceschi and Bonafe, 2003; Storey and Thomas, 2004). The definitions of these syndromes overlap to a large extent, and can be distinguished mainly through their theoretical subscription to various combinations of underlying mechanisms. For the purposes of this review, it is important to simply note that all recognize the loss of muscle mass and strength, or sarcopenia, as a central feature.

It may be more useful in many research settings to define sarcopenia as a less-than-expected, or relative deficiency of, skeletal muscle mass in an individual of a specified age, gender, and possibly race. This is the general definition preferred by epidemiologists and many clinicians, as it implies the development of criteria for diagnosing individuals as "sarcopenic", screening populations for prevalence and incidence, and for identifying risk factors and evaluating treatments and interventions. However, this approach also begs Rosenberg's key question – when does sarcopenia become a "disease"? Does it become a disease "when it induces a disability severe enough to require nursing home placement or assisted-living care?" (Rosenberg, 1997). Or can we consider it a "disease" when shown to be associated with increased levels of disability in community-dwelling elders (Baumgartner *et al.*, 1998). Just what are the "disease" sequelae of sarcopenia, and what are the medical and public health implications of defining it as a disease, rather than as an "intrinsic age-related process" (Roubenoff, 1999)?

MEASUREMENT AND CLASSIFICATION

Body weight is conventionally divided into two compartments in body composition research: fat and fat-free masses. About 60% of the fat-free mass is composed of muscle, and approximately 75% of total skeletal muscle mass is appendicular (Wang *et al.*, 1997). However, despite the fact that skeletal muscle mass is one of the largest organs in the body, well-validated methods for its accurate *in vivo* measurement are generally lacking. In addition, reference data for normal changes with age, and covariation by gender, race or ethnicity, and habitual physical activity are still relatively sparse despite the upsurge of attention on sarcopenia during the last decade.

There are several extensive reviews of *in vivo* methods for measuring or estimating muscle mass (Heymsfield *et al.*, 1995, 2000; Lukaski, 1997). Table 1 lists some methods and provides a brief summary of their strengths and limitations. In general, laboratory-based methods such as neutron activation and ^{40}K counting provide accurate estimates of body composition components, such as total body protein (TBP) or total body potassium (TBK), from which total muscle mass can be estimated (Hansen *et al.*, 2000; He *et al.*, 2003; Kehayias *et al.*, 1997). These methods are costly, require high levels of technical expertise, and are not widely available. More accessible, but still costly methods are dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI). These methods have the advantage of providing precise estimates of both total and regional lean soft tissue or skeletal muscle mass (Heymsfield *et al.*, 1995; Lukaski, 1997; McCully, 1997; Mitsiopoulos *et al.*, 1998). This is important as sarcopenia may affect striated skeletal muscle more than smooth muscle, appendicular muscle more than truncal, and arm more than leg muscle. In addition, researchers have recently begun to exploit the capacity of CT and MRI systems to measure muscle composition, particularly the amounts of interstitial and intramyocellular lipid which increases with aging and may be a key aspect of the sarcopenia process (Boesch and Kries, 2000; Goodpaster *et al.*, 2000). Ultrasound has also been explored, but is not well validated (Reeves *et al.*, 2004). Clinical methods include muscle metabolite assays (creatinine and 3-methylhistidine). Although comparatively inexpensive, these methods require careful control of factors that affect pool sizes and turnover rates, such as meat intake and renal function (Lukaski, 1997). Lastly, field methods are available for predicting muscle mass from anthropometry and bioelectric impedance that are suitable for group estimates in large epidemiologic studies but may lack sufficient precision for detecting changes within individuals (Fuller *et al.*, 1999; Janssen *et al.*, 2000a; Kyle *et al.*, 2003; Malavolti *et al.*, 2003; Pietrobelli *et al.*, 2000). Some effort has been devoted to cross-calibrating these various methods and comparing their relative accuracies (Hansen *et al.*, 1999; Mitsiopoulos *et al.*, 1998; Nunez *et al.*, 1999; Proctor *et al.*, 1999; Wang *et al.*, 1996). Figure 1 shows an example of the calibration of muscle mass from DXA with MRI. It is important to recognize that *all in vivo* methods require one or more assumptions that may differ by age, gender, or race, or limit accuracy when applied to sick individuals.

The ascertainment of individuals with sarcopenia not only requires a reasonably accurate, valid method of measuring muscle mass, but suitable reference data for variation in

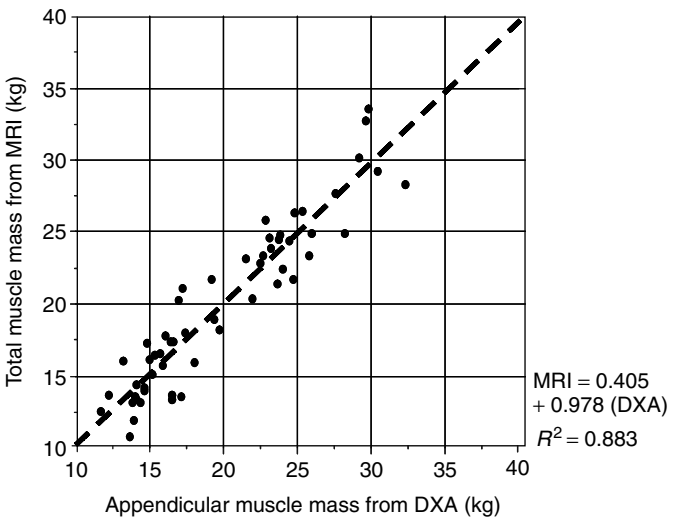

Figure 1 Association of appendicular skeletal muscle mass from DXA with total body skeletal muscle mass from MRI (Data from New Mexico Aging Process Study)

Table 1 Methods for *in vivo* estimation of muscle mass: assumptions, strengths, and limitations

Method	Quantities measured	Assumptions	Strengths	Limitations	References
Neutron activation	TBN	TBP = TBN/0.161 9.5% of TBP is skeletal muscle	Provides highly accurate estimate of TBP	Expensive Few available facilities TBP does not differentiate visceral from skeletal muscle protein mass	Hansen *et al.* (2000)
40K counting	TBK	TBK/FFM ratio of 63.3 mmol kg^{-1} Skeletal muscle SM/FFM ~48.3%	Provides highly accurate estimate of TBK	Few available facilities Concentration of K may vary with age and disease. %SM/FFM decreases with age and disease	Kehayias *et al.* (1997) Wang *et al.* (2001) Wang *et al.* (2001)
Biochemical	Urinary creatinine excretion	1 g creatinine/18 kg muscle	Relatively inexpensive	Affected by physical activity, maturity, diet, gender, and nonmuscle sources of creatinine	Heymsfield *et al.* (1983), Lukaski (1997)
Imaging (CT or MRI)	Muscle areas/volumes	Assumes a constant density for muscle tissue of 1.04 kg l^{-1}	Provides highly accurate and precise estimates of muscle areas and volumes	Very expensive	Mitsiopoulos *et al.* (1998), Janssen *et al.* (2000a)
DXA	Total and regional lean soft tissue mass	Appendicular lean soft tissue is 98% muscle, and appendicular skeletal muscle is 75% of total muscle	Provides precise estimates of lean soft tissue mass that are strongly correlated with actual muscle mass. Cannot discriminate muscle types or muscle from organ	Moderately expensive May be affected by changes in lean soft tissue composition	Wang *et al.* (1996), Hansen *et al.* (1999), Kim *et al.* (2002)
Bioelectric impedance	Total and regional electrical resistance	Conductive volume (TBW) is proportional to stature^2/resistance $TBW = \rho S^2/R$ 73% of FFM is total body water (TBW)	Inexpensive	May be affected by changes in hydration status Must be properly calibrated against a direct measure Prediction equations are sample specific	Janssen *et al.* (2000a) Salinari *et al.* (2003) Kyle *et al.* (2003)
Anthropometry	Body lengths, circumferences, and skinfolds		Inexpensive		

TBN, total body nitrogen; TBP, total body protein; TBK, total body potassium.

Table 2 Mean changes in body composition over 3- and 7-year follow-up periods: New Mexico Aging Process Study (1994–2001)

	Women			Men			Combined		
3-year change	*N*	Mean ± SD	Range	*N*	Mean ± SD	Range	*N*	Mean ± SD	Range
Weight (kg)	250	−0.45 ± 3.64	−17.2–11.8	133	**−1.10 ± 4.15**	−13.0–9.7	383	**−0.67 ± 3.83**	−17.2–11.8
Fat mass (kg)	225	−0.25 ± 3.19	−14.5–11.3	128	−0.12 ± 3.26	−9.2–9.3	353	−0.20 ± 3.21	−14.5–11.3
Muscle mass (kg)	225	**−0.29 ± 0.80**	−5.5–1.7	128	**−0.97 ± 1.29**	−6.2–2.8	353	**−0.54 ± 1.05**	−6.2–2.8
7-year change									
Weight (kg)	114	**−1.85 ± 4.59**	−14.7–11.2	72	**−1.71 ± 4.49**	−16.5–6.6	186	**−1.79 ± 4.54**	−16.5–11.2
Fat mass (kg)	85	**−1.41 ± 3.79**	−14.4–6.7	57	0.16 ± 3.96	−11.5–8.8	142	**−0.84 ± 3.91**	−14.4–8.8
Muscle mass (kg)	85	**−0.51 ± 0.92**	−2.8–1.9	57	**−1.09 ± 1.31**	−4.6–2.1	142	**−0.75 ± 1.13**	−4.6–2.1

Statistically significant ($p < 0.05$) changes shown in bold.

"normal" muscle mass from the same methods by age, gender, race, or ethnicity. There are a variety of published studies using different methods to describe changes with age in muscle mass or related body composition components such as fat-free mass, total lean soft tissue mass, or body cell mass. Most are for small, selected samples that are not population based, some do not include both genders, minorities, or are for limited age ranges (Baumgartner *et al.*, 1995; Janssen *et al.*, 2000b; Kyle *et al.*, 2001; Sugawara *et al.*, 2002). The largest, population-based reference data for muscle mass by age and gender to date were published by Janssen *et al.* (2002) for Third National Health and Nutrition Examination Survey (NHANES III), but the estimates were derived by bioelectric impedance equations and may be subject to both random and systematic errors of unknown magnitude. Longitudinal data for changes over time in individuals are scarce (Frontera *et al.*, 2000a; Gallagher *et al.*, 2000; Hughes *et al.*, 2002; Visser *et al.*, 2003b; Zamboni *et al.*, 2003). Table 2 shows changes over 3–7 years in elderly participants in the New Mexico Aging Process Study. Data for minorities are especially scarce (Aloia *et al.*, 2000; Casas *et al.*, 2001; He *et al.*, 2003).

Accurate measurement methods and reference data for muscle mass may not provide a complete description of age differences or changes in sarcopenia. Evidence is accumulating that sarcopenia also involves changes in muscle composition and quality in addition to atrophy in mass. Muscle composition is primarily obtained from muscle biopsies, and includes measurements of fiber type, size and number, capillary density, lipid content, DNA, and so on (Lexell, 1997). The only noninvasive methods are CT and MRI imaging, which can measure intermuscular adipose tissue and intramyocellular lipid (Boesch and Kries, 2000; Goodpaster *et al.*, 2000; Song *et al.*, 2004). Muscle "quality" refers to measurements of the functional properties of muscle, generally strength, power or force independent of volume or mass. For example, Newman *et al.* (2003) defined muscle quality as the ratio of strength to mass in upper and lower extremities. They found that age was significantly inversely associated with muscle quality. There are few, if any, reference data for age difference or changes in muscle composition or quality to date.

Classification of Sarcopenia

Given accurate measurement methods and appropriate reference data, criteria are needed for the classification or identification of individuals as sarcopenic. To date, there is still no clear consensus as to the "best" criteria.

We were the first to develop an operational definition of sarcopenia for use in clinical and epidemiologic studies (Baumgartner *et al.*, 1998). Our approach used sex-specific cutpoints on the distribution of an index of "relative skeletal muscle mass", appendicular skeletal muscle mass (from DXA) divided by the square of stature (ASM/S^2), to classify individuals in the New Mexico Elder Health Survey as sarcopenic. The cutpoints were defined as – 2 *standard deviations* (SDs) below the sex-specific means of the distributions for this index in a reference sample of young and middle-aged adults, in the Rosetta Study. Figure 2 illustrates this approach, which is analogous to that used for classifying individuals as "obese" or "osteoporotic".

Subsequent investigators have used this index with different cutpoints, or different indices such as calf muscle circumference or area, total muscle mass/stature^2, muscle mass as percent of body weight, or the ratio of total lean soft tissue mass to total fat mass (Kenny *et al.*, 2003; Lauretani *et al.*, 2003; Melton *et al.*, 2000; Rolland *et al.*, 2003; Sternfeld

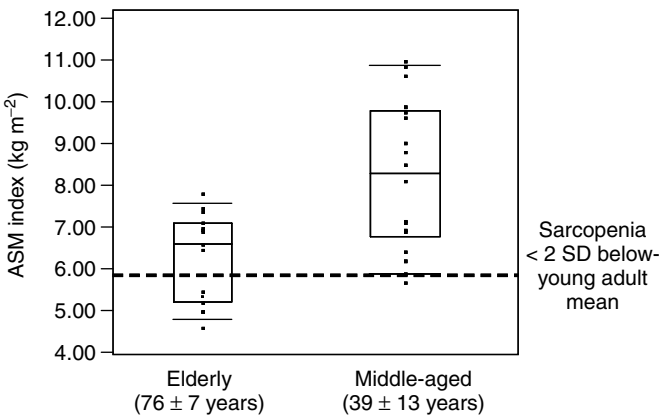

Figure 2 Method for establishing cutpoint for defining sarcopenia based on appendicular skeletal muscle mass index (ASM/S^2)

et al., 2002; Tanko *et al.*, 2002). Recently, Newman *et al.* (2003) reported that an index basic on the regression adjustment of appendicular skeletal muscle mass for stature was more strongly associated than ASM/S^2 with a spectrum of health factors and lower extremity function, suggesting increased sensitivity for this approach. Clearly, the choice of index matters as the optimal method should measure variation in muscle mass independent of body size.

The selection of optimal cutpoints for classification is another matter. To date the choice has been relatively arbitrary, based either on the distribution of an index in a reference population (i.e. >-2 SDs below the mean in a young healthy sample), or percentiles of the distribution in the primary sample (i.e. the lowest quartile). Janssen *et al.* (2004a) recently used receiver operating characteristic (ROC) curve analysis to empirically determine optimal cutpoints for sarcopenia based on the strength of association of total muscle mass adjusted for stature (TSM/S^2) with disability using data from a large, nationally representative sample (NHANES III). Skeletal muscle cutpoints of 5.76–6.75 and less than or equal to 5.75 kg m^{-2} were found to be optimal for moderate and high physical disability risk in women. The corresponding values in men were 8.51–10.75 and less than or equal to 8.50 kg m^{-2}. Remarkably, the cutpoints associated with high risk are closely similar to those originally defined by Baumgartner *et al.* (1998).

Prevalence and Incidence

We provided the first estimates of the prevalence of sarcopenia in a population-based sample of community-dwelling elders in the New Mexico Elder Health Survey (Baumgartner *et al.*, 1998). The prevalence of sarcopenia, defined as values on the ASM/S^2 index > -2 SD below the mean of a young adults in the Rosetta Study, increased from 13 to 24% in persons under 70 years of age to >50% in persons over 80 years of age, and was slightly greater in Hispanics than in non-Hispanic whites.

Most subsequent studies have produced lower prevalence estimates, including our own (Baumgartner, 2000; Morley *et al.*, 2001). We used an anthropometric prediction equation calibrated against DXA to indirectly derive estimates of appendicular skeletal muscle in our original study, which may have contained some bias and resulted in overestimates of sarcopenia prevalence. Using direct estimates of appendicular skeletal muscle mass from DXA in the New Mexico Aging Process Study, we obtained age-specific prevalences ranging from about 12% for those <70 years to nearly 30% in those older than 80 years. However, many of the samples in the subsequent studies were clinical, rather than population based, and included younger, healthier, or more obese individuals. Moreover, a variety of different definitions of sarcopenia were used, rather than a standard one, making comparisons across studies difficult.

Janssen *et al.* (2002) derived estimates for the prevalence of sarcopenia using data for 4504 adults aged 60 and older from the NHANES III. Total skeletal muscle mass was predicted using a bioelectric impedance prediction equation. "Skeletal muscle mass index" was defined as *skeletal muscle mass/body mass* $\times$ *100*; (that is "percent muscle mass"). Class I sarcopenia was defined as *SMI* within -1 to -2 SDs of the mean for young adults (aged 18–39), and class II sarcopenia was defined as *SMI* below -2 SDs of young adult values. The prevalence of class I and class II sarcopenia increased from the third to sixth decades but remained relatively constant thereafter. The prevalence of class I (59 vs 45%) and class II (10 vs 7%) sarcopenia was greater in the older (greater than or equal to 60 years) women than in the older men ($P < .001$) (Janssen *et al.*, 2002). Notably, all studies have found increasing prevalences of sarcopenia with age (Castillo *et al.*, 2003; Gillette-Goyonnet *et al.*, 2003; Iannuzzi-Sucich *et al.*, 2002; Melton *et al.*, 2000; Tanko *et al.*, 2002).

Risk Factors

Few epidemiologic studies to date have examined modifiable behavioral and environmental risk factors for sarcopenia, and nearly all have been cross sectional and have not been able to distinguish whether associated risk factors are causes or consequences of sarcopenia. We first reported that sarcopenia was significantly associated with self-reported disability, problems with balance and gait, falls in the past year, smoking, physical inactivity, and Hispanic ethnicity in the New Mexico Elder Health Survey, independent of age, ethnicity, income, alcohol intake, and body fatness (Baumgartner *et al.*, 1998). We subsequently replicated most of these associations in a separate cohort, in the New Mexico Aging Process Study (Baumgartner, 2000). In addition, we showed that variation in skeletal muscle mass was significantly associated with physical activity in both elderly men and women in the New Mexico Aging Process Study, independent of age, hormonal status, body fatness, and morbidity (Baumgartner *et al.*, 1999).

Melton *et al.* (2000) reported significant associations between total muscle mass adjusted for stature and difficulty in walking in men (odds ratio = 3.03) and osteoporotic fractures in women (odds ratio = 5.21). They also indicated there were nonsignificant trends for sarcopenic subjects to have worse gait and balance and difficulty with physical activities including shopping, housework, climbing stairs, and walking more than two blocks. Janssen *et al.* (2002) analyzed data from NHANES III for a large, nationally representative sample of adults aged 60 years and older and reported that "class II sarcopenia" (see definition in the preceding text) was significantly associated with several measures of physical function impairment, as well as self-reported disability, in both men and women. The strengths of the associations were substantially reduced in men, however, after adjusting for age, race, body mass index (BMI), health behaviors, and comorbidities. In a subsequent study also using NHANES III data, Janssen *et al.* (2004a) reported that sarcopenia, now defined as total muscle mass/stature^2 $\leq$5.75 kg m^{-2} in women and $\leq$8.50 kg m^{-2} in men, was significantly associated with

increased risk for self-reported disability, controlling for age, race, smoking, alcohol intake, comorbidity, and total body fat (odds ratio = 3.31 in women, 4.71 in men). Castillo *et al.* (2003) reported that men with sarcopenia, defined as *fat-free mass* ≥2.0 SDs below the gender-specific mean of a young reference population, in the Rancho Bernardo Study were twice as likely to have fallen in the past year compared with those without sarcopenia. Physically active women were about half as likely to have sarcopenia, but no association was found in men. In the HEALTH ABC Study, Newman *et al.* (2003) reported that sarcopenia, when defined using the residual method, was significantly associated with functional limitation on the Established Populations for Epidemiologic Study of the Elderly (EPESE) scale in both genders, adjusting for age, race, smoking, drinking, comorbidity, and physical activity. Interestingly, this study showed African-Americans to be protected from sarcopenia; additionally, current smoking was reported to be a significant risk factor in men.

There are few data for associations of sarcopenia with chronic diseases. We reported that chronic obstructive pulmonary disease (COPD) was significantly associated with sarcopenia in men in the New Mexico Elder Health Survey (odds ratio = 2.89). Cancer, stroke, coronary heart disease, type 2 diabetes, gallbladder disease, and arthritis were not significant risk factors (Baumgartner *et al.*, 1998). Variation in muscle mass had a small but significant association with cardiovascular disease in men in the Aging Process Study, however (Baumgartner *et al.*, 1999). Castillo *et al.* (2003) found no significant associations of sarcopenia with heart disease, diabetes, pulmonary disease, arthritis, and cancer or any medications, including thyroid hormones, corticosteroids, and hormone replacement therapy (HRT) in the Rancho Bernardo Study. In the HEALTH ABC Study, Newman *et al.* (2003) reported small, but significant associations with cancer, hypertension, ulcer, and ≥3 comorbidities in men only.

Health-care Costs of Sarcopenia

Janssen *et al.* (2004b) estimated the health-care costs of sarcopenia based on published data for risk of disability in sarcopenic individuals and sarcopenia prevalence rates in the older population. The estimated direct health-care cost attributable to sarcopenia in the United States in 2000 was estimated at $18.5 billion ($10.8 billion in men, $7.7 billion in women), or about 1.5% of total health-care expenditures for that year. They calculated that a 10% reduction in sarcopenia prevalence would result in savings of $1.1 billion (dollars adjusted to 2000 rate) per year in US health-care costs. In actuality, the costs of sarcopenia are probably considerable higher, as these calculations do not incorporate costs for other conditions associated with sarcopenia, such as injurious falls and bone fractures. It should also be recognized that risk and prevalence estimates are somewhat "soft" as both depend on the measurements and criteria used to define sarcopenia, for which there continues to be no consensus. Moreover, the method does not consider risks, and therefore health-care costs, associated with the combination of sarcopenia and obesity, or "sarcopenic obesity", which some data suggest are even greater.

Summary

Research on the epidemiology of sarcopenia is still in its infancy. There are several important needs that must be met for this field to advance. First there is a need for more accurate methods of measuring muscle mass. Imaging methods are the most accurate, but are much too expensive and cumbersome to apply in large population-based studies. Anthropometric/bioelectric impedance prediction equations are inexpensive and easy to apply, but may lack sufficient accuracy. DXA may be the best compromise. Second, there is a need for standardization of indices and criteria for defining sarcopenia. Several different indices of "relative skeletal muscle mass" have been developed, but there has been no systematic comparison of these. Cutpoints for classifying sarcopenia have been generally defined arbitrarily. There are few estimates to date for large, representative samples with sufficient numbers of elders >60 years, and few data for appropriate, representative young reference populations.

ETIOLOGY

The etiology of sarcopenia is most likely multifactorial and is probably best viewed as part of a complex process of age-related changes in musculoskeletal cellular and tissue structure and function. Figure 3 depicts some of the interrelated factors that have been implicated in this process, which include age-related hormonal, neurological, immunological, and metabolic changes that may be modified to some extent by dietary and physical activity behaviors and/or environmental factors influencing these behaviors. Carmeli *et al.* (2002) roughly divided the putative causes of sarcopenia into "intrinsic" and "extrinsic" factors. It is not clear which factors or pathways are relatively more or less important with regard to the rate of development and severity of sarcopenia, and it is likely that there is considerable individual variability in the "mix" of factors (Roubenoff, 2001).

Cellular–Oxidative stress and Muscle Mitochondrial Damage

The muscle atrophy that occurs in sarcopenia consists of the disproportionate loss of type IIa ("fast twitch", oxidative) muscle fibers that is accompanied by a decline in muscle cell contractility and consequently muscle strength relative to mass (Lexell, 1995). These changes occur in conjunction with a loss in alpha motor units and decline in muscle innervation (Dutta *et al.*, 1997; Welle, 2002). Although the

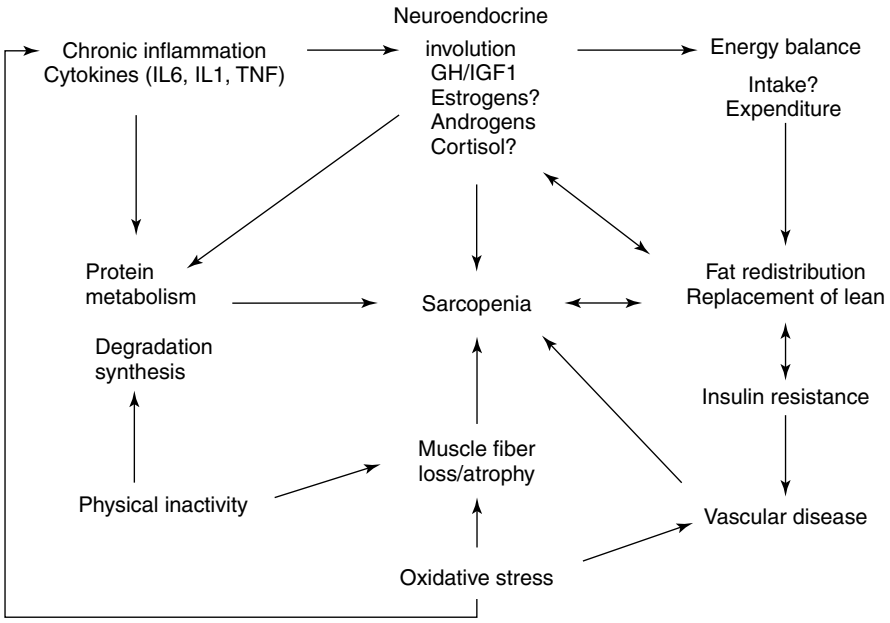

Figure 3 Pathways to sarcopenia

theory of oxidative stress and mitochondrial DNA damage have been around for decades, Weindruch (1995) was among the first to propose that cumulative damage to skeletal muscle and nerve cells in sarcopenia might result from oxidative stress. A variety of direct and indirect evidence has subsequently accumulated in support of this hypothesis.

Oxidative radicals, or "reactive oxygen species" (ROS) are formed in all tissues, including skeletal muscle, primarily as a product of energy production in the mitochondrial respiratory chain. Approximately 90% of cellular oxygen is metabolized in mitochondria with 1–5% of this being converted to ROS as a normal by-product of electron transport system (ETS) complexes. These highly reactive molecules can damage cellular components such as DNA, proteins, and lipids, and cause general cellular dysfunction. As mitochondria are the main source of ROS, they are chronically exposed. Mitochondrial DNA (mtDNA), which is a 16 kb closed circular DNA molecule, is located in close proximity to the source of ROS. A unique feature of mtDNA, however, is that it lacks cognates of the nuclear histone proteins that protect against ROS. In contrast to nuclear DNA, mtDNA has a poor capacity for repairing damage, leading to the accumulation of mutations with age in a variety of tissues. This is believed to cause dysfunction of ETS complexes and impaired production of adenosine triphosphate (ATP) (Hepple *et al.*, 2003; Waters *et al.*, 2003; Weindruch, 1995; Welle, 2002). In muscle this could theoretically lead to cellular apoptosis and loss of muscle fibers. The extent to which this plays a role in the age-related decrease of muscle mass and function, however, is not well established. Some recent studies have demonstrated that ETS abnormalities accumulate to high levels within small regions of aged muscle fibers, through selection, amplification, and clonal expansion of the initial mutation, and lead to intrafiber atrophy and fiber breakage (Dirks and Leeuwenburgh, 2002; McKenzie *et al.*, 2002; Pak *et al.*, 2003; Wanagat *et al.*, 2001). ETS abnormal segments in aging rat skeletal muscle have been reported to correlate with a decrease in fiber cross-sectional area (CSA) suggesting a causal role for mitochondrial abnormalities in fiber atrophy (Bua *et al.*, 2002; Wanagat *et al.*, 2001). The negative correlation between the length of the ETS abnormal region and change in CSA suggests that the abnormality reaches a threshold length where, in the midpoint of the abnormality, the fiber contains predominantly dysfunctional mitochondria. The regions of fiber atrophy associated with ETS abnormalities are not likely to contribute directly to the muscle atrophy, but may represent a step in the progression from fiber dysfunction to fiber loss. If this becomes a persistent process, chronic loss of fibers could ensue.

Skeletal muscle may be more vulnerable than smooth or cardiac muscle, and different skeletal muscle groups may also vary in their susceptibility (Bua *et al.*, 2002; Drew *et al.*, 2003). Oxidative stress may additionally damage the intra and intercellular membranes of the muscle fibers, the sarcoplasmic reticulum, proteins involved in excitation-contraction uncoupling, and impair the Ca^{2+} transport mechanism. The extent to which these changes contribute to sarcopenia is also not well established (Fulle *et al.*, 2004). For example, Ryan *et al.* (2003) found no significant differences in the relative abundance of α dihyropyridine receptors, fast calsequestrin, the ratio of slow to fast myosin heavy chain proteins, or modifications in Ca^{2+} or ATPase activity in muscle tissues from men aged 18–82 years. However, given the large intrasubject variability in the sarcopenic process, this question may only be answered in humans using a prospective study design.

It is important to consider that the overall level of exposure of skeletal muscle to oxidative stress is also influenced by age-associated changes in antioxidant defense. Some studies indicate that aging skeletal muscle has a decreased gene expression of antioxidant enzymes, possibly due to a diminished ability for cell signaling (Ji, 2001). This may be coupled with a decline in the dietary intake and availability of antioxidants. Indeed, Semba *et al.* (2003) reported an association between dietary carotenoid and α-tocopherol intake and muscle strength in elderly participants in the Women's Health and Aging Studies. Again, further longitudinal and interventional studies are needed to establish causality.

Muscle Fiber Apoptosis and Denervation

There is a clear association between alterations in spinal cord neurons and loss of alpha motor units at the neuromuscular junction and sarcopenia (Delbono, 2003; Lynch, 2002). It is not clear, however, what the underlying mechanisms are; specifically, how mitochondrial oxidative damage is associated with fiber denervation, myocellular apoptosis, and fiber loss. Leeuwenburgh (2003) noted that the levels of several caspases increase with aging, and that caspase-3, in particular, plays an important role in mediating apoptotic signals from mitochondria and other pathways. Alway *et al.* (2003) reported that proteins known as *inhibitors of differentiation*, that have also been implicated in apoptosis, increase with age; although this increase may not be a result of muscle denervation. The reason why type II fast twitch fibers appear to be most susceptible is also not well understood, nor the neural influences on muscle gene expression, tissue repair, and regenerative pathways. As a result, interventions aimed at delaying or preventing degeneration of the neural component of sarcopenia have been not been successful to date (Delbono, 2003).

Qualitative changes in muscle function are reported to occur well in advance of loss in muscle mass. These include slowed movements and a reduction in force control, in addition to loss of strength (Doherty, 2003; Rice, 2000). The basis of these changes may be more complex than the loss of muscle innervation and type IIa fibers. Single fibers of older muscles of both type I and II myosin isoforms show lower tension and shortening velocity compared to those from young muscles and are more resistant to isometric fatigue (Macaluso and De Vito, 2004). Frontera *et al.* (2000b) noted that intrinsic age-related defect in contractile proteins could explain variation among single fibers.

An age-related decline in capacity to repair and regenerate skeletal muscle tissue clearly contributes to sarcopenia. This reduction is partly due to a reduced pool of satellite cells to be recruited to replace damaged fibers (Fulle *et al.*, 2004; Jejurikar and Kuzon, 2003). Age-related changes in the endocrine, autocrine, and paracrine environment of aging muscle may make the reinnervation of muscle fibers, satellite cell activation, proliferation, and differentiation more difficult. Barani *et al.* (2003) suggested that sarcopenia was the result of an accumulation of repeated episodes of incomplete repair and regeneration throughout the life span.

Age-related Changes in Protein Turnover

The extent to which whole body protein turnover changes with age, in the absence of underlying disease, remains controversial (Dorrens and Rennie, 2003). However, evidence has accumulated for an age-related decrease in the rates of synthesis of mixed muscle, myosin heavy chain, and mitochondrial proteins (Balagopal *et al.*, 1997b; Nair, 1995; Proctor *et al.*, 1998; Short and Nair, 2001). The underlying mechanisms for this decrease are not completely understood, however, and there is still some uncertainty as to the magnitude of its contribution to sarcopenia (Volpi *et al.*, 2001). Physiologic age-dependent declines in anabolic hormones may contribute as well as physical inactivity and muscle "disuse". Rooyackers *et al.* (1996) reported that the rate of mitochondrial protein synthesis was about 38% lower in muscle from older compared to younger adults and was correlated with decreased activities of mitochondrial enzymes, suggesting that changes in mitochondrial oxidative capacity and function are linked to decreases in protein synthesis rates. Thus, oxidative stress and damage to mitochondria may also play a role in age-related decrease in muscle protein synthesis.

The protein content of a tissue is determined, however, by the balance between protein synthesis and degradation (Nair, 1995; Yarasheski, 2003). Sarcopenia, therefore, could also result from an age-related increase in protein degradation, or perhaps a progressive inability to recover muscle protein lost during catabolic episodes (Mosoni *et al.*, 1999). Although data for an age-related increase in rates of muscle protein degradation are slim, evidence is accumulating for an increase in catabolic signals with age, specifically an age-related "cytokinemia" (Roubenoff, 2003). Thus, increased rates of protein degradation with age, in the absence of overt disease, could contribute to sarcopenia in addition to decreased rates of protein synthesis.

Hormones and Cytokines

There is considerable evidence that age-related declines in the production of growth hormone (GH), insulin-like growth factor (IGF)-1, and androgens play a role in the pathogenesis of sarcopenia. The underlying mechanisms, however, are not well understood. Circulating levels of bioavailable testosterone, dehydroepiandrosterone (DHEA), GH, and IGF-1, are reported to be associated with muscle protein synthesis as well as muscle mass and strength (Balagopal *et al.*, 1997a; Baumgartner *et al.*, 1999; Iannuzzi-Sucich *et al.*, 2002; Proctor *et al.*, 1998). Testosterone supplementation has been shown in several studies to increase muscle protein synthesis, mass and strength, and decrease fat mass in men (Bhasin, 2003; Bhasin and Tenover, 1997). The increase

in muscle size appears to be primarily due to hypertrophy of muscle fibers (Bhasin, 2003). Bhasin has hypothesized that testosterone promotes the differentiation of stem cells into myocytes rather than adipocytes, which may explain the opposing effects of testosterone treatment on muscle and fat masses (Bhasin, 2003). It has also been proposed that testosterone may regulate the expression of myostatin, which has been shown to inhibit muscle cell proliferation, DNA, and protein synthesis (Marcell *et al.*, 2001; Taylor *et al.*, 2001).

Serum vitamin D has also been reported to be associated with sarcopenia (Iannuzzi-Sucich *et al.*, 2002; Visser *et al.*, 2002). Visser *et al.* (2003a) reported that low serum 25-hydroxyvitamin D (25-OHD) and high parathyroid hormone (PTH) were associated with risk for sarcopenia (low grip strength and muscle mass) in the Longitudinal Aging Study Amsterdam (LASA), a population-based study of elderly men and women. Some clinical trials report improved muscle strength and functional performance with vitamin D supplementation (Gloth *et al.*, 1995; Verhaar *et al.*, 2000). Muscle has vitamin D receptors, and vitamin D may affect muscle protein turnover and the number and size of type II fast twitch muscle fibers (Simpson *et al.*, 1985; Wassner *et al.*, 1983; Sorensen *et al.*, 1979). Serum vitamin is inversely associated with PTH and intracellular calcium, and hyperparathyroidism may disrupt nerve and muscle function (McCarty, 2002).

The role of estrogen is less well established. Although the menopausal transition is associated with a marked loss of bone, there is little evidence for the association of estrogen with muscle loss in postmenopausal women. Baumgartner *et al.* (1999) did not find a significant association between skeletal muscle mass and serum estrogen in women and no difference between those taking versus those not taking HRT. Kenny *et al.* (2003) reported similar findings. On the other hand, Iannuzzi-Sucich *et al.* (2002) reported an association of serum estrogen with appendicular skeletal muscle mass from DXA in women; however, this association was not significant after controlling for BMI, which was the only significant, independent predictor in women. The observation that the rate of loss of muscle mass is higher in men than in women, however, suggests that estrogen may play a protective role (Gallagher *et al.*, 1997). Estrogens are believed to modulate defense systems against oxidative stress, and concentrations are higher in the muscle tissue of women than men (Fano *et al.*, 2001; Fulle *et al.*, 2004). It is also important to consider that adipose tissue is a significant source of estrogens, and circulating levels are higher in obese than nonobese postmenopausal women (Simpson, 2003). Taken together, these observations may explain the finding of Iannuzzi-Sucich that serum estrogen was not significantly associated with muscle mass after controlling for BMI (Iannuzzi-Sucich *et al.*, 2002).

In recent years, evidence has rapidly accumulated implicating age-related increases in proinflammatory cytokines in the etiology of sarcopenia, osteopenia, frailty, both physical and cognitive functional decline and disability, and a variety of other late-life disorders, leading gerontologists to develop new theories of aging under clever rubrics such as, "inflammaging" (Franceschi *et al.*, 2000) and "cytokine-related aging process" (Morley and Baumgartner, 2004). Cytokines are soluble peptide messengers synthesized and secreted by lymphocytes, neutrophils, macrophages, and neuronal cells that modulate the inflammatory response, among other processes, and have a wide range of effects on metabolism and thereby organ systems throughout the body. They include the interleukins, tumor necrosis factors, interferons, and the newly recognized class of adipocytokines.

Interleukin-6 was the one of the first cytokines to be recognized to increase with advancing age in the apparent absence of overt infection, trauma, or stress (Ershler and Keller, 2000). Normally, IL-6 serves as a proinflammatory cytokine that is released by macrophages and lymphocytes as a part of the acute phase response to infection, trauma, or stress. Tumor necrosis factor alpha (TNFα) and IL-1-β stimulate the release of IL-6; however, IL-6 feeds back to downregulate the production of these cytokines. Hence, IL-6 is considered to have both pro- and anti-inflammatory functions. In the context of cachexia, IL-6 participates with TNFα in stimulating protein degradation via lysosomal (cathepsin) and nonlysosomal (ubiquitin-proteosome) pathways (Morley and Baumgartner, 2004). Cytokines can also cause anorexia, which may reduce protein intake (Bales and Ritchie, 2002; Roubenoff, 2003). Several studies have reported that serum IL-6 levels are associated with muscle mass and strength, functional performance, disability, and mortality in older people (Cesari *et al.*, 2004; Cohen *et al.*, 1997; Ferrucci *et al.*, 1999; Newman *et al.*, 2002; Payette *et al.*, 2003; Pedersen *et al.*, 2003).

TNFα has also been reported to increase with age, independent of diagnosed disease, although the trend is not as pronounced as for IL-6 (Newman *et al.*, 2002). Griewe reported that both TNFα mRNA and protein levels were increased in myocytes in frail, sarcopenia elders compared to younger adults (Greiwe *et al.*, 2001). It has been recognized for a long time that TNFα is associated with muscle wasting and dysfunction in inflammatory diseases; in fact this cytokine was originally named *cachectin* due to its evident role in cancer cachexia (Beutler and Cerami, 1986). It is currently believed that TNFα primarily promotes muscle protein degradation through an NF-κB mediated mechanism that upregulates the ubiquitin-proteosome pathway (Reid and Li, 2001). This process does not appear to involve apoptosis of muscle cells and loss in fiber number, but loss of protein and atrophy of existing fibers, and can occur over a long time period in chronic inflammatory diseases. TNFα has also been shown to have the capacity to adversely affect muscle contractile function in the absence of fiber atrophy (Reid and Li, 2001). These effects have been best studied in relation to cardiac and diaphragm muscle and it is not clear to what extent TNFα contributes to peripheral skeletal muscle dysfunction, weakness, or fatigue. TNFα also produces anorexia, through mechanisms that are not well defined. In the mouse, administration of TNFα causes an acute increase in leptin, followed by anorexia and weight loss, leading some to speculate that leptin is the pathway by which TNFα produces anorexia (Sarraf *et al.*, 1997).

Anorexia may subsequently contribute to sarcopenia by limiting food intake, leading to protein-energy malnutrition, which is a common problem in elders (Morley, 2001b).

Although the above discussion focuses mainly on IL-6 and TNFα, it is recognized that, *in vivo*, the inflammatory process involves a complex interplay of these and many other cytokines, as well as hormones and growth factors, and that it is really dysregulation in this "stew" of signaling pathways with age that results in sarcopenia and associated outcomes, including osteopenia, depression, cognitive decline, and immune dysfunction (Morley and Baumgartner, 2004). It should also be mentioned that soluble receptors that bind cytokine proteins can serve as both antagonists and agonists of cytokine action. For example, it is now recognized that the soluble IL-6 receptor is critical to modulating the inflammatory versus anti-inflammatory effects of IL-6 (Jones and Rose-John, 2002). Lastly, it may be important to consider the potential effects of the newly recognized class of "adipocytokines", which includes leptin and adiponectin, in relation to sarcopenia. These cytokines that are exclusively produced by adipocytes have wide ranging effects on multiple metabolic processes. Leptin, which is now considered to belong to the IL-6 family of cytokines, participates in the regulation of appetite, stimulates muscle cell lypolysis, and may participate in inflammation (Coppack, 2001). Adiponectin modulates cellular insulin sensitivity (Ukkola and Santaniemi, 2002). Adipose tissue also produces IL-6 and TNFα, and as much as one-third of circulating IL-6 may derive from adipose tissue (Mohamed-Ali *et al.*, 1997). Consequently, obesity is now recognized as representing a kind of chronic inflammation, with consequences for sarcopenia.

Roubenoff (2000b) proposed a model for the etiology of sarcopenic obesity, or the simultaneous presence of low-muscle mass and high body fat that involves a combination of obesity-related cytokinemia and age-related decline in hormonal anabolic stimulus. In this model, loss of muscle precedes the development of obesity in middle age, as it reduces physical activity and resting energy expenditure without compensatory reduction in energy intake, leading to positive energy imbalance and accumulation of stored excess energy in adipose tissue and eventual obesity. Cytokines secreted by excess adipose tissue, including IL-6, TNFα, and possibly leptin, together with further declines in anabolic hormone levels, would tip the balance of protein turnover in muscle toward degradation, thereby accelerating muscle loss. To date, there are few data to support this hypothesis. Recently, Pedersen *et al.* (2003) reported that serum IL-6 and TNFα were significantly positively correlated with truncal fat mass and inversely correlated with appendicular skeletal muscle and body cell mass in a small study of elderly healthy and type 2 diabetes patients. Recently, we found that IL-6 and C-reactive protein (CRP) levels were significantly increased in elderly participants with sarcopenic obesity compared to obese, sarcopenic, or normal body composition groups (Cesari *et al.*, 2005).

In summary, although an effort was made to distinguish sarcopenia from wasting and cachexia, as other causes of muscle loss (Roubenoff *et al.*, 1997b), the accumulating data suggest that age-related changes in both anabolic and catabolic mechanisms may be involved in sarcopenia, particularly in the rarer condition now called *sarcopenic obesity*. These mechanisms influence the balance between protein synthesis and degradation, limit satellite cell recruitment and proliferation, regulate apoptosis, and lead to a declining capacity in aged muscle to regenerate in the face of damage by oxidative stress. As these age-dependent changes leading to muscle loss may increase susceptibility to diseases that may, in turn, exacerbate muscle loss, it becomes difficult not to consider the contribution of underlying morbidity to sarcopenia (Krabbe *et al.*, 2004). If sarcopenia, severe enough to cause disability, is a result of combined age-dependent and disease-dependent processes, the question of whether sarcopenia is a "disease" or "condition" is legitimate.

Chronic and Acute Morbidity

Chronic disease morbidity and comorbidity increase with age, and most elders experience two or more chronic conditions. Although epidemiologic studies suggest that even relatively healthy elders experience sarcopenia, and that few forms of major morbidity are statistically associated with sarcopenia, the role of disease in the etiology of sarcopenia cannot be excluded. Many elders exhibit symptoms of muscle disease, and inflammatory and noninflammatory myopathies are not uncommon (O'Rourke, 2000). Neurological diseases that are more common in old age may contribute: two reports indicate that muscle loss occurs in Parkinson's disease (Payette *et al.*, 1998; Poehlman *et al.*, 1995). Peripheral arterial disease is associated with loss of muscle mass and strength, in the lower leg; however, the potential role of smaller, age-related reductions in muscle blood flow due to mild vascular disease has not been well studied (Hunt *et al.*, 1998; McCully and Posner, 1995). Chronic obstructive pulmonary disease (COPD), heart failure (CHF), and renal failure (CRF) are commonly accompanied by symptoms of muscle weakness, fatigue, and exercise intolerance. Recent studies indicate that these symptoms have complex associations with cytokinemia, cachexia, anorexia, reduced physical activity, and muscle wasting (Franssen *et al.*, 2002; Johansen *et al.*, 1999; Vaitkevicius, 2001). The relative contribution to sarcopenia of subclinical forms of these common, chronic diseases of old age is unknown. Muscle wasting is a well-known feature of rheumatoid arthritis (Roubenoff *et al.*, 1997a), but the association with other, more common forms of osteoarthritis, which may severely limit mobility, is not well established (Toda *et al.*, 2000). Muscle wasting is well recognized in cancer cachexia, but the potential contribution of cancer therapies, particularly that of hormonal ablation, to muscle loss in cancer patients, regardless of cachexia, is less well recognized (Thompson *et al.*, 2003). Moreover, the adverse effects of sarcopenia on prognosis in cancer and other chronic diseases have not been well studied. The potential contribution of chronic infections to sarcopenia has not been studied, although this is plausible given the reported association of low levels of proinflammatory

cytokines with sarcopenia and recent reports that these are elevated in patients with chronic asymptomatic bacteriuria (Prio *et al.*, 2002).

Acute trauma in elders, particularly hip fracture, is strongly associated with subsequent muscle loss, and muscle mass and strength are reduced even after rehabilitation and mobility recovery (Visser *et al.*, 2000a). As trauma is also known to invoke the acute phase response, it is likely that it also contributes to muscle loss via cytokine pathways. As with infection, repeated trauma with episodes of muscle wasting could either produce or exacerbate underlying sarcopenia.

Anorexia and Malnutrition

Many elders develop loss of appetite, or anorexia, with increasing old age, which contributes to decreased food intake, protein-energy malnutrition, and weight loss. The extent to which anorexia and malnutrition contribute to sarcopenia is controversial, however, as there are few data for an association. On the other hand, there would be theoretical reason to expect an association if they shared some underlying mechanisms. Morley and associates have extensively studied the physiologic anorexia of aging (Morley, 2001a; Wilson and Morley, 2003). The causes of anorexia in old age are diverse, including changes in taste and smell, stomach physiology, hormones regulating appetite such as cholecystokinin, ghrelin, and leptin, mechanisms controlling the efficiency of various components of energy expenditure such as basal and adaptive thermogenesis, and age-related cytokinemia. Since the discovery of leptin, it has become clear that the brain integrates humoral signals from adipose tissue and other organs, such as the stomach, pancreas, intestines, and possibly muscle, to match energy intake with expenditure. We have only begun to unravel how dysregulation in certain parts of these complex feedback circuits leads to obesity, which represents a chronic orexigenic state. How aging affects these mechanisms to produce a chronic anorexic state is less well understood. Age-related cytokinemia may provide an integrating mechanism if it indeed provokes a mild, chronic "cachexia" that includes anorexia, elevated basal energy metabolism, as well as accelerated muscle protein degradation.

Genetic Susceptibility

Scientists have only just begun to examine the issue of genetic susceptibility to sarcopenia, or to use gene expression to identify underlying molecular mechanisms. A genome-wide scan conducted in the Quebec Family Study identified the linkage of fat-free mass with several microsatellite markers in the regions of genes for the IGF1 receptor, neuropeptide Y, GH-releasing hormone, and malanocortin receptor 4 (Chagnon *et al.*, 2000). Although these genes could be plausibly related to sarcopenia, as they may be involved in the regulation of cellular metabolism as well as control of appetite, we are not aware of any subsequent studies for their association or linkage with sarcopenia. Recently, Roth *et al.* (2004) reported the association of the FokI polymorphism in the vitamin D receptor with appendicular fat-free mass, which is a better approximation of skeletal muscle mass than total fat-free mass which includes organ and bone. This genetic variant is a better candidate, given evidence for its functionality and evidence for effects of vitamin D on muscle protein turnover, fiber composition, and function. This group also reported the association of a polymorphism in the IL-6 gene with fat-free mass in men, but not women (Roth *et al.*, 2003). Several recent studies have targeted polymorphic variants in the myostatin gene (Corsi *et al.*, 2002; Gonzalez-Cadavid *et al.*, 1999; Masi *et al.*, 2002; Seibert *et al.*, 2001). Myostatin is a protein that appears to be a negative regulator of skeletal muscle growth, possibly through the inhibition of muscle satellite cell recruitment. Transgenic mice lacking myostatin have hypertrophied musculature (Reisz-Porszasz *et al.*, 2003), and recently a child with a rare inherited myostatin mutation and hypertrophied muscles was described (Schuelke *et al.*, 2004).

A variety of studies have been conducted to identify genes that may be differentially expressed in old versus young muscles under conditions such as immobilization, exercise, and caloric restriction (Alway *et al.*, 2002a,b; Pattison *et al.*, 2003; St-Amand *et al.*, 2001; Welle *et al.*, 2003). Most studies to date have been conducted in muscle tissue from small groups of animals or humans using gene array or other techniques to compare expression of numerous genes simultaneously. Although these studies are often illuminating, they also suffer severe signal-to-noise problems as the number of data points for gene expression far outnumbers the number of individuals in an experiment. As a result, many genes in multiple pathways have been detected, but results are often conflicting, and it remains to be determined which actually play a meaningful role in the pathogenesis of sarcopenia (Welle, 2002). Very broadly, differential expression has been reported for genes thought to be involved in regulation of energy metabolism, immune response, cell cycle control and apoptosis, stress/antioxidant defense, protein turnover, and the transcriptional regulation of other genes. Notably, a large number of genes have also been observed to be differentially expressed that have no known functions. It is uncertain at this time what light these experiments shed on etiology other than the indication that sarcopenia may truly be multifactorial and involve the activation of genes regulating many metabolic, immune, repair, and other pathways.

CORRELATES

Several consequences have been ascribed to sarcopenia, which include decreased basal metabolic rate, loss of muscle strength and neuromuscular impairment leading to increased problems with mobility, gait, balance, falls, and reduced

Table 3 "Vicious loops" in the etiology of sarcopenia

Immobilization loop:
sarcopenia ⟶ neuromuscular impairment ⟶ falls and fractures ⟶ immobilization ⟶ sarcopenia
Nutritional loop:
sarcopenia ⟶ immobilization ⟶ decline of nutrition skills ("empty refrigerator") ⟶ malnutrition impaired protein synthesis ⟶ sarcopenia
Metabolic loop:
sarcopenia ⟶ decline of the protein reserve of the body ⟶ diminished capacity to meet the extra demand of protein synthesis associated disease and injury ⟶ Sarcopenia

Source: Reproduced from Muhlberg W and Sieber C, Sarcopenia and frailty in geriatric patients, Zeitschrift fur Gerontologie und Geriatrie, 37(1), pp2-8, Copyright 2004, with kind permission of Springer Science and Business Media.

activity levels, development of obesity, impaired immunity, disability, depression, and death (Evans, 1997). Not surprisingly, the evidence for associations of sarcopenia is less well established for some of these outcomes than others, as these associations are complex. This complexity likely reflects the fact that the etiology of sarcopenia is not only multifactorial but includes pathways by which "consequences" feedback to reinforce "causes" (Muhlberg and Sieber, 2004). As an example, it remains unclear whether physical inactivity, or muscle "disuse", precedes muscle atrophy in sarcopenia, or whether sarcopenia due to underlying biological mechanisms, such as oxidative stress, causes reduced physical activity. Although this might plausibly be resolved through longitudinal studies, it is theoretically likely that sarcopenia is part of a "vicious cycle" that involves feedback among several physiological and behavioral systems, making the distinction between "cause" and "consequence" somewhat specious. Muhlberg and Sieber (2004) recently described three possible "loops" as shown in Table 3. Until better data are in hand, it may be more useful to discuss "correlates" of sarcopenia than "consequences" *per se*.

Functional Limitation and Disability

The most important correlates of sarcopenia to consider are the associated limitations in physical and cognitive function and disability. There has been some controversy as to whether sarcopenia or obesity is a more important determinant of physical functional limitation and disability (Visser *et al.*, 1998). This controversy is really somewhat artificial, as there is definitely an etiological connection between changes in muscle mass and body fatness, although the underlying mechanisms remain to be fully elucidated. Moreover, there is increasing evidence that fat and fat-free, or skeletal muscle, masses independently as well as jointly influence outcomes of functional limitation, falls, disability, and susceptibility to chronic diseases (Baumgartner, 2000; Evans, 1997; Newman *et al.*, 2003; Sternfeld *et al.*, 2002; Zoico *et al.*, 2004). There is a U-shaped relationship between BMI and functional limitation and disability, as there is for chronic disease morbidity and mortality (Ferraro *et al.*, 2002). Underweight elders with BMIs <18, who have low muscle as well as fat mass, have an increased prevalence of function and mobility limitation and disability. Conversely, obese elders with BMIs >30, also have increased prevalence of functional limitation and disability. Underweight in elders is likely a product of wasting due to undernutrition and disease, which impact multiple systems affecting functional ability. Obese, but otherwise healthy, elders may be at increased risk as the weight and volume of excess adipose tissue stress the cardiovascular system and thereby limit functional performance. In general, obese individuals have greater muscle mass and strength than nonobese, although muscle strength relative to total body weight may be less.

Sarcopenic Obesity

The debate as to whether sarcopenia or obesity is relatively more important for functional limitation and disability leads directly back to consideration of "sarcopenic obesity" as the body composition type that may be most strongly associated with these outcomes (Baumgartner, 2000). As far as we can determine, the term "sarcopenic obesity" was first used in print by Heber *et al.* (1996), who illustrated the use of bioelectric impedance to predict fat-free mass in obese patients and distinguish those with "reduced lean body mass" from those with normal, or "proportionate" lean body mass. They noted their clinical impression that sarcopenic obesity was common in obese patients with cancer cachexia, and reported that the prevalence of sarcopenic obesity appeared to be increased in premenopausal women with breast cancer, who otherwise appeared to have normal body mass indices. They additionally noted that studies were needed to determine the metabolic and clinical significance of sarcopenic obesity.

We developed a DXA-based method of classifying individuals as sarcopenic-obese using the ASM/S^2 index and percent body fat and showed that the prevalence of this body composition phenotype increased from about 3 to 10% from 65 to 80 years of age in population-based sample of elders in New Mexico (Figure 4; Baumgartner, 2000). Sarcopenic obesity

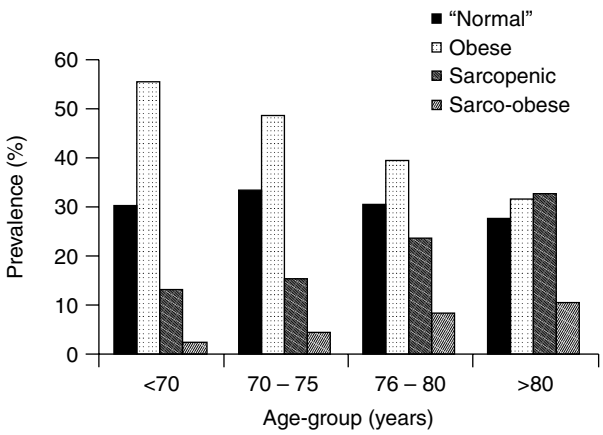

Figure 4 Relative prevalences of body composition types

Table 4 Odds ratios (95% CI) for three or more physical disabilities, balance, and gait abnormalities, and falls in the past year by sarcopenia – body fat classification: New Mexico Aging Process Study, 1995 ($N = 272$)

	3 or more	1 or more abnormalities of		
	Physical disabilities	Balance	Gait	Falls in past year
Normal muscle				
Nonobese	1.00	1.00	1.00	1.00
Obese	2.33 (0.68–8.81)	3.45 (1.23–10.7)	2.21 (0.99–5.05)	1.41 (0.80–2.52)
Sarcopenic				
Nonobese	2.07 (0.65–7.35)	2.35 (0.86–6.96)	1.44 (0.66–3.21)	2.12 (1.08–4.18)
Obese	4.12 (1.24–15.5)	6.36 (2.25–19.9)	3.21 (1.39–7.69)	3.34 (1.37–8.26)

Sarcopenic = ASM/S^2 < 25th percentile for each sex. Obese = %Fat > median for each sex. All odds ratios adjusted for age, sex, smoking, and comorbidity by multiple logistic regression.

was more strongly associated with self-reported disability, problems with balance and gait, and falls in the past year than either obesity or sarcopenia as shown in Table 4. Three subsequent studies in large, population-based samples have reported similar results (Davison *et al.*, 2002; Newman *et al.*, 2003; Sternfeld *et al.*, 2002; Zoico *et al.*, 2004).

Taken together, these studies indicate that sarcopenic obesity, or the combination of high-fat mass and low-muscle mass, is more strongly associated with functional limitation and disability than sarcopenia *per se*. This is fairly compelling, given the differences among studies in measurement methods, definitions, sample size, and representativeness. All the studies have the common weakness of being cross sectional, not allowing determination of the direction of the association.

Most recently, we examined the association of sarcopenia and sarcopenic obesity with incident instrumental activities of daily living (IADL) disability using data for 451 elderly men and women followed for up to 8 years in the longitudinal New Mexico Aging Process Study (Baumgartner, 1999). Sarcopenic obesity was defined from ASM/S^2 and percent body fat as in our previous cross-sectional study. Incident disability was defined as a loss of two or more points from baseline score on the IADL. Subjects with disability at baseline were excluded. Cox Proportional Hazards analysis was used to determine the association of baseline sarcopenic obesity with onset of disability, controlling for potential confounders. Subjects with sarcopenic obesity at baseline were two to three times more likely to report onset of disability during follow-up than lean sarcopenic or nonsarcopenic obese subjects and those with normal body composition. The relative risk for incident disability in sarcopenic-obese subjects was 2.63 (95% CI, 1.19–5.85), adjusting for age, gender, physical activity level, length of follow-up, and prevalent morbidity. This is the first study to indicate that sarcopenic obesity is independently associated with and precedes the onset of disability in community-dwelling elders.

Muscle Mass or Strength

There is also a somewhat artificial controversy as to whether muscle mass or strength is relatively more important with regards to functional outcomes (Visser *et al.*, 2000b). The question of which contributes more to functional limitation is hampered by measurement problems with these variables. As noted above, methods for *in vivo* measurement of muscle mass are subject to multiple limitations. The *in vivo* measurement of strength and function is even more difficult, as they include an important behavioral component. In many elders, measurement of these variables can be confounded by muscle and joint pain, as well as a cognitive impairment and depression, which affect volition in the application of force (Payette *et al.*, 1998). The effects of chronic diseases on muscle strength and function in the context of sarcopenia are not well established, as it is very difficult to separate these from those of aging in elderly people. Clearly muscle mass and strength are associated, although the correlation may be nonlinear and the age-related decrease in muscle force may be only partly explained by loss of muscle mass (Delbono, 2003; Harris, 1997). Moreover, muscle strength may not be linearly related to functional measures, such as chair stands, gait, or balance (Ferrucci *et al.*, 1997). Some of this may also be due to age-related changes in muscle composition rather than mass, which may include inter- and intramyocellular lipid changes in fiber type, and even molecular changes in myosin (Frontera and Bigard, 2002). Some data suggest that the phrase "muscle strength decreases with age" may be an overgeneralization; older adults may actually be relatively stronger than younger adults for movements involving lengthening, or eccentric contractions, possibly due to stiffer muscle structures and prolonged myosin crossbridge cycles in aged muscles (Vandervoort, 2002; Vandervoort and Symons, 2001). Another recent study suggests that age may affect the dynamic performance of muscle (i.e. reflex or response time and velocity of contraction) to a greater degree than isometric performance (i.e. static force production) (Lanza *et al.*, 2003).

A third controversial correlate of sarcopenia is cognitive impairment. Although an association is theoretically possible, few studies to date have detected one. In a large, population-based study of women in France, Nourhashemi *et al.* (2002) reported a significant, 43% increased risk for cognitive impairment for those in the lowest quartile of fat-free soft tissue mass compared to the highest quartile. A 35% increased risk was also found for those in the lowest

quartile of body fat mass. The authors did not examine the joint association of muscle mass and body fat. Recently, Brubacher *et al.* (2004) reported that both weight loss and weight gain were associated with decline in cognitive performance in elders.

Lastly, there are few data to date for the association of sarcopenia with mortality. Roubenoff and Harris (1997) suggested that a loss in fat-free mass >40% of "normal" was associated with death, but their data were based on patients with diseases, such as rheumatoid arthritis or HIV, which include multiple other pathological processes. Low BMI has been consistently shown to be associated with all-cause mortality, even after controlling for smoking and underlying disease (Bigaard *et al.*, 2004). Low arm muscle circumference, grip strength and, most recently, fat-free mass have also been reported to be associated with increased mortality (Metter *et al.*, 2002; Roche, 1994).

TREATMENT AND PREVENTION

Resistive Exercise Training

The vast majority of the literature on prevention and treatment of sarcopenia is related to the effects of exercise, and alternative medical approaches have been considered only recently. Several studies have demonstrated that progressive, high-intensity resistive training results in substantial improvements in muscle strength and mass in elderly adults, even those considered "frail", and this has been widely endorsed as a means of both treating and preventing sarcopenia (Evans, 1997; Evans and Campbell, 1993; Fielding, 1995; Frontera *et al.*, 2003; Hurley and Roth, 2000; Lexell, 2000; Schulte and Yarasheski, 2001; Winett and Carpinelli, 2001; Yarasheski *et al.*, 1999). Resistance exercise increases muscle protein synthetic rate over proteolysis, and results in a net increase in contractile protein mass and hypertrophy of muscle fibers, although the underlying cellular mechanisms are still not well defined (Evans, 2002; Frontera and Bigard, 2002; Hasten *et al.*, 2000; Zinna and Yarasheski, 2003). Additional benefits ascribed to resistance exercise include normalization of blood pressure, improved insulin sensitivity, decreased total and abdominal fat, increased resting metabolic rate, prevention of bone loss, reduction of risk for falls, and reduced pain and improved function in knee osteoarthritis (Hurley and Roth, 2000) Nonetheless, a host of issues remain to be resolved, including optimal duration, frequency and type of resistive exercise, combinations of resistive and aerobic training, compliance and long-term maintenance, adjuvant nutritional supplementation and/or pharmacologic treatment, and home or community-based versus clinical modes of intervention.

Most trials of high-intensity resistive exercise in elders have been relatively short, highly controlled, and supervised. Little is known about the long-term benefits and the influence of chronic exercise on muscle mass and muscle function has not been as extensively studied (Hawkins *et al.*, 2003). While high-intensity resistive exercise is effective in the short term for building muscle mass, it also increases mechanical damage and the accumulation of free radicals in muscle, which could paradoxically accelerate sarcopenia in a chronic exercise model in elders (Fulle *et al.*, 2004; Ji, 2001). Some research suggests that senescent muscle is more susceptible to oxidative stress due to underlying age-related changes that facilitate the formation of ROS, as well as declines in repair and regenerative mechanism (Fulle *et al.*, 2004; Ji, 2001). Untrained older individuals when initiating resistance exercise show equivalent or greater muscle fiber damage, soreness, and slower strength recovery than younger individuals (Roth *et al.*, 2000). Various types of morbidity that are more prevalent in elders could also exacerbate the risks of high-intensity resistive exercise. Studies are also needed that determine the optimal frequencies and intensities of exercise needed to maximize benefits while reducing risks in elders with different morbid conditions.

Other Types of Exercise

Aerobic exercise has well-established benefits for improved lipid profile and cardiovascular fitness and flexibility, but also improves mitochondrial and cytosolic proteins (Hurley and Roth, 2000; Zinna and Yarasheski, 2003). However, there have been few studies to date testing optimal combinations of resistive and aerobic exercise.

Recently, it has been noted that eccentric muscle contractions (muscle lengthening) during exercise have somewhat different effects than concentric contractions (muscle shortening), and that elders seem to have a greater capacity for and are better able to tolerate eccentric modes of exercise (Evans, 2002; Krishnathasan and Vandervoort, 2000; LaStayo *et al.*, 2003; Mayer *et al.*, 2003). In one small trial, LaStayo *et al.* (2003) reported that elderly subjects randomized to a primarily eccentric exercise intervention had greater improvements in muscle fiber CSA, strength, balance, and stair descent ability compared to those in a primarily concentric exercise program. Toft *et al.* (2002) and Ploutz-Snyder *et al.* (2001), however, have reported impaired repair mechanisms for exercise-induced muscle damage from eccentric exercise which was mitigated in elderly women who were chronically resistance trained. Although one would expect greater increases in strength and CSA with eccentric exercise, it is surprising that the subjects in the eccentric exercise group reported less muscle pain, had greater adherence to the protocol, and were able to maintain a greater relative eccentric work load than the younger subjects (Toft *et al.*, 2002). Obviously much more research is needed in this area to determine safety and efficacy in untrained elderly and to also investigate the feasibility of eccentric exercise in home and community-based programs.

Combinations of Exercise and Other Treatments

More work remains to be done testing combinations of exercise with dietary supplementation, hormone replacement,

and anti-inflammatory and other pharmacologic treatments. As noted above there is good evidence for an age-related decline in protein synthesis, suggesting that dietary protein requirements are increased in older individuals, and could be further increased by exercise training (Bonnefoy *et al.*, 2000, 2003). Several studies have examined combinations of protein or amino acid supplements with and without exercise for treating sarcopenia in animal models as well as elderly adults (Dardevet *et al.*, 2003; Paddon-Jones *et al.*, 2004; Singh *et al.*, 1999; Volpi *et al.*, 1998). It has been noted that protein supplements *per se* do not appear to have substantial effects, possibly because subjects compensate by reducing other dietary intake. However, oral amino acid supplementation clearly improves protein synthesis, and exercise results in further improvements as it increases demand for protein.

Supplementation with other nutrients has also been explored. Creatine plays a role in cellular energy metabolism and has been reported to improve skeletal muscle total phosphocreatine concentration, increase fat-free mass, and enhance high-intensity exercise performance in young healthy men and women (Tarnopolsky, 2000). However, the data on creatine supplementation in the elderly is rather scant. Smith *et al.* (1998) reported positive effects on exercise performance, Rawson *et al.* (1999) reported marginal improvements to reduce muscle fatigue and improve function without significant change in body composition or strength, and Bermon *et al.* (1998) reported no effect. Some of the discrepancies in these results seemed to stem from differences in the initial training status of the subjects. Wiroth *et al.* (2001) controlled for training status in elderly men and found oral creatine marginally increased anaerobic power and work capacity of both young and old sedentary men, whereas trained elderly men had no beneficial changes in work performance.

Despite evidence for an age-related decrease in antioxidant defense systems, there have been few studies to date testing combinations of exercise with exogenous antioxidant supplementation. Regular (chronic) exercise has been shown to increase the intracellular antioxidant/prooxidant ratio (Demirel *et al.*, 1998; Ji, 1995b, 2001; Leeuwenburgh *et al.*, 1994) and vitamin E is considered one of the most important antioxidants by quenching, or reducing, an electron from a free oxygen radical thus limiting peroxidation or breakdown of membrane lipids (Ji, 1995a). Animal studies of vitamin E and exercise were promising, whereas human studies have been ambiguous (Jessup *et al.*, 2003; Meydani *et al.*, 1993). Jessup *et al.* (2003) recently conducted an exercise and vitamin E supplementation trial and reported reduced free radical–induced lipid peroxidation following exercise training in elderly men and women. Sacheck *et al.* (2003) also reported a modest decrease in oxidative stress induced by eccentric exercise with vitamin E supplementation. Certainly future studies including other antioxidants, combination of antioxidants and exercise modalities may support the therapeutic value of this approach.

Relatively few studies have examined potentially synergistic interactions of exercise with hormones or anti-inflammatory agents (Greenlund and Nair, 2003; Kraemer *et al.*, 1999; Moulias *et al.*, 1999). Baldwin *et al.* (2001) administered naproxen sodium for 10 days immediately following eccentric exercise work bouts, and reported attenuated muscle injury and soreness and improved strength recovery in older males and females. Although no adverse reactions were reported during this short period of nonsteroidal anti-inflammatory drug (NSAID) treatment, the risk for renal and gastric complications with chronic administration needs to be carefully evaluated in the elderly who are more prone to drug-related renal dysfunction (Bennett, 1999).

A recent study of GH administration with intense resistance exercise in healthy elderly men revealed that the administration of recombinant human growth hormone (rhGH) alone or in combination with resistance training demonstrated differential regulation of at least two mRNA isoforms with the mechano growth factor (MGF) isoform induced with resistance training (Hameed *et al.*, 2004).

The MGF isoform is believed to be involved with the early stages of activation of satellite cells (Hill *et al.*, 2003). However, following 12 weeks of intensive training the gain in muscle mass and strength was no different between the groups. They stated that despite this finding, the overload provided by the training provided sufficient stimulus for upregulation of MGF at levels which would be optimal for muscle repair and adaptation. Lange *et al.* investigated the effects of GH on oxidative muscle metabolism with endurance training in elderly women and found that both treatment and placebo groups increased peak oxygen uptake, there was a 50% larger increase in citrate synthase activity in the GH exercise group and only the women receiving GH increased muscle L-3-hydroxyacyl-CoA dehydrogenase activity. The GH group also showed greater decreases in fat mass and increases in fat-free mass than the placebo group (Lange *et al.*, 2000). Thus, research in this area is still open to further investigations.

Lastly, although the treatment of sarcopenia with exercise training with or without nutrition, hormone, or other pharmacologic agents has been shown to be effective, interventions to prevent sarcopenia by increasing physical activity in the aging population are far more difficult and generally have not occurred (Roubenoff and Hughes, 2000). More work is necessary to determine appropriate exercise recommendations for older adults and to increase the access to safe and effective programs in a variety of community as well as clinical settings (Seguin and Nelson, 2003).

Hormone Replacement

There is growing interest in the use of hormone replacement for the treatment of sarcopenia and associated age-related disorders. There are several important concerns, however, with this approach to treatment. First, it is uncertain to what extent aging alters the response of muscle to hormone replacement. Some studies show blunted response in aged

muscle; some suggest that different types of muscles or muscle fibers may respond differently. On the other hand, data for the expression of hormone receptor genes in muscle indicate no significant age-related effects. This suggests that decreased circulating anabolic hormone levels, not capacity for response of muscle to these trophic facts, are to blame for sarcopenia. If confirmed, this would support hormone replacement as a therapy for sarcopenia. Second, there is controversy as to the type of hormone. Studies have been conducted mainly with GH, GH-releasing hormone, IGF-1, testosterone, and DHEA. There are significant issues for each of these with regard to selection of patients, dosage, and side effects that remain to be resolved. There have been few studies to date for combined effects of hormone replacement and other therapies, such as exercise. More long-term studies are needed to establish side effects and benefits for physical function and quality of life.

Age and obesity, particularly visceral adiposity, have well-established, independent effects on GH secretion (Veldhuis *et al.*, 1997). GH decreases substantially with age, except in obese men who have low GH secretion at all ages, and obesity also disregulates the association of GH with testosterone. It has been speculated that some of the effects of obesity on GH are partly mediated by leptin (Roubenoff *et al.*, 1998). There is ample experimental evidence that GH is essential for normal skeletal muscle growth and regeneration (Quinn, 2002). Owing to its complex pattern of pulsatile release, GH is difficult to measure in epidemiologic and many clinical studies. However, many of the somatic effects of GH are mediated by IGF1, and serum IGF1 is a widely accepted biomarker of integrated 24-hour GH secretion (Corpas *et al.*, 1993). Serum IGF1 was reported to be inversely correlated with age, and positively correlated with muscle or lean body mass in a cross-sectional study of older adults (Baumgartner *et al.*, 1999). The strength of the association with lean body mass, however, was generally weak, and was further attenuated by adjustment for adiposity and serum testosterone (Baumgartner *et al.*, 1999). Thus, the role of GH/IGF1 in sarcopenia is still regarded as something of an "enigma" (Bross *et al.*, 1999; Roubenoff *et al.*, 2003, 1997c; Veldhuis *et al.*, 1997).

Despite early indications in some clinical studies (Rudman *et al.*, 1991), GH/IGF1 treatment has not proven effective for improving muscle mass and, particularly, strength, in multiple subsequent clinical trials (Bartke, 1998; Quinn, 2002). Possible explanations include the presence of age-related impairments that prevent the actions of GH and IGF-I and the failure to deliver GH and IGF-I in a physiologically correct manner (Borst and Lowenthal, 1997). Most trials have been small, of short duration, and have used supraphysiological doses with significant side effects; thus, long-term effects of lower doses are not well established (Lissett and Shalet, 2000). One trial suggested that >2 years of treatment might be necessary to detect effects on muscle strength or physical function (Wallymahmed *et al.*, 1997). A 5-year trial in adults with adult-onset GH deficiency normalized isometric and isokinetic knee flexor and extensor strength and increased, but did not normalize, hand grip strength (Svensson *et al.*, 2003). GH/IGF1 treatment does not seem to enhance the effects of exercise on muscle (Bross *et al.*, 1999). Some recent studies have suggested that combined GH/IGF1 and testosterone therapy may have synergistic effects on muscle mass and strength (Blackman *et al.*, 2002; Brill *et al.*, 2002).

Epidemiologic studies have established that testosterone levels decline with age in men with parallel decreases in muscle mass and strength (Baumgartner *et al.*, 1999; Feldman *et al.*, 2002; Harman *et al.*, 2001; Morley *et al.*, 1997; Perry *et al.*, 2000; Roy *et al.*, 2002). The prevalence of hypogonadism in men in the general population is not well defined, but may range from 5 to 20% for men 60 to 70 years in age to 40 to 90% in those over 80 years (Bhasin, 2003). Although still somewhat controversial, there is increasing consensus that this decline is primarily an age effect and is the result of primary testicular failure, or "andropause" (Liu *et al.*, 2004; Yialamas and Hayes, 2003). A similar decline in testosterone with age in women is not well established, mainly due to absence of sufficiently sensitive assays. The role of testosterone in sarcopenia in women, therefore, remains to be defined.

The anabolic effects of testosterone have been recognized for over 60 years (Bhasin, 2003; Tenover, 1998). Numerous studies have established that testosterone treatment in young hypogonadal men increases lean body mass and decreases fat mass (Herbst and Bhasin, 2004). Supraphysiologic doses also increase muscle mass and strength in eugonadal men, but there is significant concern of side effects at high doses (Bhasin, 2003). There is some controversy as to whether older men respond as well as young men (Herbst and Bhasin, 2004). Liu *et al.* (2004) recently evaluated results from nine randomized trials in older men. Most were small (sample sizes <40) and short term (during 3–6 months), and the participants selected were hypogonadal. All nine found significant decreases in fat and increases in muscle mass; however, only one demonstrated a significant improvement in muscle strength, and none found improvements in measures of physical function, such as gait, balance, and physical activity, or in quality of life (Liu *et al.*, 2004). Recently, Wittert *et al.* (2003) reported that oral testosterone treatment over 1 year improved muscle mass, but not strength, in older men with low-normal testosterone levels. Studies conducted with nonaromatizable androgens, such as oxandrolone and nandrolone, have shown similar results (Johansen *et al.*, 1999; Orr and Singh, 2004). There have been few long-term randomized clinical trials with appropriate measures of body composition, muscle strength, physical function, or quality of life to establish efficacy and long-term safety. There are significant concerns as to increased risk for insulin resistance, cardiovascular disease, and prostate cancer in men (Bhasin, 2003; Bross *et al.*, 1999; Liu *et al.*, 2004; Yialamas and Hayes, 2003). To date, there have been no studies of the effects of testosterone treatment on sarcopenia in women.

One of the most dramatic age-related declines in circulating hormone levels has long been recognized to be the adrenal androgen DHEA. Despite evidence that DHEA administration increases serum levels of IGF1, testosterone

and estrogen in animals as well as humans, most clinical trials in elders have been small and short term and have not demonstrated significant beneficial effects on body composition, physical or cognitive function. Percheron *et al.* (2003) conducted a long-term double-blind placebo-controlled trials of DHEA in elderly subjects and reported restoration of DHEA sulfate levels to the normal range for young adults; however, there was no improvement of muscle strength or fat CSA. Lasco *et al.* (2001) also administered DHEA for 12 months in elderly postmenopausal females and reported the group treated with DHEA showed considerable improvement on insulin sensitivity, increased high-density lipoprotein cholesterol, decreased low-density lipoprotein cholesterol, and triglycerides, but no change in glucose tolerance. As for other androgens, long-term trials are needed to better establish efficacy and side effects (Nippoldt and Nair, 1998).

Other Pharmacologic Treatments

There are few data to date for the potential effects of pharmacotherapy other than anabolic hormones on sarcopenia or associated functional decline in elders. More work is needed in developing suitable animal models of sarcopenia and age-related disability for preclinical, translational testing of pharmacological approaches (Carter *et al.*, 2001). Some potential candidates include statins, ACE inhibitors, and clenbuterol (Chen and Alway, 2001, 2000; Savo *et al.*, 2004; Smith *et al.*, 2002). More novel agents may be developed. Schroeder *et al.* (2003) recently reported that oxymetholone improved muscle mass and strength and decreased fat mass in older men. Urocortin, a corticotropin-releasing factor 2 receptor agonist, has been reported to prevent the loss of skeletal muscle mass and strength resulting from disuse due to casting, corticosteroid treatment, and nerve damage in mice, and to increase skeletal muscle mass and force in normal muscles (Hinkle *et al.*, 2003). One small clinical trial reported that treatment with tibolone, a compound with established trophic effects on bone, positively affected lean soft tissue mass in postmenopausal women (Meeuwsen *et al.*, 2001). Treatment with monoclonal antibodies to myostatin has been shown to increase muscle mass and strength in some animal models (Bogdanovich *et al.*, 2002; Whittemore *et al.*, 2003). Morley (2002) has suggested trials with combinations of therapies that stimulate appetite, reverse catabolism, and stimulate anabolism. Gene therapies targeting specific molecular pathways to sarcopenia, including stem cells, may also be on the horizon (Ouyang and Alway, 2004; Spangenburg *et al.*, 2002).

Caloric Restriction

As caloric restriction has been shown to extend longevity in various animal models, and to have multiple beneficial effects, including reduction of steady-state levels of oxidative stress in muscle, so there is interest in its effects on sarcopenia. Aspnes *et al.* (1997) reported that caloric restriction initiated at 17 months of age preserved fiber number and type in the vastus lateralis muscle in rats. McKiernan *et al.* (2004) also reported that caloric restriction did not prevent loss of muscle with age in older mice, but appeared to prevent its loss in middle-aged (21-month) mice compared to age-matched controls. Taken together these studies suggest that caloric restriction begun in middle age can retard age-related muscle loss.

These and other studies have indicated that calorically restricted animals show less evidence of oxidative mitochondrial damage, including lower levels of mtDNA deletion products, oxidized mitochondrial proteins (protein carbonyls) and lipids peroxides (TBARS, malondialdehyde), superoxide anion radicals, mitochondrial enzymes cytochrome *c* oxidase (COX) and succinate dehydrogenase (SDH) enzyme activities, ETS abnormalities, and apoptotic regulatory proteins than *ad libitum* fed rats (Bua *et al.*, 2004; Dirks and Leeuwenburgh, 2004; Lass *et al.*, 1998; Zainal *et al.*, 2000) Gene microarray studies indicated that caloric restriction alters transcript levels of several genes in skeletal muscle, including ones involved in reactive oxygen scavenging (Sreekumar *et al.*, 2002).

Whereas the data for potential benefits of caloric restriction on sarcopenia in animals are intriguing, they have yet to be translated to humans. Dietary restriction and weight loss in humans result in loss of both fat and fat-free tissues, and caloric intake is generally weakly positively correlated with lean body mass, regardless of age. Moreover, muscle loss accelerates with age after ~age 50, independent of caloric intake. Hence, it is unclear how caloric restriction implemented at any age may protect against sarcopenia in old age. Data from long-term longitudinal studies or trials are not available. It is even more difficult to demonstrate the protective effects of lifelong caloric restriction on sarcopenia in humans. Thus, it is uncertain whether caloric restriction can be established as either an effective treatment or preventive measure for sarcopenia.

SUMMARY AND CONCLUSIONS

Considerable progress has been made toward understanding causes and consequences of age-related muscle loss in the last 15 years since Rosenberg gave it the name, "sarcopenia". The epidemiology of sarcopenia is still in its infancy. Various methods have been applied resulting in widely discrepant prevalence estimates. There is a need for consensus as to the best methods for defining sarcopenia in population-based studies. This should include a careful consideration of sensitivity and specificity in relation to multiple outcomes as well as practicality of implementation in community surveys. It seems reasonable that the optimal approach would combine some measures of relative muscle mass and strength. More accurate methods should be applied in clinical studies.

The etiological picture that has emerged clearly indicates that sarcopenia is multifactorial, involving age-related

declines in anabolic stimuli, protein synthesis, oxidative stress defense systems, and tissue, cellular and possibly DNA repair mechanisms, coupled with increases in proinflammatory, catabolic signals, protein degradation, and tissue, cellular and DNA damage, particularly mtDNA, which is likely due to oxidative stress. These changes affect skeletal muscle size, fiber and lipid composition, and metabolic and physiologic function. The associated decrease in skeletal muscle resting energy expenditure, coupled with a decline in physiological capacity for exercise, results in energy imbalance, which leads to increased deposition of triglycerides in adipose tissue as well as within muscle cells. Increases in inter- and intramuscular lipids ("mysosteatosis") reduce skeletal muscle insulin sensitivity, with broad systemic metabolic consequences that may further exacerbate loss of function. Cytokinemia, due to aging, obesity, or chronic underlying morbidity, accelerates muscle loss by stimulating protein degradation (cachexia), and producing anorexia (wasting), which decreases protein intake and substrate for muscle repair and regeneration. Consequences of sarcopenia, particularly decreased physical activity, feedback to become additional "causes" or exacerbating factors. In summary, the progression of sarcopenia involves several, entangled "vicious cycles". Ultimately this complex web of changes leads to functional limitation, disability, morbidity, and death.

In Figure 5 we postulate two new models for the development of sarcopenic obesity. In the "acute" model, sarcopenic obesity arises from a precipitating event, such as an injurious fall, stroke, cancer diagnosis, or other illness that causes a transient or permanent loss of mobility coupled with an acute phase response that stimulates muscle loss via cachexia and anorexia, from which there is incomplete recovery. Sarcopenic obesity then increases the risk for subsequent acute events which lead to additional functional limitation, or disability that further exacerbates sarcopenic obesity. This model is not necessarily age-related, although it is assumed that aging adversely affects the ability to recover from the cascade initiated by the precipitating event. The "chronic" model proposes that sarcopenic obesity arises in people with long-standing obesity as a result of a combination of increased oxidative stress, subclinical vascular disease, insulin resistance, chronically depressed hormone levels and elevated proinflammatory cytokines, including leptin. These obesity-associated processes, together with independent age-related ones, cause accelerated muscle loss leading to sarcopenic obesity. Sarcopenic obesity directly increases risk for functional limitation and disability, or indirectly via increased susceptibility to acute events such as injurious falls, and so on. As in the acute model, these "consequences" feedback to further exacerbate sarcopenic obesity, increasing risk for further events in "vicious cycle".

Taken together, the data from various clinical trials to reverse sarcopenia strongly suggest that no one approach will be entirely efficacious. Although difficult to test in clinical trials, multimodal approaches that combine exercise with nutritional supplementation (amino acids, antioxidants) and/or hormone replacement and anti-inflammatory therapy may be indicated. As shown in Figure 6, the outcomes should be increased muscle mass and strength, decreased total, visceral, and intermuscular fat, improved functional status, reduced effects of chronic morbidity, and improved mobility and quality of life. Preventive interventions remain to be developed and tested. At present the candidates are limited to the promotion of exercise and improvement of diet.

The confluence of the "epidemics" of aging and obesity are predicted to result in increases in the incidence of multiple chronic diseases, mainly type 2 diabetes, cardiovascular diseases, and cancer. Taken together, these will

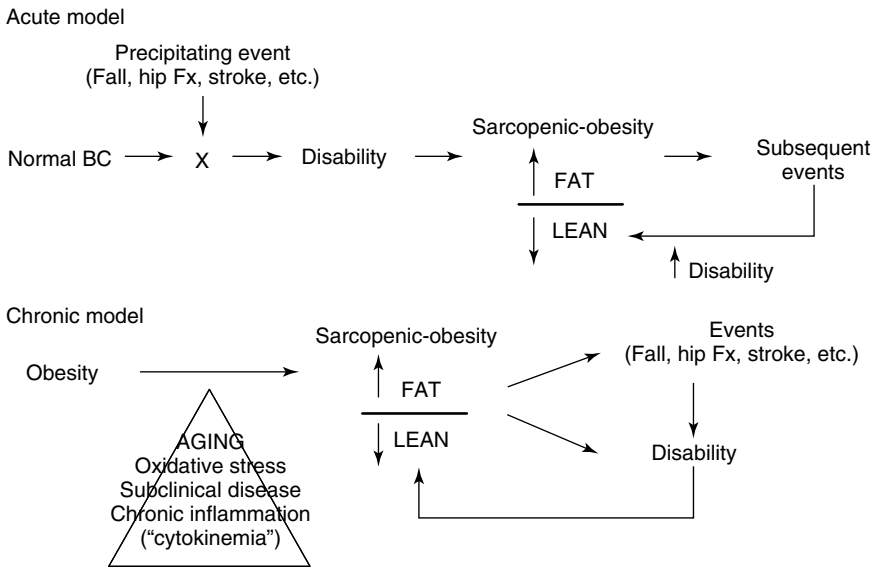

Figure 5 Acute and chronic models of etiology of sarcopenic obesity

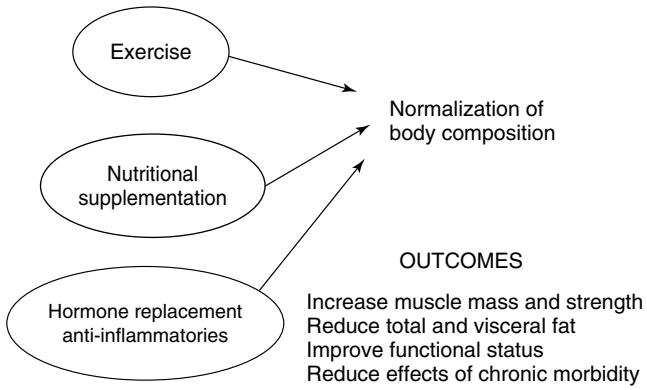

Figure 6 Multimodal treatment model for sarcopenia

contribute to increased rates of disability in old age and massive health-care costs for treatment and care. It is important to determine how sarcopenia will contribute to this future scenario. Sarcopenia has been shown to be an important risk factor for functional limitation and disability in relatively healthy, nonobese elders. If it is true that obesity contributes to accelerated muscle loss in old age, resulting in sarcopenic obesity which conveys a significantly greater risk for disability than sarcopenia *per se*, then we can anticipate an epidemic of this disorder with an unknown, but substantial increase in health-care costs over and above those presently expected.

KEY POINTS

- Sarcopenia is a major cause of disability in old age.
- Sarcopenic obesity, which combines high body fatness with low-muscle mass, has an even stronger association with disability than sarcopenia *per se* and is also a risk factor for certain types of morbidity, such as congestive heart failure.
- The etiology of sarcopenia is multifactorial and complex.
- Multimodal treatment approaches are needed for sarcopenia.
- Preventive measures are not well established.

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Muscle Disorders

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INTRODUCTION

Myopathies may be inherited or acquired. Although the latter are more common in geriatric practice, several inherited myopathies may present for the first time in middle age or later and may raise genetic issues for other family members. The acquired myopathies, with a few notable exceptions, often recover with appropriate management. For all of the conditions that are discussed in this chapter, appropriate support, even in the absence of specific therapy, will help improve quality of life and reduce morbidity.

The clinical features of myopathies are relatively limited and include weakness and muscle wasting, fatigue, pain, tenderness, myotonia, and muscle twitching. At the bedside it may be impossible to decide whether weakness and wasting is due to a myopathy or a neurogenic disorder. Thus, the differential diagnosis of myopathy includes anterior horn cell disorders (e.g. amyotrophic lateral sclerosis and spinal muscular atrophy), nerve root and plexus disorders, peripheral neuropathies, and myasthenic disorders. The presence of upper motor neurone signs and sensory symptoms and signs clearly suggests a more proximal cause of problems than skeletal muscle, but in their absence it is important not to forget that weakness alone is often due to nerve rather than muscle disease. The role of laboratory investigations in helping to distinguish between neurogenic and myopathic diseases is discussed below.

There are several ways of approaching the classification of muscle disorders. For example, inherited disorders can be classified by phenotype or by gene/protein product. For everyday usage, a subdivision into acquired and inherited disorders is useful (Tables 1 and 2). In the elderly (Table 3) the most frequently encountered disorders are the idiopathic inflammatory myopathies, drug-induced myopathies, and muscle disease in association with endocrine and metabolic disease.

CLINICAL ASSESSMENT

The patient's history is likely to be more revealing than physical examination, although laboratory investigations may be required to establish the precise diagnosis (Hilton-Jones *et al.*, 1995; Hilton-Jones and Kissel, 2001). In the history, particular attention must be paid to determining the site of onset and rate of progression of skeletal muscle involvement and the presence of associated symptoms such as muscle wasting and pain. There must be a detailed recording of the family history and drug history. For myopathies secondary to systemic disease (Table 1) the underlying cause may be identified from the history and physical examination.

In practice, the most frequently encountered pattern of skeletal muscle involvement is that of painless proximal weakness affecting the pelvic girdle more than the shoulder girdle. In the acquired myopathies (Table 1) onset may be acute or chronic, whereas in the inherited myopathies (Table 2) progression is usually slow. Asymmetric involvement is uncommon but may be a striking feature in inclusion body myositis (IBM) and facioscapulohumeral (FSH) muscular dystrophy. Early involvement of distal muscles is seen in myotonic dystrophy and IBM.

There is early involvement of the extraocular muscles (causing ptosis and/or ophthalmoplegia) in mitochondrial cytopathies, Graves' ophthalmopathy, and oculopharyngeal muscular dystrophy. Ptosis and facial weakness are seen in myotonic dystrophy, and facial weakness is a particular feature of FSH muscular dystrophy and some of the congenital myopathies.

Weak muscles eventually become wasted, but in many myopathies the bulk is maintained for a long time, whereas in neuropathies, wasting is generally an earlier feature. The tendon reflexes also tend to be lost earlier in neuropathies. Muscle hypertrophy is rare in acquired myopathies but is a feature of some of the muscular dystrophies (e.g. Duchenne/Becker dystrophy).

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Table 1 Acquired myopathies

Idiopathic inflammatory myopathies
– Polymyositis
– Dermatomyositis
– Inclusion body myositis
– Myositis associated with connective tissue disorders
Toxic
– Alcohol
– Drugs
Endocrine and metabolic
– Acromegaly
– Hypothyroidism
– Hyperthyroidism
– Cushing's syndrome
– Addison's disease
– Disorders of vitamin D and calcium metabolism
Infection
– Viral
– Bacterial
– Parasitic
Paraneoplastic myopathies

Table 2 Inherited myopathies

Muscular dystrophies
– (see Table 8)
Myotonic dystrophies
Congenital myopathies
– Central core disease
– Nemaline myopathy
– Myotubular/centronuclear myopathy
– Multi-mini-core disease
Metabolic myopathies
– Glycogenosis (e.g. McArdle's syndrome)
– Lipid disorders (e.g. disorders of fatty acid β-oxidation)
– Mitochondrial cytopathies
Channelopathies
– Sodium (hyperkalemic periodic paralysis, paramyotonia congenita)
– Calcium (hypokalemic periodic paralysis)
– Chloride (myotonia congenita)
– Ryanodine receptor (Malignant hyperthermia, core diseases)

Table 3 Major myopathies in the elderly

Idiopathic inflammatory myopathies
Toxic myopathies
Endocrine and metabolic myopathies
Oculopharyngeal muscular dystrophy
Mitochondrial chronic progressive external ophthalmoplegia

Respiratory muscle weakness may be asymptomatic, but evidence of it can be found on examination in the form of paradoxical abdominal movement. The best method of evaluation is by measurement of the forced vital capacity (VC). In the presence of diaphragmatic weakness the VC falls when the patient lies down.

Most myopathies are painless at rest. Acute dermatomyositis (DM) may be painful, but rarely markedly so, and there is a striking difference between the modest pain and severe weakness seen in this condition, and the severe pain and stiffness and absence of weakness seen in polymyalgia rheumatica. Aching is a common feature in hypothyroid myopathy and bone pain a major feature of osteomalacia. Acute drug-induced and acute alcoholic myopathies are often painful. Exercise-induced muscle pain is seen in several metabolic myopathies (Hilton-Jones *et al.*, 1995), and in Becker muscular dystrophy.

Clinical features alone usually provide a strong pointer toward the diagnosis and help determine the path of laboratory assessment (Mastaglia and Laing, 1996).

LABORATORY INVESTIGATIONS

A rather common pathway from the clinical evaluation to diagnosis is via biochemical studies, electrophysiological assessment, and muscle biopsy. For the inherited myopathies, this pathway is gradually being supplanted in part or in whole by specific DNA tests (Mastaglia and Laing, 1996).

Biochemical Studies

Despite its lack of specificity, estimation of the serum creatine kinase (CK) is a useful marker for muscle disease. High levels are seen in Duchenne and Becker muscular dystrophy, acute drug-induced and toxic myopathies, inflammatory myopathies, some forms of limb-girdle muscular dystrophy and some metabolic myopathies. Levels are normal in many congenital myopathies, myotonic disorders, chronic drug-induced myopathies and many metabolic myopathies. Moderate elevation (up to $1000\,\text{iu}\,\text{l}^{-1}$) may be seen in anterior horn cell disorders. The serum aspartate aminotransferase (AST) level generally parallels the CK level in muscle disorders and not infrequently its elevation in the presence of otherwise normal liver function tests is the first indication of a myopathic disorder.

Dynamic studies (such as estimation of lactate generation during exercise, and magnetic resonance spectroscopy) are of value in the investigation of suspected metabolic myopathies involving carbohydrate and mitochondrial metabolism, and tandem mass spectrometry is of value in evaluating disorders of fatty acid β-oxidation (Hilton-Jones *et al.*, 1995).

Electrophysiology

In primary disorders of the muscle, electromyography (EMG) characteristically shows reduction in the size and duration of the motor unit potentials, and an increase in the number of polyphasic units. Fibrillation potentials and positive sharp waves indicate muscle fiber irritability and are seen in inflammatory myopathies and some metabolic myopathies. Myotonic discharges are seen in myotonic dystrophy and myotonia congenita.

EMG may help in distinguishing between neurogenic and myopathic disorders, which may sometimes be difficult on clinical grounds alone.

Muscle Biopsy

With the exception of DNA tests, muscle biopsy remains the single most powerful tool for the specific diagnosis of myopathies (Sewry and Dubowitz, 2001). The muscle to be biopsied must be chosen with considerable care (Mastaglia and Laing, 1996). Tissue handling is extremely important and correct processing requires specialist facilities (Hilton-Jones *et al.*, 1995). Biopsy findings in individual disorders are discussed throughout this chapter. Biopsy samples are also used for biochemical studies and mitochondrial DNA analysis.

Molecular Studies

There has been rapid progress recently in the identification of the genetic basis of many of the inherited myopathies (see Gene Tables at http://www.worldmusclesociety.org/). This offers the prospect of rapid and precise diagnosis and the option of prenatal diagnosis. However, a number of practical difficulties remain in moving tests from the research arena to accredited diagnostic laboratories (Wicklund and Hilton-Jones, 2003).

ACQUIRED MYOPATHIES

The acquired myopathies (Table 1) are of particular importance because many of them are either treatable or reversible. The idiopathic inflammatory myopathies are the subject of considerable research activity, which has aided classification and our understanding of pathogenetic mechanisms, and is starting to help in determining therapeutic approaches. Toxic and drug-induced myopathies are seen at all ages but are particularly important in the elderly because of polypharmacy. Myopathy, occasionally severe, is common in many endocrine disorders and usually responds rapidly to correction of the underlying condition. Disorders of calcium and vitamin D metabolism in the elderly are an important cause of muscle weakness. Several forms of paraneoplastic myopathy exist but, in general, the condition is overdiagnosed.

Idiopathic Inflammatory Myopathies

Dermatomyositis (DM) and polymyositis (PM) share many clinical features and there are common approaches to treatment, but recent studies have shown that they have very different immunopathogenic mechanisms (Dalakas and Karpati, 2001). Inclusion body myositis may not be a true primary inflammatory myopathy but it is often confused clinically with PM and is particularly important in the present context because it is seen most frequently in the elderly.

Myositis may be seen in association with connective tissue disorders (including systemic lupus, scleroderma, Sjögren's syndrome, rheumatoid arthritis, and mixed connective tissue disease) and these are sometimes referred to as *overlap syndromes* (Dalakas and Karpati, 2001). Care must be taken to distinguish a true inflammatory myopathy as the cause of weakness in these conditions from other associated causes, such as peripheral neuropathy, muscle ischemia, cachexia, and drug-induced myopathy. Overall, clinically relevant inflammatory myopathy in these overlap syndromes is uncommon.

Dermatomyositis (DM) (see Chapter 135, Skin Disorders in the Elderly)

1. **Clinical features**

DM can develop at any age, is twice as common in females when compared to males, and has an annual incidence of about two per million population. Onset of weakness is usually subacute (weeks) but, in rare cases, has a more explosive onset with profound weakness, respiratory muscle involvement and rhabdomyolysis with myoglobinuria developing within a few days. Exercise-induced muscle pain and discomfort on palpation may be present but severe discomfort of the type associated with polymyalgia rheumatica is not seen. Dysphagia is common.

Clinical evidence of skin involvement is present in most, but not all, cases. The commonest features are a nonspecific erythematous rash over the face and upper anterior chest wall, a red-purple discoloration over the knuckles and dilatation of capillaries at the base of the nail bed (Figure 1). Characteristic, but seen less often, is a violaceous (heliotrope) discoloration of the eyelids. Raynaud's phenomenon, which may long predate the myopathy, and arthralgia are frequent. Interstitial pulmonary fibrosis may be asymptomatic, cause breathlessness and cough, or occasionally be relentlessly progressive despite treatment and lead to death. There is an association between lung involvement and the presence of serum anti-Jo-1 antibodies. Cardiomyopathy and rhythm disturbances are underestimated and may also lead to death.

In about 20% of cases overall, but more frequently in older patients, there is an association with carcinoma, but not with a particular carcinoma. Thorough clinical assessment is therefore essential, including rectal, vaginal and breast examination, sigmoidoscopy or more extensive endoscopy if there is a suggestive history, abdominal and chest scanning, testing for fecal occult blood, and basic haematological and biochemical studies (Sparsa *et al.*, 2002).

2. **Diagnosis and pathological features**

The serum CK is usually elevated and in acute cases the level may be very high. It is a useful but not absolute indicator of disease activity. The erythrocyte sedimentation rate (ESR) is normal in the majority of patients. Autoantibodies are frequently found but their identification is of little value with respect to diagnosis or prognosis, except perhaps for

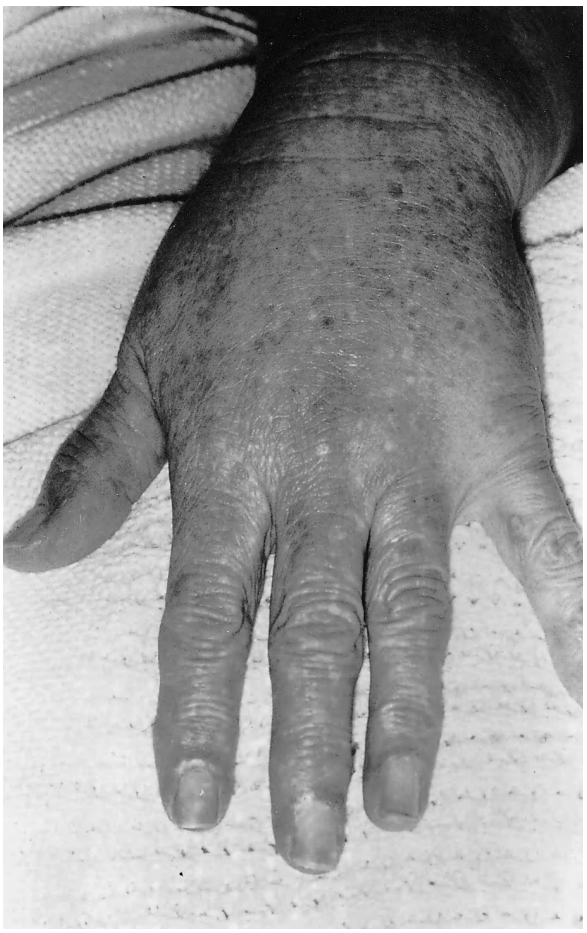

Figure 1 Dermatomyositis. Note erythema over knuckles and dilatation of the nail-bed capillaries

the association noted above between anti-Jo-1 and interstitial lung disease (Ioannou *et al.*, 1999). EMG shows an alteration in the motor unit potentials (reduced duration and an increase in polyphasic units) and electrical irritability (fibrillation potentials and positive sharp waves).

The diagnosis is confirmed by the muscle biopsy findings. Characteristic features include perifascicular atrophy, focal myofibrillar loss and areas of infarction. Vascular changes include capillary necrosis, undulating tubules in endothelial cells, arteriolar thrombosis, and lytic membrane-attack complex deposition in vessel walls. Inflammatory infiltrates are typically found in septa and around blood vessels (Figure 2), and consist of B-lymphocytes, helper T-lymphocytes and plasma cells.

3. Pathogenesis

On the basis of the characteristic immunopathological muscle biopsy findings noted above, it is believed that DM is caused by humoral immune mechanisms which lead to destruction of capillaries and occlusion of arterioles. Muscle fiber damage is thus secondary to ischemia. This contrasts with PM in which cell-mediated immune mechanisms lead to muscle fiber destruction.

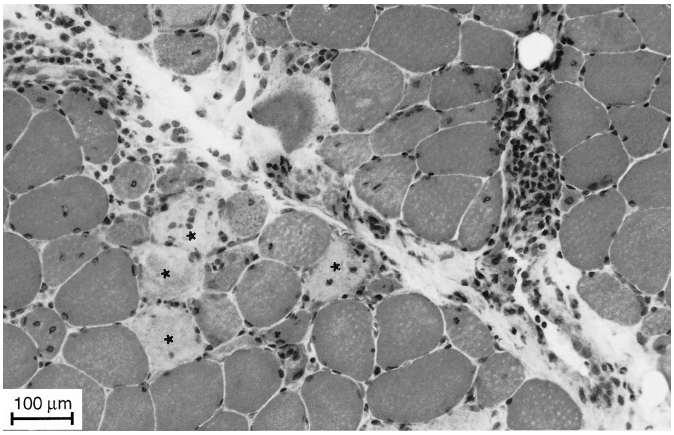

Figure 2 Dermatomyositis. Muscle biopsy (H&E X115). Note the perivascular inflammatory infiltrate, and necrotic fibers (*)

4. Treatment

Knowledge of the natural history of DM is limited and there have been no completely satisfactory, controlled trials of drug therapy. Prednisolone is the mainstay of treatment and a reasonable starting dose is 1 mg kg^{-1} body weight/day. In severe cases this may be preceded by intravenous methylprednisolone 500 mg daily for 5 days, although the evidence for additional benefit is lacking. Azathioprine (2.5 mg kg^{-1} body weight/day) or methotrexate (10–20 mg weekly) are widely used in combination with prednisolone, as long-term steroid sparing agents. The steroid dose is maintained for 1–3 months (at least until the CK has returned to normal) and then lowered slowly at a rate determined by the clinical response and to a lesser extent by changes in the serum CK. A rise in the CK may precede exacerbation of weakness. As the disorder settles, the prednisolone can be changed to an alternate day regime, which may reduce steroid side effects.

If the patient does not respond to, or cannot tolerate, the above regime, then there are several other options. Alternative immunosuppressant drugs that are used (but without trial data) include mycophenolate mofetil and cyclophosphamide. Plasma exchange and leucapheresis appear to be ineffective. Intravenous immunoglobulin is almost certainly effective (Dalakas, 2003) but there is insufficient data to recommend it over prednisolone as a mainstay of treatment, although it is quite widely used in severe cases at first presentation together with high doses of steroids.

The cutaneous lesions respond to systemic steroid treatment. In the absence of significant muscle involvement, topical steroids may have a role. The skin is photosensitive and light-exposed areas should be treated with an ultraviolet blocking cream. Malnutrition (e.g. due to associated dysphagia) must be avoided to prevent muscle catabolism. Physical activity should be encouraged.

The prognosis with respect to muscle function and life expectancy is good if treatment is started early and there is no associated malignancy.

Polymyositis (PM)

1. Clinical features

Polymyositis is a disappearing disease as many cases previously diagnosed as PM have been reclassified as having IBM or myositis associated with connective tissue disease (van der Meulen *et al.*, 2003). As in DM the weakness is predominantly proximal but the onset is often insidious and the rate of progression slower. Muscle pain and tenderness are very uncommon. Elderly patients often give a history of deterioration of gait over 1–2 years, which is not infrequently attributed to arthritic hips.

2. Diagnosis and pathological features

The serum CK is usually elevated but may be normal in very slowly progressive or late stages of the disease. The ESR is unhelpful. Electromyographic changes are the same as those described for DM.

Muscle biopsy shows scattered necrotic and regenerating fibers. The vascular changes noted in DM are absent. Inflammatory infiltrates (Figure 3) tend to be within fascicles (endomysial) and are composed of cytotoxic T-lymphocytes and macrophages with fewer B-lymphocytes. A characteristic finding in PM, and also in IBM, is partial invasion of muscle fibers. Cytotoxic T-lymphocytes penetrate the basal lamina but not the muscle fiber membrane and appear to compress the fibers without causing necrosis. These fibers, and also noninvaded fibers, express class I major histocompatibility complex (MHC) protein products, which are not expressed in normal muscle.

3. Pathogenesis

In PM it is presumed that cytotoxic T-lymphocytes recognize an antigen, bound to class I MHC products, on the muscle fiber surface. Muscle fiber function is compromised by the invading lymphocytes, which are also associated with lymphokine release. The nature and origin of the antigen is unknown.

4. Treatment

Despite the different pathogenetic mechanisms postulated, the immunosuppressive drug management of PM is the same as described above for DM. If there is extensive weakness and wasting at presentation the prognosis for significant improvement is poor, although disease progress may be arrested.

Inclusion Body Myositis (IBM)

1. Clinical features

IBM is rare before the fifth or sixth decade of life and shows a strong male predominance (Tawil and Griggs, 2002). Its incidence is uncertain and many cases have previously been labelled as (steroid-resistant) PM. Rare familial cases have been described (Sivakumar *et al.*, 1997).

The characteristic pattern of muscle involvement, which is often asymmetrical, involves wasting and weakness of quadriceps, and distal weakness affecting finger flexion and ankle dorsiflexion. Symptomatic presentation is with falls due to the knees giving way and weakness of grip.

Dysphagia is relatively common and may be the presenting symptom (Houser *et al.*, 1998). Systemic features are not present. IBM has been reported in association with many other disorders, some autoimmune, but no consistent association has been recognized (Derk *et al.*, 2003).

2. Diagnosis and pathological features

The serum CK is normal or moderately elevated. EMG shows changes similar to those described for DM and PM but, in addition, "neuropathic" features (long-duration, high-amplitude motor unit potentials) are often present. Whether this truly reflects neurogenic involvement or is a secondary consequence of primary muscle disease remains much debated.

The diagnosis is established by light and electron microscopy (Griggs *et al.*, 1995). Characteristic features (Figure 4)

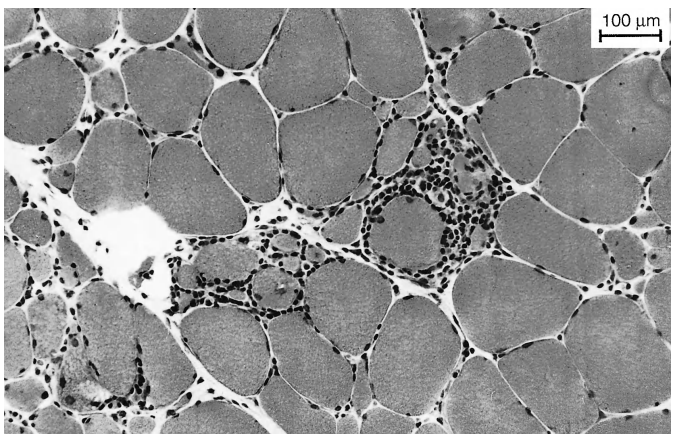

Figure 3 Polymyositis. Muscle biopsy (H&E X115). Note the endomysial inflammatory infiltrate

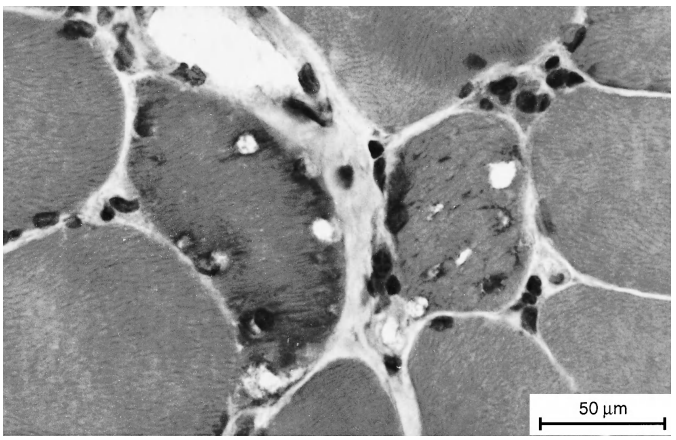

Figure 4 Inclusion body myositis. Muscle biopsy (H&E X460). Note the two fibers containing characteristic rimmed vacuoles

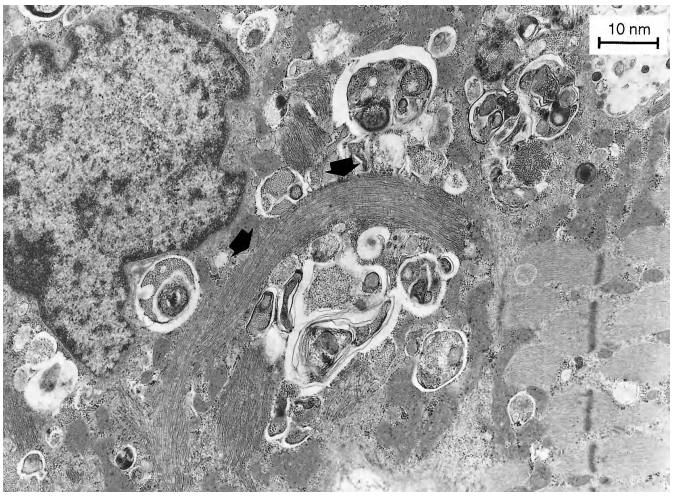

Figure 5 Inclusion body myositis. Muscle biopsy (electron micrograph X13,000). Bundle of characteristic 15-nm tubulofilaments (arrows)

include the variable presence of inflammatory infiltrates (with a predominance of cytotoxic T-lymphocytes), partial invasion of muscle fibers, rimmed vacuoles, intracellular amyloid deposits and, diagnostically, 15–18-nm tubulofilaments (Figure 5).

3. Pathogenesis

Pathogenesis remains hotly debated. Although there is evidence of T-cell mediated cytotoxicity, it is not clear that this is of primary importance. The presence of myonuclear abnormalities suggests that IBM may be due to a disorder primarily affecting the cell nuclei. Protein aggregates in the characteristic inclusions contain amyloid and other proteins typical of the inclusions seen in the brain in Alzheimer's disease. Despite the pathological similarities, there is no clinical link between the two disorders, but it has been postulated that there may be similar protein degradation abnormalities in each disorder (Askanas and Engel, 2003).

4. Treatment

IBM appears to show little or no response to immunosuppressive therapies of the type that are successful in DM and PM and many specialists no longer recommend using such drug regimes. Early suggestions that intravenous immunoglobulin might be helpful have not been substantiated (Dalakas *et al.*, 2001).

The disease shows a relentlessly progressive course with loss of ambulation 10–20 years after onset.

Toxic and Drug-induced Myopathies

Toxic and drug-induced myopathies is an important, and almost certainly underdiagnosed, group of disorders, not least because prompt removal of the offending agent may lead to full recovery. Ethanol can cause a dramatic acute myopathy. It is much debated whether proximal weakness in chronic alcoholics is primarily myopathic or neurogenic in origin. Myopathy may be seen in association with drug-abuse but of much greater significance are the myopathies associated with the therapeutic use of drugs.

Ethanol-related Myopathies

Three forms of myopathy have been attributed to alcoholism. Firstly, chronic alcoholics can develop painless proximal weakness, affecting the pelvic girdle more than the shoulder girdle. Serum CK may be modestly elevated. Muscle biopsy shows type II fiber atrophy (Preedy *et al.*, 2001). Secondly, acute alcoholic myopathy follows a binge. There is muscle pain, swelling and weakness, which may be localized to one or two muscles or be generalized. The serum CK is markedly elevated. Myoglobinuria is present and may threaten renal function. Recovery of muscle function occurs over 1–2 weeks. Muscle biopsy shows muscle fiber necrosis and inflammatory infiltrates. Thirdly, acute or subacute severe, painless, proximal weakness may be caused by hypokalemia. Potassium loss may be secondary to diarrhea or vomiting. Repletion of potassium leads to recovery.

Drug-induced

With the exception of drugs that cause hypokalemia, the pathogenetic basis of most drug-induced myopathies remains unclear (Argov *et al.*, 2001). In practice, the most useful classification is based on the clinical features of the myopathy (Table 4). Statins have been associated with several forms of myopathy. Although the incidence is low, their widespread, and ever-growing, use means that most clinicians will encounter statin-induced myopathy at some stage and thus it merits separate discussion.

1. Painless Myopathies

Painless myopathy is the most prevalent form of drug-induced myopathy, with corticosteroids being the commonest cause (Table 5). The clinical picture is of proximal weakness with either subacute onset or, more usually, chronic progression. Muscle atrophy develops in long-standing cases. Those drugs that produce hypokalemia may also cause intermittent (periodic) weakness.

The clinical features of corticosteroid myopathy and Cushing's syndrome are similar. Women are more susceptible to steroid myopathy than men and 9-α-fluorinated steroids (e.g. dexamethasone, betamethasone) have the greatest myopathic

Table 4 Patterns of drug-induced myopathy

Painless
Painful
Acute rhabdomyolysis
Periodic weakness
Focal

Table 5 Drugs causing painless myopathy

Amiodarone
Amphotericin[a]
Carbenoxolone[a]
Chloroquine
Colchicine
Corticosteroids
Diuretics[a]
Heroin
Liquorice[a]
Perhexiline
Purgatives[a]

[a]Drugs that cause hypokalemia.

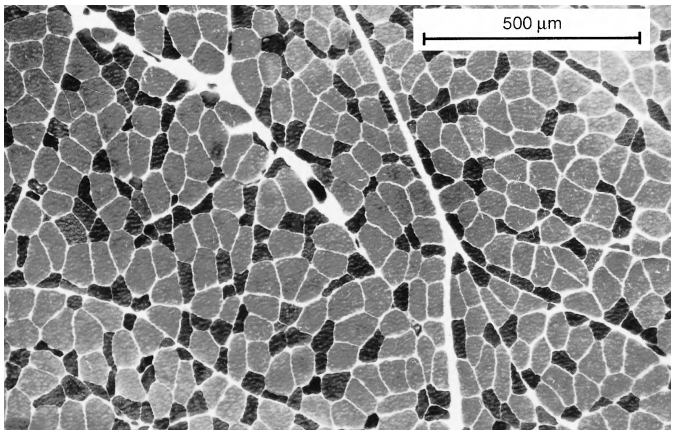

Figure 6 Type II fiber atrophy. Muscle biopsy (ATPase pH 9.4 X30). The type II fibers stain darkly

potential. The serum CK is usually normal. EMG may be normal or show "myopathic" features. Muscle biopsy shows nonspecific type II fiber atrophy (Figure 6). Full recovery usually follows drug withdrawal.

2. **Painful**

Many drugs may cause an acute or subacute painful myopathy and the list in Table 6 is certainly incomplete. Weakness is usually proximal but may be generalized and the muscles may be tender. The serum CK is often elevated and EMG shows changes of primary muscle disease. In some, there may be a direct toxic effect of the drug on muscle. In others, indicated in Table 6, there is an inflammatory myopathy.

3. **Acute rhabdomyolysis**

Acute rhabdomyolysis represents an extreme form of necrotizing myopathy with myoglobinuria and the clinical presentation is acute with severe generalized weakness and muscle pain. Muscle swelling may require fasciotomy and renal failure is common. Serum CK is very high. Drugs that cause this syndrome (Table 7) include drugs of abuse and addiction and drugs already noted to cause either painless or painful myopathy.

Table 6 Drugs causing painful myopathy

Amiodarone
Cimetidine[a]
Clofibrate
Cyclosporin
Danazol
D-Penicillamine[a]
Emetine
Gemfribrozil
Gold
Labetalol
Lithium
L-Tryptophan[a]
Nifedipine
Procainamide[a]
Salbutamol
Statins
Vincristine
Zidovudine

[a]Drugs causing an inflammatory myopathy.

Table 7 Drugs causing acute rhabdomyolysis

Amphetamine
Amphotericin B
Barbiturates
Carbenoxolone
Clofibrate
Cocaine
Diazepam
Gemfibrozil
Heroin
Isoniazid
Labetalol
Meprobamate
Methadone
Phenformin
Statins

4. **Periodic weakness**

Drug-induced hypokalemia (Table 5) may cause persistent or intermittent (periodic) weakness. Areflexia may be present during bouts of weakness. Serum CK may be elevated.

5. **Focal**

Intramuscular injection of many drugs may cause local tissue damage. Repeated injections, particularly of certain antibiotics, pentazocine, and opiates may lead to muscle fibrosis and contractures.

Statin-induced myopathies – Statins (HMG-CoA inhibitors) interfere with cholesterol synthesis and thus lower serum cholesterol levels. Already widely prescribed, some countries are now planning to allow these drugs to be sold over the counter. A variety of myopathic syndromes have been reported and they probably represent a spectrum relating to a common mechanism rather than separate mechanisms. Theories of causation include interference with intermediary energy metabolism but this has not yet been proved. Many reviews have appeared, mostly in the cardiology literature, and terms such as myositis and rhabdomyolysis have often

been used inappropriately causing some confusion (Rosenson, 2004).

Myopathic features include:

- Asymptomatic elevation of serum CK
- Myalgia with elevated serum CK (probably the commonest)
- Myalgia with normal serum CK
- Acute rhabdomyolysis with risk to renal function

The risk is higher when the statin is started at a high dose, and when combined with certain other drugs, notably fibrates and cyclosporin. Although it has been suggested that a preexisting myopathy increases the risk of statin-induced myopathy the evidence is not convincing, and it should certainly not be considered an absolute contraindication to their prescription. There have been many reports of patients who have been identified as having a myopathy (e.g. McArdle's disease) following investigation of an elevated serum CK, which was measured only because the patient was on a statin! Another important catch is the patient with subclinical hypothyroidism causing myalgia, hypercholesterolemia, and an elevated serum CK. Interpretation of symptoms such as myalgia is difficult when patients have been forewarned of its possibility. Despite the low incidence of statin-induced myopathy it is recommended in the United States that CK be measured before starting a statin, but that regular monitoring of CK is unhelpful (Pasternak *et al.*, 2002). Patients should be counseled at the time of prescription about the potential myopathic effects and to report symptoms such as myalgia, weakness, or myoglobinuria.

Endocrine and Metabolic Myopathies

Myopathy, typically in the form of chronic painless proximal weakness, is common in endocrine disorders and of particular importance because treatment of the underlying disorder almost invariably leads to full recovery (Hilton-Jones *et al.*, 1995). In the elderly the most frequently encountered endocrine myopathies are those associated with thyroid disease, glucocorticoid excess (Cushing's syndrome and iatrogenic steroid myopathy) and disorders of vitamin D metabolism.

Thyroid Disorders

1. **Hypothyroidism (*see* Chapter 120, Thyroid Disorders)**

Symptomatic myopathy is present in about 80% of patients with hypothyroidism but is rarely the presenting feature. Symptoms include weakness (mild and proximal), fatigue, stiffness, and myalgia. Examination may show delayed tendon reflexes, and myoedema – a ridge or mound of contracted muscle seen transiently after pinching or percussing muscle.

The serum CK is elevated, often markedly, in most patients and thyroid function studies should be performed in any patient with unexplained elevation of the CK.

Thyroid function studies are invariably abnormal and the myopathy resolves on restoration of the euthyroid state.

2. **Hyperthyroidism (*see* Chapter 120, Thyroid Disorders)**

Up to one-half of thyrotoxic patients will have weakness as a symptom and over 80% of patients have signs of weakness at presentation. Onset of myopathy is usually subacute or chronic and the weakness, which is proximal, is generally greater than that seen in hypothyroid myopathy. However, in thyrotoxic myopathy the serum CK is often normal. The weakness resolves upon resolution of the thyrotoxicosis.

3. **Graves' ophthalmopathy**

Thyroid-associated eye disease, although most frequently associated with hyperthyroidism, can occur in euthyroid and hypothyroid patients (El-Kaissi *et al.*, 2004). Diplopia may be the only feature but the typical order of progression of eye symptoms and signs is: eyelid lag and retraction, itchiness, redness of the conjunctivae, eyelid swelling, proptosis, diplopia, corneal ulceration, papilloedema, and optic nerve compression. These changes may be unilateral.

Biochemical evidence of thyroid dysfunction is usually readily evident but if thyroid-associated eye disease is suspected and serum thyroid hormone and thyroid-stimulating hormone levels are normal, then immunological studies may be helpful (Gunji *et al.*, 1998).

Orbital ultrasonography, CT, and MRI show characteristic extraocular muscle swelling which may aid diagnosis if laboratory support for the diagnosis is lacking.

The first stage of treatment is to return thyroid function to normal. If major eye signs persist, options include surgical decompression of the orbit, steroids, and orbital irradiation (Bartalena *et al.*, 2000).

Pituitary-adrenal Axis Disorders (see Chapter 119, The Pituitary Gland)

The clinical features of Cushing's syndrome (whether pituitary, adrenal, or ectopic) and iatrogenic steroid myopathy (see the earlier sections) are similar (Hilton-Jones *et al.*, 1995). Weakness starts around the pelvic girdle and later ascends to the trunk and then the shoulder girdle musculature. Myalgia is common. It is rare for myopathy to develop without other features of glucocorticoid excess.

The serum CK is usually normal, EMG shows myopathic features and muscle biopsy shows type II fiber atrophy (Figure 6). The myopathy resolves once the glucocorticoid excess is removed.

Rarely, an acute myopathy (acute quadriplegic myopathy – AQM) may develop following high-dose parenteral steroid therapy, with or without concomitant use of neuromuscular blocking agents, for example, for the treatment of myasthenia gravis or status asthmaticus (Argov, 2000). Pathologically, it is characterized by loss of thick (myosin) filaments (Perea *et al.*, 2001).

Disorders of Vitamin D Metabolism (see Chapter 108, Age-related Changes in Calcium Homeostasis and Bone Loss)

The myopathic disorders associated with osteomalacia and with primary hyperparathyroidism show clinical similarities (Hilton-Jones *et al.*, 1995).

1. **Osteomalacia**

Pelvic girdle weakness, causing a waddling gait and difficulty climbing stairs and getting out of low chairs, is the presenting symptom in about one-third of patients with osteomalacia (Schott and Wills, 1976). It is almost invariably associated with bone pain, most prominent in the ribs, pelvis, and femora.

The serum CK is usually normal, as is muscle biopsy, although nonspecific changes may be seen.

With appropriate treatment the weakness slowly improves, but the bone pain usually resolves more rapidly.

2. **Primary hyperparathyroidism (*see* Chapter 118, Endocrinology of Aging)**

Weakness and fatigue may be late features of primary hyperparathyroidism but it is not clear whether this is neurogenic or myopathic in origin (Hilton-Jones *et al.*, 1995). Successful treatment (usually involving removal of a solitary parathyroid adenoma) leads to resolution of the neuromuscular symptoms.

Paraneoplastic Myopathies

Up to 20% of patients with DM, but probably significantly more in the elderly, have an associated malignancy (see in the earlier sections) but the pathogenetic mechanism is unclear.

Serum electrolyte disturbances (hypokalemia, hyperkalemia, hyponatraemia, and hypercalcemia) caused by neoplastic disorders, including tumors of endocrine glands, are one cause of paraneoplastic muscle weakness. Benign or malignant tumors of endocrine glands may also cause weakness through hormone deficiency or excess (Hilton-Jones, 1994).

The term carcinomatous neuromyopathy is sometimes used to describe a syndrome of proximal weakness and wasting (usually pelvic more than shoulder girdle), of subacute or chronic course, and with depressed tendon reflexes. Most evidence suggests that this is probably neurogenic rather than myogenic in origin.

INHERITED MYOPATHIES

Muscular Dystrophies

The term muscular dystrophy encompasses a group of progressive, inherited disorders in which the primary pathological process is degeneration of muscle fibers. Although clinically highly variable, common histological features include muscle fiber necrosis, abnormal variation in fiber size, central nucleation, fiber splitting, and replacement of muscle by fibrous tissue.

Table 8 Classification of the muscular dystrophies

X-linked inheritance
– Duchenne
– Becker
– Emery-Dreifuss
Autosomal dominant inheritance
– Facioscapulohumeral
– Oculopharyngeal
– Limb-girdle
– Emery-Dreifuss
Autosomal recessive inheritance
– Limb-girdle

The classification of the muscular dystrophies is in a state of change as the genetic and molecular basis of each disorder is identified. In everyday clinical practice, the most useful classification is based upon the mode of inheritance and phenotype (Table 8). Myotonic dystrophy is considered separately (see in the following sections). Most muscular dystrophies present in childhood or early adult life, but there are important exceptions (including myotonic dystrophy). Some may first present in middle and late middle age, while others may be asymptomatic and be identified serendipitously when a relative is assessed following identification of another affected family member.

Dystrophinopathies

Duchenne and Becker muscular dystrophy are allelic disorders. A mutation causing complete absence of the protein dystrophin causes the severe Duchenne phenotype, but mutations resulting in the production of some functional dystrophin cause Becker muscular dystrophy, which itself has a variable clinical presentation.

In Duchenne muscular dystrophy, the onset is between 2 and 4 years of age, and death occurs in early adult life. In typical Becker muscular dystrophy onset is during adolescence. Rarely, first presentation, with pelvic weakness, may occur in late middle age (Bosone *et al.*, 2001). Cardiomyopathy is common and may be severe even in the absence of significant skeletal muscle weakness (Muntoni *et al.*, 2003).

About 10% of female Duchenne/Becker dystrophy carriers may manifest myopathic features, ranging from asymptomatic calf hypertrophy to severe limb-girdle weakness, the latter sometimes not presenting until middle age.

Limb-girdle Dystrophies

About 90% are autosomal recessive and 10% autosomal dominant. The common phenotype is progressive limb-girdle weakness, usually affecting the pelvic girdle more than the shoulder girdle, but with a very wide range of age of onset and severity. In the majority, presentation is in childhood or early adult life. A few are associated with

cardiomyopathy. None typically present beyond middle age. Diagnosis depends upon immunohistochemical techniques applied to muscle biopsy, and DNA analysis

Facioscapulohumeral (FSH) Muscular Dystrophy

FSH muscular dystrophy is relatively common (prevalence about 2/100 000 population). It is an autosomal dominant disorder associated with deletion of a repeat sequence, not within a gene, on chromosome 4.

The name describes the highly characteristic pattern of early muscle involvement. The patient may not be aware of facial weakness and it may be missed by an inexperienced clinician. The patient may report an inability to whistle, use a straw, or blow up balloons. Weakness and wasting of the scapular fixator muscles (Figures 7 and 8) limits upper limb abduction and patients complain of difficulty combing their hair and reaching up to shelves. There is weakness and wasting of the humeral muscles (biceps more than triceps) but preservation of deltoid. Unlike other forms of muscular dystrophy the weakness is often asymmetric (Figure 9). Tibialis anterior is involved early and weakness is nearly always found on examination. The patient may have symptomatic foot drop.

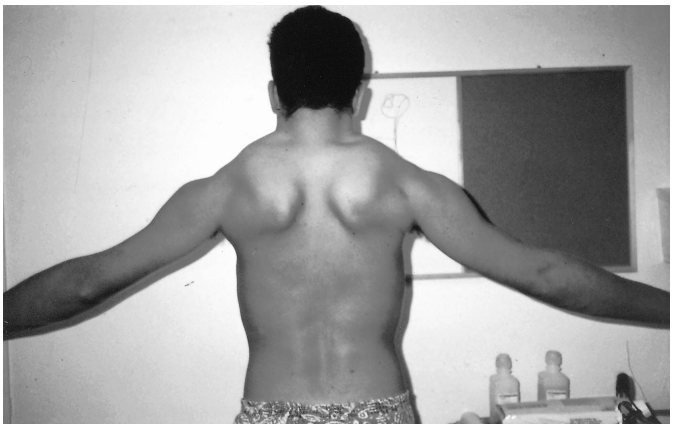

Figure 7 Facioscapulohumeral muscular dystrophy. (See text)

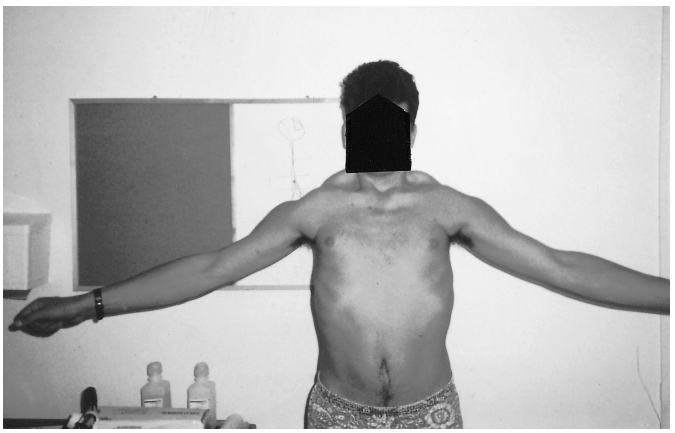

Figure 8 Facioscapulohumeral muscular dystrophy. (See text)

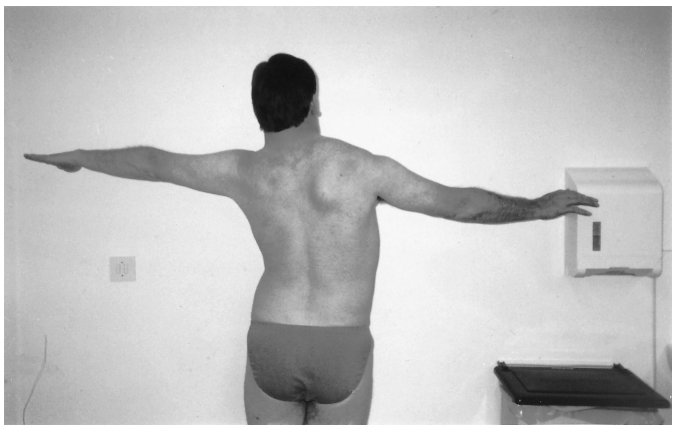

Figure 9 Facioscapulohumeral muscular dystrophy. (See text)

The age of onset is highly variable but is typically in adolescence and early adult life. Mildly affected cases are common, and family studies frequently identify asymptomatic individuals with mild weakness. There is slow progression of the weakness, with later involvement of the pelvic girdle.

The serum CK may be normal or modestly elevated. Diagnosis is by DNA analysis.

Oculopharyngeal Muscular Dystrophy

This is an autosomal dominant, late-onset, disorder which is probably underdiagnosed (Brais, 2001). Onset is usually in the fifth decade, or later, and most frequently with ptosis (Figure 10), which can be asymmetric. There is overactivity of frontalis in an attempt to compensate for the ptosis (Figure 10). Dysphagia develops within a few years and is occasionally the presenting symptom.

In later stages, eye movements may be restricted (external ophthalmoplegia) but diplopia is rare. Limb involvement is usually confined to mild shoulder girdle weakness, but the pelvic girdle can be involved and rarely there is more debilitating limb weakness.

Ptosis can be severe enough to impair vision – surgical correction can be highly successful. Dysphagia may respond to esophageal dilatation or cricopharyngeal myotomy but requires detailed preoperative assessment.

Diagnosis is by DNA analysis, demonstrating an expansion in the PABPN1 gene. The differential diagnosis of late-onset ptosis and dysphagia includes myasthenia gravis and mitochondrial chronic progressive external ophthalmoplegia (CPEO) (see in the following sections).

Myotonic Dystrophy

Two forms of myotonic dystrophy (DM) are now recognized, sharing a common molecular mechanism. They are autosomal dominant multisystem disorders. In each, an unstable

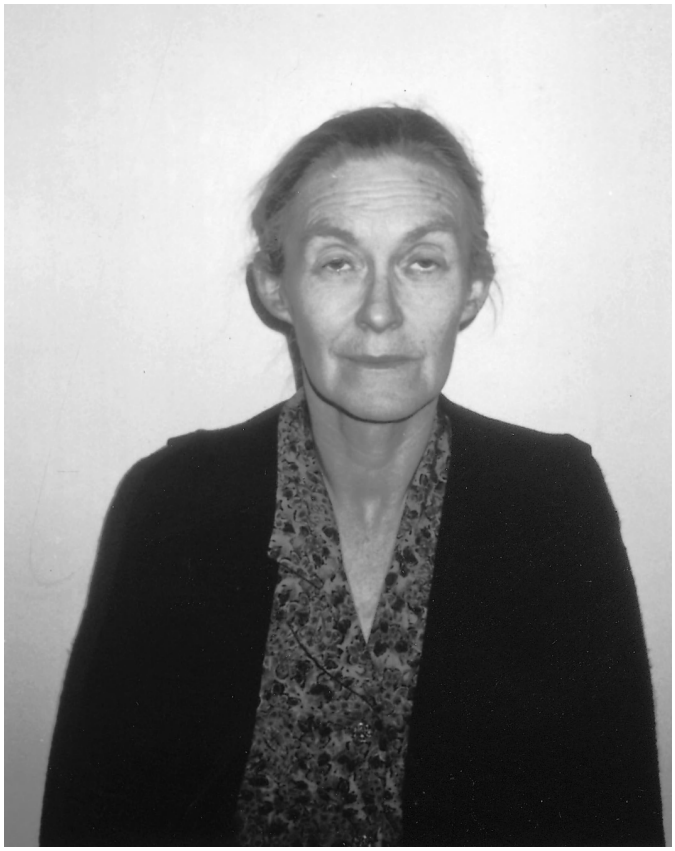

Figure 10 Oculopharyngeal muscular dystrophy. (See text)

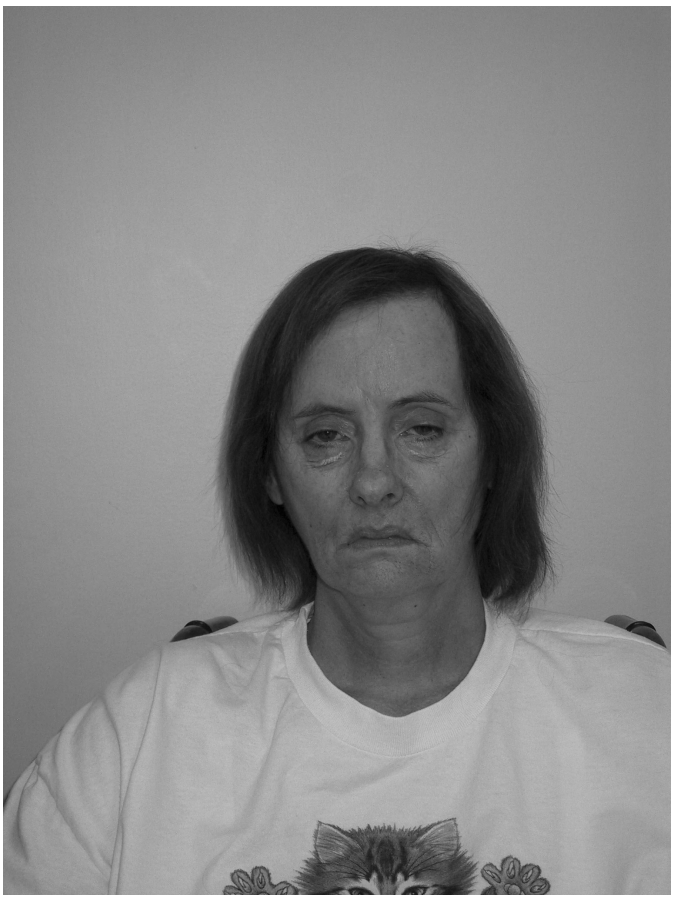

Figure 11 Myotonic dystrophy. Characteristic facial appearance. Note the ptosis, and wasting of the facial muscles and temporalis

nucleotide repeat expansion probably has its effect through disruption of mRNA metabolism (Ranum and Day, 2004). Diagnosis is by DNA analysis.

DM1 is the commonest form of muscular dystrophy in adult life (Harper, 2001). The disease shows anticipation, by which subsequent generations tend to show a more severe expression of the disease, as a result of the instability of the underlying repeat expansion.

Clinical features of the 'classical' form include onset from late-childhood to middle age, ptosis, weakness that involves initially facial muscles (Figure 11), sternomastoid, and distal upper limb muscles but later spreads to proximal muscles, respiratory muscle involvement, frontal balding, cataracts, cardiac conduction defects, gonadal atrophy and impaired fertility, excessive daytime sleepiness and impaired smooth muscle function. Myotonia is most evident in the hands and patients complain of difficulty in relaxing their grip. Overall, IQ scores are lower than average. A severe congenital form is seen in a proportion of children born to mothers who themselves have the later-onset form.

In family studies it is common to identify family members in late middle age who are unaware that they have the disorder. They may be asymptomatic, but frequently have had cataracts that were not recognized as being due to myotonic dystrophy. Even though oligosymptomatic, it is important to identify such patients because they are still at risk of developing cardiac conduction defects and respiratory insufficiency (with particular risk of both during and after anesthesia).

Major management issues include the identification and appropriate treatment of cardiorespiratory problems, and identification of asymptomatic family members who carry the gene and are at risk of themselves developing cardiorespiratory problems or, for women, of having a congenitally affected child (Harper *et al.*, 2004).

DM2 shows many similarities, but tends to be a relatively milder disease presenting later in life, and the weakness is more proximal than distal (Day *et al.*, 2003). Muscle pain is a common presentation.

Chronic Progressive External Ophthalmoplegia (CPEO)

Progressive ptosis and limitation of eye movements, with or without diplopia, may be seen in a number of disorders (Table 9). Myasthenia gravis must always be considered and diagnosis can be difficult if the disease is limited to the ocular muscles. In oculopharyngeal muscular dystrophy, ptosis is an early feature but limitation of eye movements occurs late and is rarely severe.

Table 9 Differential diagnosis of chronic progressive external ophthalmoplegia

Myasthenia gravis
Oculopharyngeal muscular dystrophy
Mitochondrial cytopathy
Thyroid eye disease

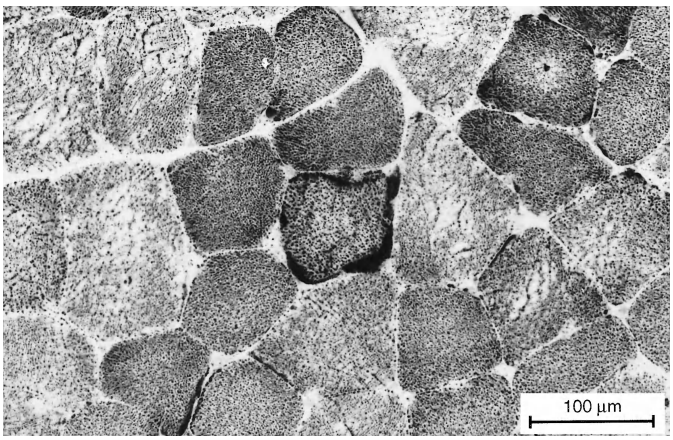

Figure 12 Mitochondrial cytopathy. Muscle biopsy (Modified Gomori trichrome X230). Note the single ragged red fiber

Most patients with mitochondrial CPEO have an abnormal muscle biopsy showing ragged red fibers (Figure 12). Mitochondrial DNA studies typically show a deletion. In the elderly, most cases are sporadic, but autosomal forms exist (Agostino *et al.*, 2003).

Acknowledgment

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KEY POINTS

- Drug-induced myopathies are common and underdiagnosed.
- Statins are likely to become the commonest cause of drug-induced myopathy.
- A few inherited myopathies may not present until late middle age.
- The history and examination are generally more powerful tools than laboratory investigation.
- Inclusion body myositis is the commonest acquired myopathy in the elderly.

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Motor Neurone Disease

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The first clear account of motor neurone disease (MND) emerged from the Salpetriere Hospital in Paris in the mid-nineteenth century (Charcot and Joffroy, 1869). The timing of this description, about 50 years after the start of the industrial revolution raises speculation about neurotoxin exposure resulting in anterior horn cell damage. MND care remained fragmented, well into the 1980s (Newrick and Langton-Hewer, 1984) and it is only in the last 20 years that the disease has received much public and professional attention. Inroads have been made into understanding its pathophysiology, attempts at slowing disease progression have met with some, *albeit* limited, success and our ability to help patients and their families deal with this unpleasant condition has increased markedly. In part, we owe the increased profile of MND to a few well-publicized public figures who have recently suffered from the disease; for instance, David Niven, the actor and Lou Gehrig, the sportsman. The role of patient support organizations in many different countries must also be acknowledged in bringing the disease into public and professional limelight and for fighting their corner to obtain more resources for treatment and research. It is also likely that a change in the ethos of neurological practice from being largely a diagnostic service (as was the case 30 years ago) to also being a therapeutic service has played a role in this development. Well-publicized cases of patients campaigning on "end-of-life" issues have further put MND into public attention. Much of the current medical and legal interest in euthanasia and physician-assisted suicide has centered on MND and similar disorders. New developments in medications, both disease-modifying (Lacomblez *et al.*, 1996) and those involved in symptom control, assistive technology, and innovative health-care delivery systems have given hope and relief to patients with MND and to their caregivers. Multidisciplinary teams are now widely involved in MND care and there is a greater acceptance of involving palliative care services at an early stage.

DEFINITION AND TERMINOLOGY

Motor neurone disease can either be used as a narrow term describing the condition also known as *amyotrophic lateral sclerosis* (ALS) or it can be a more general term for other motor neurone diseases including bulbar palsy and progressive muscular atrophy (PMA) which are closely allied to ALS and others such as Kennedy's disease or Hirayama disease that have a less clear association. Conditions such as progressive bulbar palsy and PMA can develop into ALS although pure forms of these conditions also occur. Bulbar-onset MND is a more rapidly progressing condition and carries a worse prognosis than limb-onset disease. PMA can either be a very slowly progressive disorder with an outlook better than for ALS or can progress rapidly sometimes over a few months. This bimodal distribution of survival makes accurate prognosis difficult to give at initial diagnosis of PMA. It is further complicated by the fact that in over half of all cases of PMA the corticospinal tracts are involved (at autopsy) and ubiquitin inclusions typical of MND are also found in the central nervous system (CNS) (Ince *et al.*, 2003). Bulbar symptoms and signs are seen in a minority of patients with PMA. The spinal muscular atrophies are a heterogeneous group of allied conditions that are recessively inherited and can cause symptoms starting in childhood or in adult life. Childhood-onset varieties tend to be more rapidly progressive. This chapter deals largely with the ALS form of MND.

Bulbar palsy remains a useful term referring to dysarthria and/or dysphagia being the presenting symptoms but in most cases the condition eventually progresses to a clinical picture similar to that of MND. The usefulness of the term, bulbar palsy is a prognostic one – the life expectancy in bulbar palsy, that is, bulbar-onset MND is significantly worse than in limb-onset MND. A subcommittee of the World Federation of Neurology made a significant contribution to the

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definition of MND or ALS when it met in El Escorial to formulate a set of internationally agreed diagnostic criteria (Brooks *et al.*, 2000). The El Escorial criteria for diagnosis of possible, probable, or clinically definite MND have made it possible to directly compare the results of research investigations carried out in different countries. Having said this, the El Escorial criteria are not free of difficulties and it is likely that they will be modified and updated over the years (summarized in the following text).

Definite ALS: Upper and lower motor neurone signs in bulbar and two spinal regions or in three spinal regions (cervical, thoracic, and lumbosacral).

Probable ALS: Upper and lower motor neurone signs in at least two regions with some of the upper motor neurone signs rostral to the lower motor neurone signs.

Probable ALS/Laboratory supported: Upper motor neurone signs in at least one region and lower motor neurone signs on electrodiagnostic testing in at least two regions.

Possible ALS: Upper and lower motor neurone signs in one region (the same region) or upper motor neurone signs in two or three regions or upper and lower motor neurone signs in two regions with no upper motor neurone signs rostral to the lower motor neurone signs.

The term "suspected ALS" was dropped in 1998 revised criteria. It previously referred to a condition in which lower motor neurone signs were found in two or three regions.

Certain clinical features were listed as deflecting one from the diagnosis (although not absolute exclusions). These included sensory dysfunction, sphincter disturbance, autonomic signs, visual abnormalities, involuntary movement disorder, and cognitive dysfunction.

CLINICAL FEATURES

MND is a progressive neurodegenerative disorder of the upper and lower motor neurones, resulting in weakness, muscle wasting, fasciculation, and spasticity as a part of the clinical picture. There is a profound difference between the motor pathways, which are severely affected and the sensory pathways, which are relatively preserved. Sensory pathway involvement is sufficiently unusual as to spark off a search for an alternative diagnosis. About one-third of patients with MND present with bulbar symptoms, the others with limb problems (Tandan, 1994). Only a few have other initial presentations such as dementia or respiratory failure. These groups follow significantly different clinical courses and the distinction between them remains important. Furthermore, the diagnostic pitfalls in the two main modes of presentation may be quite different. For instance, myasthenia gravis is more likely to be a differential diagnosis for bulbar-onset disease than for limb-onset MND and vice versa for cervical spondylosis. Confusion persists over the use of the term "progressive muscular atrophy". Many patients who appear not to have any signs of upper motor neurone dysfunction at disease onset later develop these and therefore satisfy the diagnostic criteria for MND. A few, however, do not develop such signs and may have a very long, protracted course of progression. Some of these can be found at postmortem examination to show features indistinguishable from ALS despite the lack of clinically apparent upper motor neurone signs. It is debatable whether this condition with its highly variable clinical course should be regarded as MND or ALS or whether it represents a truly distinct disorder.

MND is slightly more common in men and the mean age at presentation is about 57 years (Tandan, 1994). This is a few years younger than the mean age for other neurodegenerative disorders of adult life, such as Parkinson's disease (PD) and Alzheimer's disease. A few patients with MND develop parkinsonism as well and a further few develop dementia. (Hedera *et al.*, 1995). The dementia of MND is a frontotemporal one and distinct from Alzheimer's disease. It is characterized by behavior disturbance, impaired judgment, language, and memory problems and a dysexecutive state (Neary *et al.*, 1990). Only small numbers of patients develop these features but they do underline the point that common mechanisms of disease etiology may be involved in these seemingly disparate disorders. In an even smaller number of cases, patients can present with simultaneous development of both ALS and PD-like features.

LIMB-ONSET MND

It can arise in either arms or legs and common modes of presentation are with weakness, wasting, cramp, spasms secondary to spasticity, and fasciculation. The symptoms are progressive usually over a period of months or occasionally over a few years. Loss of manual dexterity secondary to involvement of small hand muscles is a frequent presenting symptom, as is a disturbance in gait, and in older patients, falls. A cramp in muscles not normally thought of as being prone to cramp, for instance, forearm flexors or abductor pollicis brevis can be a useful clinical pointer. A history of progression is an essential requirement for the diagnosis. The disease commonly starts in just one limb. Clinical and prognostic separation of different limb-onset varieties of MND is still poorly developed but distinct entities such as flail arms MND, hemiplegic MND, and paraplegic MND are recognized. Pain, which is not uncommon in late disease (O'Brien *et al.*, 1992) is usually not a problem at presentation and its early occurrence should encourage a search for alternative diagnoses. Although fasciculation is seen very commonly in MND, it is unusual for prominent fasciculation to be the sole presenting symptom in MND but it is a common symptom in patients with benign fasciculation or those with a fear of developing MND. Patients with a family history of MND are exceptions, in that they frequently have fasciculation as a presenting symptom. The early recognition of the significance of fasciculation may be ascribed to having seen it before in other family members with the disease.

BULBAR-ONSET MND

This is somewhat more frequent in women (Tandan, 1994) (unlike limb-onset disease) and the first presentation is usually with dysarthria or anarthria. Progression from dysarthria to anarthria can, in some cases, be so rapid as to lead to an erroneous diagnosis of stroke. Dysphagia is also common in the disease but is a surprisingly infrequent presenting symptom. Incidentally found aspiration pneumonitis, particularly recurrent aspiration, should alert the physician to the possibility of MND. Choking spells are also uncommon at presentation. Dyspnea secondary to respiratory muscle weakness with or without aspiration pneumonitis is another rare mode of presentation but can become a more troublesome problem later in the disease, as discussed below. Emotional lability is often encountered but only rarely at first presentation and then not as troublesome as other bulbar symptoms.

In establishing a diagnosis of MND the absence of certain symptoms is just as helpful as the presence of others. Sensory symptoms are usually absent in MND and when present, they are usually trivial in comparison with the motor problems. When sensory symptoms are present, it is usually in more advanced disease so that the presence of sensory symptoms in a patient at first presentation should activate a search for a condition other than MND. Clinically relevant sensory signs are even less common and when they are found, are often attributed to, but cannot always be explained by, the consequences of nutritional deprivation or pressure palsies secondary to profound wasting and weakness. Sophisticated electrophysiologic measurements can demonstrate involvement of sensory pathways in up to 50% of patients (Shefner *et al.*, 1991a). Certain other pathways are relatively spared in MND. These include innervation of the bladder. Urinary urgency and frequency, encountered so commonly in other patients with limb spasticity are very uncommon in MND. Similarly, it is curious that the anterior horn cells responsible for eye movements should be relatively resistant to the diffuse process that damages other anterior horn cells in MND. In societies where invasive artificial ventilation is used more often than in the United Kingdom for late stage MND, ocular motor abnormalities have been described more often indicating that these pathways are only partly resistant to the disease process (Okamoto *et al.*, 1993). Cognitive function is also relatively spared in the majority of cases of MND but as mentioned above, there is a small subgroup of MND sufferers who develop a progressive dementia (Neary *et al.*, 1990) and others without dementia can be shown to have neuropsychological evidence of frontotemporal dysfunction.

Troublesome symptoms developing during the course of MND and their treatment are discussed later in this chapter.

FAMILIAL MND

It is reported that up to 10% of MND is familial and inherited in an autosomal dominant pattern. The age of onset and the clinical course of this condition are very similar to that of the sporadic disease, indicating that common mechanisms are probably involved in disease causation. Interest in this condition increased with finding mutations in the gene encoding superoxide dismutase type 1 (SOD 1) in about 10% of families with this disease (Rosen *et al.*, 1993). A large number of missense mutations and a few nonsense mutations and deletions have been identified in SOD 1 in familial MND. The clinical course of the familial disease is similar to that of the sporadic disease. Some mutations (e.g. A4V) encode for more rapidly progressive disease than others (e.g.G37R) (Cudkowicz *et al.*, 1997). SOD 1 MND more commonly starts in the legs. Other genes have also been identified as causing MND (Alsin or ALS2) but none are as well studied as SOD 1. Various genetic loci are also linked with familial MND but the genes and gene products are unknown (ALS 3–5). Both dominant and recessive patterns of inheritance are identified. The X-linked disorder Kennedy's disease or spinal bulbar muscular atrophy (SBMA) is an MND-like disorder with a better outlook than MND and should be considered in cases where maternal transmission of MND is likely or when specific clinical features (see section on differential diagnosis below) alert one to the diagnosis. It is caused by an unstable expansion of a CAG repeat in exon 1 of the androgen receptor gene (La Spada *et al.*, 1991). There are various genetic factors that may alter disease expression in sporadic MND. For instance, homozygous survival motor neurone 2 (SMN2) gene mutations are over represented in the MND population but SMN1 seems normal (Veldink *et al.*, 2001). SMN mutations are linked with recessive, childhood-onset spinal muscular atrophy. Mutations in the gene encoding vascular endothelial growth factor (VEGF) (Lambrechts *et al.*, 2003) may also have a disease-modifying effect. Other potential genetic risk factors for MND include mutations in the apurinic/apyrimidinic endonuclease (APEX nuclease) gene (Hayward *et al.*, 1999), the neuronal apoptosis inhibitory polypeptide (NAIP) gene (Jackson *et al.*, 1996), cytochrome c oxidase gene and the APO E4 genotype. Young patients with an MND-like syndrome may have mutations in the hexosaminidase A gene, causing an accumulation in tissues, of GM2 ganglioside. The principles of investigation and management of familial disease are the same as those of sporadic MND with the exception of issues of genetic counseling and perhaps additional psychological support for those patients who have nursed other family members through a distressing and ultimately fatal condition. Genetic counseling is made more difficult by the incomplete penetrance of the mutant gene. At present, gene testing is in its early stages and probably still best regarded as a research tool rather than a help in the management of familial MND (FALS). In time to come this may change and leave us facing the same dilemmas and difficulties faced by those looking after patients with Huntington's disease (Simpson and Harding, 1993) and other genetic disorders that can be identified at a presymptomatic stage and for which there is no effective treatment to alter the course of the disease. Where ethical considerations permit this, FALS may give us our best opportunity to study the effects of potentially neuroprotective strategies in altering the

course of disease expression in presymptomatic individuals who are known to carry pathogenic disease mutations.

The human SOD 1 mutant gene has made it possible to develop a very good mouse model of MND (Gurney *et al.*, 1994). This allows screening of potential therapeutic compounds before they are tried on patients.

CLINICAL COURSE

Both, bulbar-onset and limb-onset MND progress inexorably and the disease proves ultimately fatal. The rate of progression is variable but the clinical course is more predictable than for many other fatal conditions such as some of the malignant diseases. This point is important in enabling the health-care needs of patients to be anticipated and planned for. Median survival in MND is approximately 3 years from the first symptom. Survival up to 5 years and beyond is certainly seen but it is unusual for patients with MND to survive 8 years and very unusual to survive 10 years. Survival to 8 years or beyond should activate a search for alternative diagnoses. This figure may have to be revised as the survival of patients is prolonged by improved care and by drug interventions some of which are already proving promising (Lacomblez *et al.*, 1996; Lai *et al.*, 1997). Despite the anecdotal observation of more patients surviving to previously exceptional durations of disease, systematic studies do not show an overall increase in survival in MND. Although some patients appear to go through periods of relative stability, these are the exception rather than the rule in MND. Each 6-month period usually sees an increase in disability (Brooks *et al.*, 1995).

There is a male preponderance in MND. Women are overrepresented in the bulbar-onset group and have worse prognosis than men. Other prognostic factors include short latency between symptom onset and diagnosis (perhaps coding for more rapidly advancing disease), older age at presentation and poor social support network. MND patients with a spouse-carer live longer (del Aguila *et al.*, 2003).

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC PITFALLS

Motor neurone disease does not have a diagnostic test and is a progressive condition leading to death in 3–5 years in the majority of cases. This makes it imperative that due consideration be given to looking for alternative diagnoses that may be more treatable or carry a better outlook. Diagnostic errors are more likely to happen if there is pressure to diagnose the condition in its early stages. This is happening now owing to advances in treatment and to increased publicity for the disease. One group who worry about having MND includes patients with a limited knowledge of MND, who have fasciculation either as a constant finding or more often as an intermittent symptom, confined to one muscle or segment such as one calf. In the absence of other signs of a progressive disorder these patients are likely to have benign fasciculation requiring explanation and reassurance but no other intervention. Some other diagnostic pitfalls are discussed below but the list is not an exhaustive one. In an Irish study of diagnostic pitfalls, errors included patients regarded as having clinically definite or clinically probable MND who later turned out to have postpolio syndrome or Kennedy's disease (Traynor *et al.*, 2000).

CERVICAL AND/OR LUMBAR SPONDYLOSIS (*see* Chapter 85, Cervical and Lumbar Spinal Canal Stenosis)

Spinal root and cord compression by cervical and lumbar spondylosis is common. Root compression can lead to segmental muscle wasting and weakness and is the commonest cause of calf muscle fasciculation. Although in the younger patient this is usually a single segment, in the elderly, multiple root compression can cause quite widespread lower motor neurone signs. This combined with the spasticity that can be caused by spinal cord compression can mimic MND. Usually there are clinical pointers that enable a distinction to be made between the two conditions. Sensory pathways are commonly involved in spondylosis but are spared in MND, bladder disturbance is very uncommon in MND but relatively more frequent in spondylotic myelopathy, neck pain, and restriction of neck movements are more common in spondylosis than in MND at its onset. Bulbar signs, when present, clearly point more strongly toward MND. Tongue wasting with fasciculation can be diagnostic in this setting and other bulbar signs can be suggestive – for instance, brisk jaw jerk or jaw clonus, spastic dysarthria, or emotional lability.

OTHER SPINAL PATHOLOGY

In the absence of bulbar findings and sometimes even with a few bulbar symptoms and signs, the distinction between MND and spinal conditions such as syringomyelia can be difficult (a few patients with syringomyelia present with motor rather than sensory features) and may necessitate spinal MRI. Other intrinsic spinal pathology may also mimic MND but such cases are rare in the western world. Cysticercosis of the spinal cord has been linked with an MND-like presentation (Kurland, 1977) and needs to be considered in endemic areas particularly when the presentation is with a disturbance in one limb, so-called monomelic myelopathy or amyotrophy. Hirayama disease is a term applied to a disorder of younger men causing distal and usually unilateral amyotrophy of an arm (Restuccia *et al.*, 2003). It can be familial and may involve dynamic spinal cord compression during neck flexion, resulting in damage to genetically predisposed anterior horn cells. The flail arm presentation

of MND may be an example of bilateral involvement in Hirayama disease. Inherited disorders of spinal neurones can be mistaken for MND including its familial form. Hereditary spastic paraparesis can be a predominantly motor disorder of the upper motor neurones, and lower motor neurone disturbance is not a feature but spontaneous clonus can mimic fasciculation and the unwary can be caught out. The prolonged history and relatively indolent clinical course are also powerful indicators away from MND (Figlewicz and Bird, 1999). A sporadic upper motor neurone disturbance is also sometimes seen and in the few patients who are found to have oligoclonal immunoglobulins in their cerebrospinal fluid (CSF) a label of chronic progressive multiple sclerosis is applied; probably incorrectly in patients with normal or atypical MR head scans. The absence of any sensory difficulties may also make this label inaccurate. The term *primary lateral sclerosis* was coined to describe those patients who have a slowly progressive upper motor neurone disturbance without sensory symptoms or signs. The progression of this condition is slower than that of MND (Bruyn *et al.*, 1995). Spinal muscular atrophies, previously classified as forms of MND are now recognized as distinct disorders with a more benign course. The recessive inheritance of these conditions is also quite different from the dominantly inherited familial MND. Kennedy's syndrome or X-linked bulbospinal neuronopathy is a disorder characterized by lower motor neurone disturbance of spinal and bulbar neurones and was previously frequently mislabeled MND. This should not happen now as certain morphologic features such as gynecomastia should lead to the search for the trinucleotide repeat expansion in the androgen receptor gene (La Spada *et al.*, 1991). A family history suggestive of an X-linked disorder may also help but this is not usually the case in societies with small nuclear families where the number of at-risk individuals may be small and where the medical condition of relatives such as maternal uncles may not be known. Sandhoff disease, a variety of gangliosidosis with hexosaminidase A deficiency, can present in an MND-like fashion and needs to be considered as a possible diagnosis in any very young patient with apparent MND (Thomas *et al.*, 1989).

INFLAMMATORY LOWER MOTOR NEURONE DISORDERS

Poliomyelitis is now an uncommon cause of anterior horn dysfunction in the west, but its control requires vigilance and worldwide effort (*see* **Chapter 148, Infections of the Central Nervous System**). It is a subacute condition often with a devastating respiratory presentation. The common forms of polio are not easily mistaken for MND but there is a syndrome of late deterioration in patients who have had polio in childhood or in early adult life. This postpolio syndrome can resemble MND but follows a different clinical course. Its recognition is easy if the history of preexisting polio is known. Similarities between the viral condition and idiopathic MND have prompted searches for an etiologic association between the two disorders (Gastaut, 1995). Other enteroviruses have also been implicated in the etiology of MND.

Vasculitis affecting either the spinal cord or the spinal roots or both can resemble MND. Unusually marked sensory symptoms or other features of systemic vasculitis can act as clues. CSF examination can be helpful in this situation as the CSF protein concentration is often elevated in CNS vasculitis and there may be a pleocytosis (Futrell, 1995) even in the absence of clinical meningitis. The rise in CSF protein concentration is more marked than that usually seen in MND. The disturbance of anterior horn function associated with the vasculitides including polyarteritis nodosa may respond to immunosuppression. Chronic inflammatory demyelinating polyneuropathy (CIDP) is a radiculoneuropathy with predominantly motor symptoms and signs and without upper motor neurone pathology. It can mimic the lower motor neurone disturbance of MND but the finding of slowed nerve conduction velocities and elevated CSF protein should lead to the correct diagnosis of a neuropathy rather than an anterior horn cell disorder. This is a treatable disorder often responding well to immunomodulation with steroids or intravenous immunoglobulins. A more patchy neuropathy and hence one that is difficult to recognize is the condition, multifocal motor neuropathy (MMN) with proximal conduction block (Chaudry *et al.*, 1994). In terms of etiopathogenesis it may just be a more limited form of CIDP; although in MMN the response to steroids and plasmapheresis is poor and the response to intravenous immunoglobulins rather better to begin with, although it may not be as sustained (Nobile-Orozio *et al.*, 1993) as in CIDP. It too, is worth thinking about in the patient with few or no upper motor neurone signs and without bulbar involvement. There have been reports of successful treatment of MMN with immunomodulatory therapies including cyclophosphamide and intravenous immunoglobulins. Upper motor neurone features are usually absent, as are bulbar signs. Reflexes can be preserved and although it is a neuropathy, fasciculation can be prominent. Limited autopsy studies suggest that anterior horn cells may be affected as well. Gangliosides have been used as treatment – this has proven unsuccessful and is potentially hazardous in increasing the risk of subsequently developing a Guillain Barre syndrome (Lacomblez *et al.*, 1989). The pathology of MMN is not well characterized but inflammatory mechanisms are thought to be responsible for disease development as are immunologic changes. Antibody binding to the nodes of Ranvier indicates that this may be the site of damage (Santoro *et al.*, 1990).

OTHER NEUROPATHIES

Paraneoplastic neuropathy can mimic MND. Sometimes it is truly an MND-like disorder and on occasion even a Lambert Eaton myasthenic syndrome (LEMS) has been mistaken for MND (Nobile-Orazio *et al.*, 2001; *see* **Chapter 79,**

Disorders of the Neuromuscular Junction). Clearly, awareness of this possibility should help in sorting out the paraneoplastic disorders from the degenerative condition, MND. Paraneoplastic disorders are associated with an increasing spectrum of circulating antibodies, for example voltage-gated calcium channel antibodies linked to LEMS. Some writers have used the term neuromyopathy, not just to cover clinical and diagnostic uncertainty but also to emphasize the point that it can be difficult even using electromyography (EMG) to always tell whether a lesion is just neurogenic or whether there is a combination of a neurogenic change and a myopathy. A rare myopathy that causes some difficulty is acid maltase deficiency, which can cause severe respiratory muscle compromise in mobile patients; a condition that is mimicked by a few sufferers of MND. A careful search for upper motor neurone signs may help to avoid diagnostic confusion.

Lead poisoning is uncommon at all ages and particularly so in adult life. Children with lead poisoning present with an encephalopathy with or without abdominal pain and may be noted to have a blue lead line over their gingival margins. When it occurs in adults, lead toxicity can present a picture of a virtually pure motor neuropathy. In the past, much discussion has centered on whether lead toxicity could cause MND. No case of lead poisoning has been described in terms that could convincingly be recognized as MND. Certainly, several cases of a lower motor neurone–type disorder have been linked with lead poisoning but in these cases bulbar or upper motor neurone signs have not been found. On current evidence there is no case for treatment of MND with lead chelating agents. A similar controversy has surrounded the link between mercury and MND but again there is no convincing evidence of an etiologic link. The occurrence of MND-like disorders in lead and mercury poisoning is however of great interest in view of the close association between metal ion concentrations and free radical generation (Pall, 1994); disorders of free radical action are likely in MND as discussed below. Both lead and mercury are known to increase the rate of iron-catalyzed free radical reactions (Quinlan, 1988), so their toxicity may occur via an indirect mechanism that promotes oxidant stress. Other causes of a predominantly motor neuropathy should always be thought of when looking at a patient with suspected MND. These include the paraneoplastic disorders referred to above, porphyria and polyarteritis nodosa. Treatment of porphyria with avoidance of the precipitants of acute relapses and treatment of polyarteritis nodosa with immunosuppression can improve disease outcome quite remarkably and prove a more rewarding condition to treat for both patient and physician than is sporadic MND.

Some of the hereditary motor neuropathies [HMN2 and HMN5] can be mistaken for a predominantly lower motor neurone form of familial MND (Auer-Grumbach *et al.*, 2000). HMN2 is also referred to as *distal* spinal muscular atrophy (SMA).

DIFFERENTIAL DIAGNOSIS OF BULBAR MND

When bilateral tongue wasting and fasciculation are present the diagnosis of MND is very likely to be correct. However, the physical findings both in the limbs and sometimes even in the mouth can be equivocal in a patient with clear and severe bulbar symptoms and disability. In this situation a diagnosis of myasthenia gravis must always be considered, as this is an eminently treatable condition. Usually but not always, a history of fatigable ptosis or diplopia is helpful. These are both very uncommon in MND and are not seen in ambulant patients with MND. A tensilon test can aid diagnosis but interpretation must be cautious as a weak-positive tensilon test can be found in MND – this has formed the basis for treatment with anticholinesterases such as pyridostigmine; a practice that persists in some neurologic clinics. The major difficulty in making a diagnosis of myasthenia gravis is not thinking of the condition. The rare and relatively acute bulbar disorders, botulism, and diphtheria should not pose any diagnostic confusion with the slowly developing disorder, MND. Prominent autonomic disturbance including pupillary changes in a young patient with rapidly progressive neurogenic weakness should spark off a search for botulism (including that caused by wound infection in heroin users). However, this is sufficiently rapidly progressive to be more easily mistaken for Guillain Barre syndrome than MND.

A pseudobulbar presentation should activate a search for structural brain pathology such as cerebrovascular disease. It is extremely common for the severe dysarthria or anarthria of MND to be thought of as dysphasia resulting from a stroke. The progressive history and the recognition that the patient's ability to express himself/herself using gesture or writing is totally intact at a time when they are unable to make any sound should clarify whether the problem is dysphasic or anarthric. A proportion of MND patients develop dementia and in rare cases this can be a prominent feature at diagnosis. On sophisticated psychometric testing impaired intellectual function is found more commonly (in upto one-third of patients) but it is clinically relevant in a minority of these. A combination of dementia and amyotrophy (muscle wasting) with fasciculation can rarely signify a prion protein disorder of Creutzfeldt–Jakob type.

INVESTIGATIONS THAT AID DIAGNOSIS

The diagnosis of MND is a clinical one. The role of investigation is largely to look for other conditions that may mimic MND. These have been discussed above and where appropriate, diagnostic tests have been suggested. All patients in whom a diagnosis of MND is considered should have nerve conduction studies and these may be combined with EMG. The EMG can confirm electrical evidence of denervation in marginal cases or may demonstrate denervation in clinically normal limbs but more importantly, nerve conduction studies which should be normal in MND may point to

alternative diagnoses such as a motor neuropathy as seen in CIDP or multifocal motor neuropathy with conduction block (MMN). CSF examination for elevated protein concentrations or pleocytosis may also be helpful in swaying one away from the diagnosis. Having said this, slight increases in CSF protein are seen in MND so that the elevation has to be marked for it to be of significant negative predictive value. Serologic tests have not been as useful as was hoped about 15 years ago. Antiganglioside antibodies are found in low titer in many patients with MND and are found more consistently and at higher titers in patients with MMN and CIDP. Paraproteins are found more frequently in the serum of MND patients than would be expected in an age-matched population (Duarte *et al.*, 1991). Treatment of the paraprotein in these cases does not influence the outcome of MND except in the rare circumstances where the paraprotein is the marker of a condition mimicking MND. Other tests ranging from looking for antiacetylcholine receptor antibodies to magnetic resonance scanning of the cervical spine may be appropriate in certain clinical settings as discussed above.

DIAGNOSIS OF MND

Despite the large number of differential diagnoses listed above, one often sees patients who at their first presentation to a hospital specialist already have a combination of clinical features that make the diagnosis of MND inescapable. Even in these circumstances, my practice is not to discuss the diagnosis in terms of MND unless the patient or their attendants press for an immediate name for the condition. I have a preference for carrying out nerve conduction tests, an electromyogram, and any other tests indicated; prior to mention of the words, motor neurone disease. A busy outpatients' clinic is hardly a suitable setting for the unhurried imparting of bad news (Bradley *et al.*, 2001). A planned reattendance, arranged with a minimum of delay after the initial consultation is my preferred option. Following the tests and preferably on the same day, the diagnosis can be discussed with the patient and their family by the senior doctor and a counselor with an interest in MND. In the United Kingdom, nurses have taken the lead in developing counseling skills but any health-care professional with an interest in MND and the time to be able to discuss matters calmly and unhurriedly could develop counseling skills and become an MND counselor. Patients and their families usually appreciate written information and most appreciate receiving a transcript of or letter about the consultation. The hospice movement in particular and the experience of oncology in general have taught us much about imparting bad news. Amongst the important principles are obvious ones such as the use of a private room and other not-so-obvious ones such as fractionating the news so that the patient is not completely overwhelmed by the information and remembering to emphasize some positive features, for instance our increasing ability to help all the symptoms of the disease. In some cases it may be appropriate to admit the patient to hospital for a day or two, so that questions that gradually come to the patient's mind can be immediately addressed rather than waiting for their next outpatient visit. In our unit, the MND nurse counselor plays an important role in maintaining contact with the patient and their family, not just while they are in hospital but also when they are at home. This outreach function has proved invaluable in reducing the morbidity of the disease and later on, in facilitating discussions about end-of-life issues.

As the diagnosis of MND is essentially based on the clinical picture and as there is no one diagnostic test for it, most patients who are told of this diagnosis will wonder how certain the doctor is or whether he/she might be wrong. This thought is, of course understandable and entirely reasonable and occurs so often as to make it important that the patient is offered the opportunity to obtain a second neurological opinion. This may be a counsel of perfection as many parts of the world have difficulty with access to one neurologist let alone two. However, wherever feasible this course is to be recommended as confident acceptance of the diagnosis by the medical team and by the patient and their family forms the basis of all subsequent management.

EPIDEMIOLOGY

MND is a ubiquitous disorder. The overall incidence and prevalence are greater in men than in women. However, the bulbar-onset type of MND is more frequently seen in women. The average age at first presentation is about 57 years and the clinical course relentlessly progressive over 3–5 years (Tandan, 1994). As in many diseases that do not have a diagnostic test, MND is subject to diagnostic errors with both false positives and false negatives. This confounds accurate study of its incidence, which is variously estimated at between 0.6 and 2.6 per 100 000 per year (Chancellor and Warlow, 1992). Although case ascertainment must play a part in this variability, geographic differences almost certainly account for some of the difference. Even within fairly small areas there can be considerable variation in the incidence of the disease as shown, for example, by the differences on either side of the river in the Mississippi area of the United States (Bharucha *et al.*, 1983). In England, there is a difference in the prevalence of MND between the north and the south even after allowing for demographic differences. In the United Kingdom fewer cases than expected seem to occur amongst the immigrant Asian and Afro–Caribbean population than in the native population (Elian and Dean, 1993). It is unlikely that this could be accounted for merely by differences in the age distribution of the populations. Age-specific incidence figures show increase in the occurrence of MND into the 70s but with an apparent fall in the 80s and 90s (Piemonte and Valle d'Aosta Register for Amyotrophic Lateral Sclerosis (PARALS), 2001), partly explained by the

small population groups in the age ranges and possibly by their lack of access to specialist care services. The incidence of MND is increasing especially in the elderly. Only part of this can be explained by improvement in diagnostic accuracy. Other factors such as varying exposure to a putative neurotoxin and decreasing death rates from other causes may also play a role in increasing the number of observed cases of MND.

The occurrence of a type of MND on the island of Guam and on the Kii peninsula and the decreasing death rates from this disease in those areas indicates that the cause of sporadic MND may be exposure to a neurotoxic agent (Kisby *et al.*, 1992). Several epidemiologic lines of enquiry have looked into this but so far no convincing candidate toxin has emerged. Military personnel deployed in the first Gulf War are reported to have a higher risk of developing MND than the general population or than their nondeployed soldiers (Haley, 2003). This warrants further research but that may prove impossible in view of the low statistical power for a relatively rare disease. It is reported that patients with MND engage in more physical exercise than the general population and it is also likely that they have a stronger previous history of trauma including bony fractures (Chio *et al.*, 1991). These may of course be linked as fractures in young people occur more commonly in those engaging in physical activity. A case has been made for abnormalities of parathyroid hormone playing a role in the pathophysiology of this disorder but the link seems tenuous. Electromagnetic fields and electric current (e.g. as electrocution) have been linked with MND (Rose, 1994). Exposure to solvents and, in particular, halogenated hydrocarbons has been associated with MND both as anecdotal cases and in the leather industry (Hawkes *et al.*, 1989). Organophosphate exposure is also postulated as a risk factor. For nearly three decades there has been much interest in metal exposure as a risk factor for MND. The main metals implicated have been lead and mercury (Pall, 1994). Undoubtedly, toxic concentrations of these metals can cause an MND-like picture but usually with sufficient atypical clinical features to make the diagnosis apparent and certainly different from ordinary MND. More recently interest in metals has been reawakened by the finding of antioxidant abnormalities in familial MND (Rosen *et al.*, 1993). Metal ions can promote the production of free radicals and can increase tissue oxidant stress. Lead and mercury are known to promote iron-mediated lipid peroxidation (Quinlan, 1988). It has been suggested that MND is a late consequence of infection with the polio virus in a situation analogous with the development of an MND-like condition in later life in patients who suffered from polio in younger days. However, the postpolio type of MND is clearly different from ordinary MND (Dalakas and Illa, 1991). If polio exposure plays a part in MND the effect of polio vaccination should soon result in decreasing incidence of the disease.

In about 10% of cases of MND, there is a family history of the disorder suggesting an autosomal dominant mode of inheritance. Individuals with this condition (FALS or familial MND) are indistinguishable from those with sporadic disease. The age distribution is similar in the two disorders. Interest in FALS has increased since the finding of mutations in the gene encoding SOD 1 in a proportion of families with FALS (Rosen *et al.*, 1993).

PATHOLOGY OF MND

Prominent degeneration of the pyramidal tracts is seen in the spinal cords of patients dying with MND characterized by loss of motor neurones with changes such as spheroid formation, chromatolysis, and neuronophagia of motor neurones. Gliosis can be prominent in a few cases and surviving cells can show accumulations of lipofuscin. This may be an important point in considerations of the mechanisms of cell damage as lipofuscin accumulations are conventionally associated with free radical attack on polyunsaturated fatty acids (Gutteridge and Halliwell, 1990). In many cases, there is an infiltration of CD8 positive T lymphocytes into the spinal cord (Kawamata *et al.*, 1992). Some pathological changes have been described in the posterior columns, the sympathetic pathways, and even in Onuf's nucleus underlying the clinical observation that sensory pathways and bladder innervation are only relatively but not absolutely resistant to the process of MND (Shefner *et al.*, 1991b). A variety of inclusion bodies in anterior horn cells are associated with MND; some of these contain ubiquitin, a housekeeping protein involved in the designation of proteins due for removal. Ubiquitin is involved in the degradation of oncoproteins such as c-myc, c-fos and p53 (Ciechanover *et al.*, 1991). The inclusion bodies include Bunina and Hirano bodies and other inclusions similar to Lewy bodies seen in PD are also described. Similar abnormalities are found in the brain stem nuclei of cranial nerves that are involved in MND. Those spared in MND for instance, those of extraocular muscles are less affected. The upper motor neurone cell bodies and dendritic processes show degeneration and inclusions and there is increased gliosis in layers II and III of the motor cortex and in subcortical white matter (Kushner *et al.*, 1991) with some changes also found in the sensory cortex. More widespread changes are found in the brains of dementia patients who die with MND. These include finding intraneuronal inclusions that are ubiquitin positive but tau and alpha synuclein negative (Yoshida, 2004). Tau 1 positive inclusions are found in astrocytes and other tau aggregates in the neuropil in MND patients with dementia. Dementia is an uncommon clinical feature of MND afflicting up to 15% of patients although significant cognitive decline can be identified in 35% of patients (Neary *et al.*, 1990). Spinal root atrophy is frequently seen at autopsy but involvement of peripheral nerves is rare. Some studies have shown loss of large myelinated fibers secondary to anterior horn cell loss. Biochemical abnormalities are also found in the parietal cortex and in the cerebellum although these areas are largely clinically unaffected (Kim *et al.*, 2004). This indicates the multisystem nature of MND.

Small group atrophy of muscle fibers is seen on muscle biopsy affecting both type I and II fibers with some compensatory hypertrophy of surviving muscle cells. Mononuclear

inflammatory infiltrate may also be seen but whether as a cause or an effect of the disease process is unknown. On antemortem liver biopsy a variety of abnormalities are linked with MND. These include intramitochondrial inclusions, giant mitochondria, and abnormalities of endoplasmic reticulum (Nakano *et al.*, 1987).

Neurofilament accumulations occur in the site of damage in MND (Itoh *et al.*, 1992). Neurofilament transport, degradation, and phosphorylation all seem to be impaired in MND. The role of these in disease pathophysiology is unknown.

ETIOLOGY AND PATHOPHYSIOLOGY

Much progress has been made in these areas of research and the results are now being translated into encouraging clinical trial findings. While this should not lead to exaggerated overoptimism, the research inroads into understanding this disease have been remarkable. Some of these are discussed below. Although discussed under separate headings for ease of reading, there are many areas of overlap; for example, xenobiotic compounds may exert their toxic potential through free radical mechanisms and free radical action may be increased by the action of excitatory amino acids.

FREE RADICALS (*see* Chapter 2, A Biological Perspective on Aging)

Chemical species that are capable of independent existence and contain unpaired electrons are termed *free radicals*. In biological systems, oxygen free radicals, that is, the products of partial reduction of molecular oxygen are particularly important. A role for them has been postulated in many disparate conditions, based on their high reactivity and consequent capacity to damage biomolecules. One of the enzymes that protects tissues against free radical attack is superoxide dismutase type 1 or SOD 1. This enzyme catalyses the conversion of superoxide free radicals to hydrogen peroxide. Rosen *et al.*'s (1993) finding of mutations in the gene encoding SOD 1 in some families with FALS led to a dramatic increase in the interest in this mechanism of tissue damage in MND. Similar mutations have not been found in sporadic MND and in fact, only a small proportion of families with FALS have SOD 1 gene mutations (Hosler and Brown, 1995). However, other abnormalities believed to represent impaired oxidant metabolism have been found in the spinal cords of patients dying with MND (Shaw *et al.*, 1995). These include increases in a product of free radical attack on DNA, 8-hydroxy 2-deoxyguanosine and in some of the products of protein oxidation such as protein carbonyls. In sporadic MND, the concentration (in the spinal cord) of other antioxidants such as glutathione peroxidase is impaired. These observations suggest that free radical mechanisms may be one means of cell injury in MND. There is some recent evidence that indicates that the situation is more complex than implied above. For instance, as in many dominantly inherited conditions, the means by which SOD 1 mutations cause damage in MND may not be merely through loss of dismutation activity of the SOD 1 protein but as in most dominantly inherited mutations, through some new and additional property of the mutant protein (Hosler and Brown, 1995) – the nature of this additional function remains unclear. It has been reported that mutations in the SOD 1 enzyme change its function from an antiapoptotic one to a proapoptotic one (Rabizadeh *et al.*, 1995).

On the basis of the hypothesis that impaired defences against free radical attack are important in the pathophysiology of MND, trials of therapy with antioxidants have been attempted. Selegiline, an inhibitor of monoamine oxidase type B (whose action produces peroxide), has been used without benefit (Mazzini *et al.*, 1994). Metal chelating agents with antioxidant properties, such as *N*-acetylcysteine have also been used with unconvincing benefit (Louwerse *et al.*, 1995). Some practitioners have, on quite empirical grounds, recommended that patients take supplements of vitamin C, vitamin E, and other commonly available antioxidants. In the absence of convincing evidence of benefit from these interventions, such recommendations should properly form a part of a randomized clinical trial. As newer antioxidants with more adverse effects than the naturally occurring ones become available for study, it becomes even more important that we know the efficacy or otherwise of the safer, naturally occurring agents.

In addition to causing direct damage to nucleic acids, structural support proteins and membrane lipids, free radicals, and other reactive oxygen metabolites such as hydrogen peroxide can induce profound changes in intracellular signaling mechanisms. For instance, they can modulate the conversion of the inactive form of NFKB to the active form. They have an effect on gene transcription, for example, as shown by the redox sensitive regulation of transferrin receptor and ferritin production. The gene dysregulatory effect of free radical abnormalities are marked and in cell culture can lead to neuronal loss by a process of apoptosis or programed cell death. There is therefore much interest in apoptosis in MND as indeed in many other neurodegenerative disorders (Heintz, 1993). Another cell-signaling compound whose activity is modified by oxygen free radicals is nitric oxide (Schulz *et al.*, 1995). This can combine with superoxide radicals to form peroxynitrite, a precursor of hydroxyl free radicals, which have a great capacity to cause intracellular damage, and can lead to calcium influx into the cell and consequent cell death. Nitric oxide abnormalities are also linked with abnormalities of excitatory amino acid neurotransmission; this helps to establish a link between the two front-runners in the mechanism of tissue damage in MND – namely, free radicals and excitotoxicity (Dugan and Choi, 1994).

Excitatory Amino Acids

Glutamate is a major neurotransmitter in the CNS. It is an excitatory amino acid which stimulates the anterior horn

cell that is, the main transmitter between the upper and lower motor neurones. Convincing evidence from cell culture studies and experimental animal models demonstrates the toxicity of excessive concentrations of glutamate (Meldrum and Garthwaite, 1991). This damage is often referred to as excitotoxic damage. The finding of defects in the distribution of glutamate receptors in the spinal cords of patients with MND and the demonstration of a defect of the glutamate transporter in MND support the hypothesis of excitotoxic damage in this disease. The more controversial finding of elevated concentrations of glutamate in the CSF of patients with MND also lends support to this hypothesis. The toxicity of glutamate is believed to be mediated via increase in calcium entry into cells (Rothstein, 1995). Calcium entry into cells is carefully regulated and can be disturbed by a variety of mechanisms including free radicals and excitatory amino acids. This, along with the involvement of compounds such as nitric oxide (NO) in both, excitatory amino acid neurotransmission and in free radicals suggests that several mechanisms acting together may conspire to cause anterior horn cell damage in MND. The postulated role of excitatory amino acids in MND led to a search for antiglutamate drugs as treatment for MND. A number of agents have been examined for their antiglutamate properties – amongst these are the branched chain amino acids (BCAA) leucine, isoleucine, and valine (The Italian ALS Study Group, 1993); lamotrigine (Eisen *et al.*, 1993); and riluzole. Riluzole has shown positive results (Lacomblez *et al.*, 1996), which are discussed below.

Growth Factors

A whole family of peptide neurotrophic factors is known to affect the growth and survival of human neurones. Some of these have profound effects on human lower motor neurones but have not been shown to influence upper motor neurone survival. Nerve growth factor is produced within a target cell and is believed to be transported retrogradely along an axon to a cell body. The survival of cells deprived of these trophic factors is reduced. Much interest has centered on three neurotrophic agents as possible protectors against the degenerative process of MND. These are ciliary neurotrophic factor (CNTF), brain derived growth factor (BDNF), and insulin-like growth factor (IGF). Glial-derived neurotrophic factor (GDNF) has also been of interest in neurodegenerative disorders. *In vitro* GDNF is more potent than either CNTF or IGF at promoting neuronal survival.

Decrease in the concentration of growth factors such as CNTF is associated with decreased motor neurone survival (Masu *et al.*, 1993). CNTF protects against inherited lower MND in a mouse model of motor neuropathy (Sendtner *et al.*, 1992) and improves muscle strength in the wobbler mouse – a model for human MND. CNTF binding is reduced in the ventral horns in human MND. An initial clinical trial of CNTF was abandoned when no benefit was identified and significant adverse effects occurred. Some of the adverse effects could have been foreseen, for instance, through recognition of its interaction with leukemia inhibitory factor. There was also some doubt as to whether the method of administration of the CNTF would have allowed the drug to reach the site of action, namely the spinal cord – beyond the blood-spinal cord barrier. However, an important study in an animal model of MND, the wobbler mouse showed an arrest of the degeneration of motor neurones when these animals were treated with a combination of CNTF and BDNF; suggesting that combinations of growth factors may be required to promote neuroprotection (Mitsumoto *et al.*, 1994).

IGF 1 can induce sprouting of spinal motor neurones and its binding sites are increased in the spinal cord in MND (Festoff *et al.*, 1995). Much of this spinal binding may be to glial sites rather than neuronal ones. IGF has also been tested in a clinical trial setting and has been found to be helpful in increasing muscle strength in MND without significant effect on survival (Lai *et al.*, 1997). This is an important observation as the only other drug that is currently proving encouraging in the treatment of the disease process of MND, riluzole appears to prolong survival without effect on muscle strength. Parenteral BDNF proved ineffective in MND (The BDNF Study Group, 1999). A new, nonpeptide neurotrophic factor with 5HT1a receptor activity also failed to prolong survival when given along with riluzole in MND (Meininger *et al.*, 2004). VEGF is proving interesting in MND. Mutations in the gene encoding VEGF (Lambrechts *et al.*, 2003) and altered activity of the peptide in CSF (Devos *et al.*, 2004) have been reported in MND.

Viruses

Dating from the time of Charcot, a large number of viruses are linked with MND but convincing evidence of a causal association is missing. Agents as diverse as enteroviruses such as the polio virus, retroviruses such as HIV and Human T lymphotropic virus 1 (HTLV 1), and even prions are implicated. Circumstantial evidence links enteroviral infection with MND (Gastaut, 1995). However, some studies have found no association between polio and MND (Swingler *et al.*, 1992). Both are somewhat commoner in men than in women; enterovirus affinity for the anterior horn cells has been demonstrated by the disease poliomyelitis and recent evidence indicates that these viruses can persist in tissues as latent or persistent infection for many years; supporting the idea of chronic damage. Enterovirus genome has been reported in the spinal neurones of patients dying of MND but not in control specimens (Woodall *et al.*, 1994). It is suggested that a state of restricted replication may exist in these neurones; a situation akin to that seen in subacute sclerosing panencephalitis (caused by the measles virus) or in tropical spastic paraparesis (caused by HTLV 1). The similarities between the postpolio syndrome and MND have further suggested the possibility of an etiologic connection.

Autoimmunity

An increased incidence of known autoimmune diseases such as diabetes is described in MND. Paraproteinemias may occur more frequently in MND (Duarte *et al.*, 1991) (although some recent evidence casts a doubt over this long-held belief), also pointing towards immune mechanisms in the disease process. However, in the majority of these patients the paraprotein does not recognize antigens on motor neurones. A guinea pig model of both the lower motor neurone disturbance and the upper motor neurone problems of MND can be induced by inoculation with spinal cord or brain homogenates and neurophysiologic changes detected in other species following passive antibody transfer but the disease is not replicated in these experimental animals after such antibody transfer. The spinal cords of patients dying from MND contain activated T lymphocytes and immunoglobulin deposits in both the cerebral cortex and the spinal cords at autopsy further implicate dysimmune mechanisms in this disease. Appel *et al.* (1995) report finding antibodies against calcium channels in the majority of their patients with sporadic MND – antibodies that are similar to those found in the LEMS. Treatments directed against a possible autoimmune disorder, for instance with cyclophosphamide or with whole body irradiation have failed to give positive results. A critical analysis of the data on autoimmunity in MND was carried out by Drachman *et al.* (1995). In some cases, the paraprotein found in patients with MND has been identified as an *antiganglioside antibody*. Gangliosides are antigens found on neuronal tissues and antibodies against these have been identified in a number of peripheral nerve disorders such as Guillain Barre syndrome and MMN with proximal conduction block. Low titers of antiganglioside antibodies are occasionally found in MND and although this may be no more than coincidence or merely a reflection of tissue damage with secondary immunologic response, it does implicate immunologic mechanisms in MND.

Xenobiotic Metabolism

In a number of disorders, it is becoming clear that a combination of genetic and environmental factors may be responsible for disease development. Some of these are well-established examples of the interaction of heredity and the environment. For instance, in the condition glucose-6-phosphate dehydrogenase deficiency, the genetic disorder in itself is not sufficient to lead to hemolytic episodes but cells that are deficient in this enzyme are unable to cope with the additional burden of environmental challenges such as the fava bean. The enzymes that deal with toxins arising from outside the body (xenobiotic toxins) frequently show polymorphisms, that is, there are fast and slow metabolizers of xenobiotic compounds. Most of the body's reserve in dealing with xenobiotic compounds resides in the liver in microsomal enzymes including the cytochrome P450 system. The idea that a genetically predisposed individual, when exposed to a xenobiotic toxin that his enzyme makeup is unable to detoxify efficiently ends up getting disease, whereas another individual may escape disease either because he has the necessary enzyme activity to detoxify or he may not have been exposed to the toxin, can serve to explain the apparent sporadic nature of a number of diseases. This has been implicated in atherogenesis, in Alzheimer's disease, in diabetes, and in Parkinson's disease to name a few.

Williams and his colleagues (Heafield *et al.*, 1990) have found abnormalities of the enzymes that metabolize sulphur-containing compounds in MND. These include the enzymes that catalyze sulphur oxidation, which appears to be impaired, and the ones that methylate sulphur (thiol methyl transferase) which appear excessively active. Failure to oxidize a sulphur toxin would impair its excretion via the kidney. This combined with increased methylation would facilitate entry into central nervous tissue, where the brunt of damage occurs in MND. If the effect were an immediate one, as occurs in for instance, migraine and chocolate ingestion the connection would be obvious; but if each event of toxin exposure just resulted in the loss of a few anterior horn cells the overall effect might not be noticeable until late in life.

Vascular Insufficiency

In chronic hypoxic conditions, VEGF production is increased to attempt to overcome the hypoxic state. Finding mutations in the gene encoding VEGF (Lambrechts *et al.*, 2003) suggests that vascular phenomena may play a role in the development of MND. Pentoxyfylline, a vasodilator molecule was tested for clinical effect in a placebo-controlled, randomized trial, and initial indications are that the drug is not effective in slowing down the progression of MND. Changes in spinal blood flow may be speculated to explain the association between physical exertion and MND.

Mitochondrial Dysfunction

Structural mitochondrial abnormalities are found at an early stage of MND, in both neural and nonneural tissues (Vielhaber *et al.*, 2000). The mouse model of MND (the wobbler mouse and also the SOD 1 mouse) show early mitochondrial dysfunction (Kong and Xu, 1998). Creatine and phosphocreatine are intricately involved with cellular energy metabolism and these considerations led to a search for a clinically useful therapeutic effect in MND to mirror the improvement seen with creatine use in the SOD 1 mouse. Unfortunately, these studies have been negative. Excitotoxic, apoptotic, and oxidant mechanism have all been proposed as the pathway by which mitochondrial permeability is damaged. All are implicated in MND.

Inflammation

A prominent CNS inflammatory reaction is found in MND. Microglia are involved and their inflammatory mediators

such as CD11b are overexpressed. COX 2 mRNA expression may be increased sevenfold in MND spinal cords (Yasojima *et al.*, 2001). COX 2 inhibitors were until recently regarded as good candidates for use as treatment in MND. However, the newly identified problems of cerebrovascular disease in patients taking COX 2 inhibitors for rheumatic diseases have stopped these avenues being explored.

SYMPTOMATIC TREATMENT

Cramp

This is prominent quite early in the disease and may affect muscles not normally prone to cramp, for instance, forearm flexors. As the disease progresses weakening muscles no longer cause painful cramp. Quinine sulphate is anecdotally helpful and although evidence of its effectiveness is lacking it is worth trying as a short-term measure. Antispastic medications such as baclofen and tizanidine may help in cramp control. The hepatotoxic effect of tizanidine needs to be monitored particularly in those patients also taking riluzole. Other aggravating factors such as electrolyte imbalance may also need treatment. In a few cases, phenytoin has been used with good effect particularly for painless hand cramp.

Fasciculation

Although this is a prominent physical sign in MND it is uncommon for this to be symptomatic except in patients with benign fasciculation in whom it is more constantly a source of anxiety. Patients with MND are usually more bothered by more disabling symptoms and may not even be aware of the fasciculation, until pointed out by the physician. Beta adrenoceptor blocking agents such as propranolol are occasionally helpful in the few cases when pharmacological treatment is warranted. Low-dose benzodiazepines can also be useful in reducing the discomfort of fasciculation.

Spasticity

When spasticity is marked it can interfere with the efficient function of limb and bulbar muscles and antispastic drugs such as low doses of baclofen can help reduce the spasticity. Dantrolene and benzodiazepines can also be used but dantrolene is not widely used for this purpose and there are well-founded anxieties about the sedative and respiratory depressant actions of the benzodiazepines. Having said this, their use in some circumstances can alleviate much anxiety and reduce the pain associated with spasticity. The effect of baclofen on jaw clonus and masseter spasticity can be useful in helping chewing and sometimes even speech. In other neurologic disorders, spasticity can be treated with intramuscular injection of botulinum toxin. In MND, there is a worry that weakening muscles with botox may help spasticity but the cost in terms of increased weakness would be even more unacceptable than with baclofen and other antispastic drugs such as tizanidine. As a consequence, botulinum toxin injections are not currently recommended for the treatment of spasticity in MND. Tizanidine may prove helpful in some patients with MND and spasticity but there are some anxieties about its possible adverse effects on the liver.

Salivary Dribbling

Many patients with MND are troubled by this symptom caused by immobility of bulbar muscles and dysphagia. The discomfort of excessive dribbling of saliva is often greater than that of spasticity or of cramp. It is also more difficult to treat. Patients with MND have decreased saliva production. The cause of dribbling is the impaired swallowing of saliva secondary to muscle weakness. Anticholinergic drugs can ease salivary dribbling by further reducing saliva formation. Drugs such as benzhexol or hyoscine/atropine are generally not well tolerated when given as a tablet. Hyoscine skin patches can be useful and better tolerated. In my experience, *oral* administration of atropine eye drops 1% is better tolerated and appears to give good symptomatic relief. The dose required varies but can be only 2 drops per day. Generally, systemic side effects are uncommon but occasionally patients will complain of other anticholinergic adverse effects such as constipation, bladder disturbance, and blurred vision. Sublingual hyoscine has also been used. Glycopyrrolate injections or subcutaneous hyoscine infusions can be helpful in resistant cases. Radiotherapy of one parotid gland has been used when pharmacotherapy has failed but in such cases the radiotherapy is also usually unsuccessful. Botulinum toxin is increasingly used to reduce saliva formation in those patients who are PEG (percutaneous endoscopic gastrostomy) fed. Botox can spread from the parotid to the pharyngeal muscles and can aggravate pharyngeal weakness, which of course is invariably present in patients with salivary dribbling. When saliva and laryngeal secretions are too thick and stringy to be expectorated, beta adrenoceptor blockers such as propranolol can help. When thick mucus is resistant to such measures, manually assisted coughing techniques and insufflation–exsufflation cough machines can help with its removal from the airway (Bach, 1993).

Oropharyngeal suction can reduce the consequences of excessive salivary pooling and in some cases can help alleviate the fear of nocturnal choking spells caused by salivary pooling. As salivary dribbling at night can be even more troublesome than during the daytime, strategies that reduce nocturnal salivation can also help, for instance, avoidance of late night meals or drinks.

Dysarthria

Most patients with MND develop dysarthria or anarthria at some time during disease progression. Sometimes this can

happen in the absence of dysphagia but often the two symptoms coexist. In the early stages, speech therapy strategies can help and as disease advances increasing reliance must be placed on communication aids (*see* **Chapter 73, Communication Disorders and Dysphagia**). These can range from a notebook and pen to sophisticated computerized aids some of which can be linked to voice synthesizers to produce a semblance of the patient's voice. By the time writing aids are needed, dominant arm weakness can clearly add to the disability. The clinical art in dysarthria management is to determine what the most appropriate aid/appliance is for the degree of the patient's disability; for instance, mention of computer-aided speech can dishearten rather than help a patient with mild dysarthria. The assistance of a rehabilitation team including a speech therapist can be invaluable.

Dysphagia (*see* Chapter 73, Communication Disorders and Dysphagia)

A mild degree of impairment of swallowing occurs in early disease. This can be measured as impaired swallowing speed. As dysphagia advances and is coupled with impaired respiratory protective mechanisms (for instance weakened cough) aspiration pneumonia becomes a serious concern and can cause death in MND. Judicious use of antibiotics can aid comfort. Dysphagia is more marked for liquids and very dry solids. Semisolid foods or foods with puréed consistency are more easily swallowed. Avoidance of very hot or very cold foods/drinks is also helpful. Occasionally, when the bulbar impairment is asymmetric attempts to swallow can be more successful with the head rotated to one side. Dietitian and swallowing/speech therapists help should be called upon.

In recent years, percutaneous endoscopic gastrostomy (PEG) has dramatically helped feeding patients with severe bulbar MND. Gastrostomies are inserted endoscopically, sometimes using sedation but occasionally with just a pharyngeal local anesthetic spray. Usually they are well tolerated and although most patients have severe misgivings about having a gastrostomy, few regret having had one after insertion. The majority indicate that their concerns prior to insertion were unfounded. PEG does not prevent aspiration and must not be seen as a means of stopping the patient from eating. Food or drink that the patient enjoys or can swallow can be taken by mouth. The patient and his/her family must appreciate that oral intake increases the risk of aspiration pneumonia and so long as they are cognizant of this increased risk the patient may choose whether or not to eat and drink. PEG probably prolongs survival but is better regarded as a symptomatic treatment that frees up the patient from the chore of swallowing just to make up normal daily intakes of food and drink and avoids nutritional weight loss which would otherwise compound the weight loss caused by the disease process. In some cases (centers), radiographically inserted gastrostomies (RIG) may be used instead of PEG. Thirty-day mortality after PEG insertion is markedly increased in those patients whose forced vital capacity is less than 50% of predicted (Light *et al.*, 1995). When recurrent respiratory infections complicate PEG placement, gastric motility promoting agents such as metoclopramide may be worth trying.

Respiratory Failure

This is the commonest cause of death in MND. Dyspnea is a common symptom and the fear of breathlessness and choking is usually marked but frequently not voiced. Other symptoms include early morning headaches and fatigue secondary to carbon dioxide retention. Respiratory failure most often occurs secondary to respiratory muscle weakness including diaphragmatic weakness. Large airway obstruction is uncommon. Aspiration pneumonia also accounts for some deaths in MND but the number of these is fortunately decreasing – aided by improvements in speech/swallowing therapists' involvement and by better multidisciplinary team efforts. Some of these patients may have coexistent pulmonary disease such as asthma and others may develop bronchospasm secondary to aspiration or infection. Whether for this reason or for some other pharmacological reasons, salbutamol and other β-agonists via inhaler can be helpful in easing dyspnea in some patients with MND. In some patients, β-blockers given to ease other symptoms may be the cause of dyspnea and fatigue. The judicious use of oxygen (domiciliary oxygen if necessary) supplements by mask or nasal cannulae can help relieve symptoms as can anxiolytic medication including benzodiazepines. In advanced disease, it may not be appropriate to use antibiotics to treat the dyspnea associated with pulmonary infection. In this situation, and in other cases of unremitting dyspnea symptom control may require opiates sometimes in combination with hyoscine. The respiratory depressant effect of opiates causes understandable and necessary concern in this situation but this adverse effect should not impair the search for rapid and effective relief of symptoms in the terminal phases of MND.

Increasing evidence demonstrates the effectiveness of non-invasive mechanical ventilation as treatment for palliating respiratory symptoms in MND (Aboussouan *et al.*, 1997). Non-invasive positive pressure ventilation (NIPPV) is effective in improving early morning headaches, fatigue, alertness, and orthopnea. Any increase in depression caused by the need for assisted ventilation is offset by the sense of well being caused by the mechanical ventilation. Overall depression rates are no different in the ventilated or nonventilated patients. Nocturnal oximetry can help decide whether NIPPV is appropriate. Many patients face the problem of Advance Directives for the first time when considering using NIPPV. Initially, most patients use the mechanical ventilation systems at night. They need to decide whether they would extend use into daytime hours; potentially even 24 hours a day. What are to be the stop rules and how is withdrawal to be effected, for example with removal of supplemental oxygen, removing end expiratory positive pressure

then using a T tube and then using opiates or benzodiazepines to relieve distress, and so on? Some patients decide to go on to a tracheostomy with full invasive ventilation. Leaving aside considerations of the resource implications of such a decision, patients and their families need to be counseled fully to prepare them to make these decisions. Most patients and their carers indicate a strong wish to make positive decisions regarding resuscitation status, antibiotic use for bronchopneumonia and treatment of multiorgan failure and want the physician to introduce this topic.

Pain

Pain is common in MND (Newrick and Langton–Hewer, 1985) (up to 40%) but this is not generally appreciated and less attention is given to this aspect than it deserves. A doctor's capacity to ease pain is far greater than his/her ability to ease many other symptoms. For this reason, questioning patients about pain can be a rewarding therapeutic experience for patient and physician alike. Sometimes the pain is caused by cramp but more often it is attributed to the effects of ligamentous strain secondary to weak muscles. Anxiety and fear are common exacerbating factors. In many cases, the cause of pain is obscure. In part, it may arise from subtle abnormalities of central pain pathways. The management of pain in a terminal care setting is the same whether the pain is due to secondary spread from cancer or due to MND.

Weakened muscles and ligamentous stretching can lead to partial subluxation and support or orthoses to avoid further subluxation and use of intra-articular steroids and lignocaine can help ease the pain. Weak neck muscles can cause cervical pain and in some patients this can be helped by wearing a cervical collar. The right collar for each individual is one that can be worn comfortably and eases discomfort. Unfortunately, no one-collar type fits this bill and the help of a rehabilitation team with experienced physiotherapist and occupational therapist can be helpful.

Depression

Emotional lability is common in MND, particularly in those with bulbar problems. As a result, patients may cry, sometimes inappropriately. However, the disabling nature of the disease can lead to appropriate crying either due to frustration or depression. Frustration and other affective difficulties such as anger are more prevalent than clinical depression. They can be helped by supportive counseling that aims to bring close family and possibly friends into a support structure, the hallmark of which should be open and honest discussions; avoiding the tendency to mistakenly trying to protect one another by failing to voice anxieties and concerns. When the affective difficulties extend to causing impaired sleep, loss of appetite, loss of self worth, and so on, pharmacotherapy may be needed for the depression. A low threshold to using antidepressant medication needs to be maintained either as the tricyclic antidepressants whose anticholinergic effects may help excessive salivation or as one of the selective serotonin reuptake inhibitors (SSRI), which are said to be safer when, for instance, taken in overdose. Emotional lability which may show as pathological crying or laughter may be treated with the tricyclic drug, amitriptyline, or by fluvoxamine.

Given the nature of the disease it is surprising that suicide is not more common and perhaps this reflects the success of the support structure that carers and medical services have set up. A counselor who may be a nurse or other professional with the appropriate knowledge, inclination and communication skills may be able to identify patients at risk of attempting suicide and be able to intervene to prevent it.

Leg Weakness

Gait impairment is a frequent presenting symptom in limb-onset MND. Progressive weakness, wasting, fasciculation, and cramp cause much morbidity. Weakness about the ankle causes most marked early morbidity. Foot drop can be managed in the early stages by a physiotherapy type approach; sometimes using foot drop splints or other orthoses. More sophisticated orthoses are rarely needed for leg disturbance but seeking the advice of a neurophysiotherapist or orthotist can help. The decision of progressing from ambulant mobility to wheelchair needs to be made carefully and is never easy from a psychological viewpoint. Guidance from a disability team can help the patient decide when the time is right for this transition. One individual, whether a doctor or a nurse is less likely to be persuasive than a multidisciplinary team of people. Which type of wheelchair is used may need to be determined with expert help. Few MND patients have arm strength good enough to allow self-propulsion of a mechanical wheelchair. Some will benefit from an electric wheelchair but these too require an attendant, as powered chairs can be heavy and difficult to lift, for instance, in and out of cars. Mobility inside the home also needs attention. Patients may be fine to walk on level ground but unable to go safely up and down stairs. This can require single level existence, stair-lift or even a through-ceiling lift. Not many patients want the disruption of a through-ceiling lift and as with all recommended interventions the place of the health professional is to advise the patient of the best options and where safely possible, to try to accommodate the wishes of the patient and their family.

Arm Weakness

Hand weakness with wasting of muscles innervated by the T1 nerve root can be the first sign of MND. It is usually asymmetric and even with profound wasting in several myotomes, arm tendon reflexes are usually preserved and even exaggerated, indicating a combined upper and lower

motor neurone lesion. Fine motor tasks are impaired and the patient may complain of cramp in the early stages. The combination of anarthria and dominant hand weakness is a particularly disabling one. Communication is impaired by not being able to speak, compounded by not being able to write. In this setting, computer-aided communication with bespoke switching and pointing devices comes into its own. Recent trial data suggest that treatment with IGF may slow the progression of muscle weakness in MND. Physiotherapy and occupational therapy involvement become more important as the weakness increases. Passive exercises to prevent contractures and simple splints to aid comfort by maintaining neutral postures can help. Weak limbs with wasted muscles are prone to suffering secondary problems such as entrapment neuropathies of nerves previously cushioned by a mass of muscle. Avoidance of pressure over the elbow or the carpal tunnel is necessary. They are also prone to subluxation at several joints, for instance, at the shoulder when the arm is a flail dependant limb. Adequate arm support with appropriate local measures such as intra-articular steroid and local anesthetic injection may be warranted. Splints and arm supports must be customized to maximize the efficient use of the weak arm. For example, a high-set arm support mounted on either a wheelchair or a fixed chair, may make the difference between self-feeding and being reliant on others for this need; the patient may have the strength to move the arm horizontally between a plate and his/her mouth but may not be able to move the arm against gravity as required in normal eating.

ADVANCES IN DRUG TREATMENT

Riluzole

Riluzole is a glutamate antagonist that acts on voltage-gated presynaptic sodium channels. It was initially developed as an antihypertensive agent but does not have significant antihypertensive action in man. In fact, it sometimes induces hypertension as an adverse effect. A pilot study (Bensimon *et al.*, 1994) suggested that riluzole slowed down the rate of progression of bulbar type of MND with no discernible effect on the course of limb-onset disease. This was followed by a much larger and dose-ranging multicenter study across Europe and the United States (Lacomblez *et al.*, 1996). This second riluzole trial demonstrated increased lifespan in patients taking riluzole compared with those on placebo with no demonstrable difference between a dose of $200\,\mathrm{mg\,day^{-1}}$ and $100\,\mathrm{mg\,day^{-1}}$. However, adverse effects were, as expected, higher in the high-dose group. These included potentially serious impairment of liver function, mild anemia, leukopenia, malaise, GI upset, and dizziness. A few patients became hypertensive. The extent to which life was prolonged by the study medication is not known but is measurable in a few months. From a scientific viewpoint, this development is exciting as for the first time, two well-conducted trials have shown significant benefit, from a pharmacological intervention in MND. However, from a clinical viewpoint the trial results are less impressive but nevertheless encouraging. Few patients who start on medication have to give up owing to side effects. A few stop because of abnormal liver function and some give up when swallowing deteriorates to the point when tablets become a chore and they do not want to crush tablets and inject a suspension down a PEG tube. Riluzole is useful in offering hope to patients and their families and in providing a weapon to combat the disease with. This aspect of its effect and its impact on quality of life is not easily measurable.

The development of riluzole as a useful medication for MND sets the scene for investigation of other antiglutamate drugs in this setting and taking the analogy of the survival prolongation by treatment interventions in acute myeloid leukemia we can reasonably hope for refinements in treatment in the near future – treatments that result in more significant prolongation of life and result in improved quality of that prolonged life.

Insulin-like Growth Factor

Insulin-like growth factor or IGF 1 is a neurotrophic substance that has been shown to increase muscle strength in MND without any effect on survival (Lai *et al.*, 1997). This neurotrophic substance has been used widely outside the UK. Its effect may be mediated via a mechanism involving growth hormone.

Clinical Trials of Other Agents

Negative clinical trials in MND have included *N*-acetylcysteine as a chelator, branched chain amino acids as inhibitors of glutamatergic transmission, the growth factors BDNF and CNTF, the serotoninergic growth factor SR57746A, the muscle growth promotor creatine, and the vasodilator oxypentifylline. Drugs that block the presynaptic production of or release of glutamate may be neuroprotective. Gabapentin may be one such drug that has been used in MND (Miller *et al.*, 2001). Its more conventional use is in epilepsy where its mode of action is unknown. In a trial in MND, no significant benefit was found with gabapentin treatment suggesting that the drug should not be used in this setting. A US trial of topiramate in MND failed to show benefit.

Minocycline is causing interest among patients with MND (Yong *et al.*, 2004) and recent findings of the *in vitro* effects of antibiotics on motor neurone function suggest this to be a fertile area for further study. Cox 2 inhibitors were similarly interesting until the recent worries about their vascular effects. Stem cell therapy holds more hope for many patients (Silani *et al.*, 2004). At present, it is difficult to see how this would translate from laboratory to the clinic. Attempts to use stem cell infusions as treatment in the United States, Canada, and Mexico have, so far, proved ineffective.

MULTIDISCIPLINARY TEAM APPROACH

MND is an uncommon disease. The average general practitioner will only see one or two cases in a lifetime. Even hospital physicians will only see a handful of cases unless they have a particular interest in the condition. As seen above, it is a disease which progresses rapidly and in which the patients disability needs require addressing quickly before progression makes the measures ineffective and redundant. These requirements of prompt intervention, anticipation of future difficulties and awareness of the sources of help requires a specialist team of health-care professionals. Several ways of delivering care are possible but a multidisciplinary approach has got to be followed in all of these. The geographic area covered by an MND team or clinic will vary according to local need and availability of resources but the larger the area covered, the greater the need for an outreach service that avoids making patients and carers travel long distances to hospital-based services. The core structure of an MND team should ideally include a consultant with an interest in MND and its rehabilitation needs (usually a neurologist in the United Kingdom), a nurse counselor, a point of quick contact that the patient and their family can access (either the nurse counselor or a secretary with some arrangement for out-of-hours contact), a physiotherapist, an occupational therapist, a speech therapist, a dietitian, and a social worker (in the United Kingdom). Many others also have a contribution to make and can be involved by the core team as necessary. For example, a gastroenterologist's help is needed to insert a PEG for feeding, an orthotist may be needed for simple appliances and the assistance of a specialized rehabilitation center may be required for patients with marked disability needs. Liaison with the community services is critical and requires one member of the MND team to maintain contact with community disability teams, general practices and with social services departments. These comments apply to the health delivery system in the United Kingdom but the general principles are equally applicable in other countries.

This model of care is an expensive one but is capable of providing good-quality, rapid access to health and disability needs. The speed of response is again emphasized – the time to provide a patient with a stair-lift is when they are still able to use it; a system that only responds to this need when the patient has become bed-bound is clearly failing. In countries with a state-supported welfare system, such as found in the United Kingdom, attention must also be given to whether the patient and their carers are receiving their full entitlement to financial benefits. In an ever more complicated benefits system, the guidance of a social worker, knowledgeable in this area is important. For example, the department of social security in the United Kingdom can assess requests for disability allowances under certain special rules that are applicable to patients with terminal conditions, that is, conditions in which the patient is only expected to survive a few months. Knowing this can accelerate provision of services for the most severely affected patients.

Hospice Care (*see* Chapter 170, Management of the Dying Patient)

The hospice movement and the cancer services generally have made a contribution to the management of the terminal phase of MND. Some hospices have an interest in MND and are helpful in disseminating the expertise to other hospices. They can help with symptom management by liaison with the GP and the MND team and, particularly in the final phases of the disease, can be very helpful. Some patients will die unexpectedly – for instance, will go to bed and not wake up "having had a peaceful death". In an audit of hospice care, 94% of patients dying with MND were judged as "peaceful and settled" at death in the hospice. Some will have a fairly short period of deterioration, usually at home and the patient and their carers may not wish for any outside help/intervention/ interference. Many will welcome offers of help which we should be able to offer, whether the patient chooses to stay at home or comes to a hospice or a hospital ward. If it is a hospital ward, all efforts should be made to provide a private room rather than leaving the patient on an open ward. At this stage of the disease (if not well before) the clear decision to relieve distress and discomfort should be made jointly, by the MND team, other health-care professionals such as the patient's GP, the patient, and their family. Judicious use of opiates and benzodiazepines helps to relieve distressing symptoms and although there are well-founded worries about the respiratory suppressant effects of these drugs, my view is that these worries must not stand in the way of symptom relief accompanied by a full explanation of the situation to the carers and the patient. Ideally, these discussions should have been carried out before a crisis is reached so that the physician is aware of the patient's and their family's stance on this. Management by consensus is usually more successful than what may be seen as a high-handed decision.

End-of-life Issues

Much of the press and lay interest in end-of-life issues in MND has centered on voluntary euthanasia and physician-assisted suicide, and while these are important topics for society to give the medical profession clear guidance on, the concept of end-of-life issues is a wider one. It includes nonmedical areas, for example, making a will and may include, for instance, patients making their peace with estranged relatives. The scope of these discussions is as wide or as narrow as the patient wants to make it. Furthermore, the patient may choose to discuss different aspects with different team members. They may wish a social worker or a counselor to be involved in family reconciliations but a doctor in discussions on ventilatory support. MND care must take account of the cultural and psychosocial needs of the patient. Within the constraints that this places, early discussion of major management decisions is desirable, particularly for interventions such as PEG and ventilatory support. Advance

directives on such interventions should be reviewed every six months, as evidence shows that MND patients may change their minds over this period of time.

A mentally competent patient is clearly able to make judgments of what is best for him. Mental competence is usually satisfactory in MND except in those patients with frontotemporal dementia in whom poor judgment and impaired executive function can be a disadvantage.

Physician-assisted suicide (PAS) remains illegal in the United Kingdom and in many other jurisdictions. Patient pressure is increasingly asking for the law to be relaxed, some patients even choosing to travel abroad to seek doctors' help in their suicide. One survey of doctors' views showed a significant minority support a change in the law to accommodate PAS. Others see the pressure for PAS as a failure of a medical system that cannot relieve a patient's distress sufficiently to deter them from such a course. Yet others are worried about the proper implementation of safeguards to protect vulnerable patients. The UK House of Lords has introduced draft legislation to debate these issues, with a view to legalizing PAS. Currently, society accepts and permits application of the principle of "dual effect" in medical practice in palliative care. Doctors may give increasingly larger doses of medication including opiates and benzodiazepines to relieve patients' distress in a terminal disease such as MND, accepting that a second consequence of this action is respiratory depression and possibly, acceleration of death. However, the primary motive remains one of relieving distress and not accelerating death. Any crossing of the current boundaries must examine the concept of the "slippery slope" to determine whether permitting PAS would necessarily lead, in steps, to other interventions that are currently undesirable or abhorrent.

KEY POINTS

- Early diagnosis and speedy multiagency interventions facilitate good palliative care in MND.
- Many MND-mimic disorders are eminently treatable.
- Riluzole prolongs survival in MND.
- Superoxide dismutase 1 mutations cause familial MND.
- End-of-life issues and symptom relief are inextricably linked.

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Abnormalities of the Autonomic Nervous System

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INTRODUCTION

Investigations of the autonomic nervous system may focus on one or more of the three efferent divisions: sympathetic, parasympathetic, and enteric (which is intrinsic to the gut wall and regulated by extrinsic sympathetic and parasympathetic pathways), the afferent nerves of the reflex arcs, the central nervous components of autonomic control, and the effector target organs. Not surprisingly, no single test can provide a global assessment of autonomic function. Accumulated evidence suggests that some deterioration in selected areas of autonomic function occurs with "normal" aging, that is, in the absence of signs of disease. The biological importance of the autonomic control of peripheral target organs becomes clear in old age when components of the autonomic system diminish in effectiveness and precision in their control of many vital functions. The close relationship between autonomic nerves and their target organs means that the nerve–target and target–nerve interactions become essential for optimum function. This two-way relationship, best known in early development, applies to the mature organism and also to the aging process. The present review attempts to link some of the classical syndromes of autonomic dysfunction in old age, for example, orthostatic hypotension, thermoregulatory lability, gastrointestinal disturbances, with more recent progress in understanding the neurobiology of the autonomic nervous system. For further detailed information, the reader is referred to Apenzeller (1994), Cowen and Santer (2002), Kenny (1996), Mathias and Bannister (1999), and Wade (2002). There are many technological advances that have led to effective noninvasive investigation of the autonomic nervous system, and methods of microneuronography, neuroimaging, immunocytochemistry, and computed analysis of heart rate and blood pressure variability continue to provide further insights into the autonomic aging process.

NEUROBIOLOGY OF THE AGING AUTONOMIC NERVOUS SYSTEM

Though relatively few central or peripheral neurons undergo cell death during aging (Finch, 1993), nerve fiber atrophy and changes in receptor expression affect different populations of neurons. These changes correlate with functional impairments. Neurodegeneration in the aging nervous system is, in fact, highly selective, affecting particular groups of neurons while leaving others apparently unaffected. Similarly, while autonomic neurodegeneration plays an important part in the aging process, it is not generalized, and subpopulations of sympathetic neurons show contrasting changes.

Plasticity, that is, growth or retraction, regeneration, shrinkage, changing expression of neurotransmitters, is generally associated with the development of the nervous system. However, it has become increasingly clear that plasticity continues to be important in the mature, and even the aged, nervous system. Trophic interactions with target tissues are important elements of plasticity at all stages of life, but the nature of these interactions may change with age. Recent evidence (Cowen, 2002) suggests that reduced uptake of neurotrophic factors (e.g. nerve growth factor (NGF)) impairs the capacity of aging enteric autonomic neurons to cope with free radical damage, leaving those with the lowest levels of uptake vulnerable to age-related neurodegeneration and, perhaps, cell death.

Sympathetic Nerve Activity and Neurotransmission

Several lines of evidence indicate that resting muscle sympathetic nerve activity (MSNA) is increased with aging and that there appears to be a secondary downregulation of adrenergic receptors (Pierpont and Gornick, 1999). It is possible that an age-related reduction in arterial baroreflex

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inhibition of MSNA could contribute to increased sympathetic activity. Investigations on normotensive young and elderly people using peroneal microneuronography to study sympathetic activity and phenylephrine infusion to assess baroreflex function appear to refute this suggestion (Davy *et al.*, 1998). Hajduczok *et al.* (1991) have suggested that there is an augmented central sympathetic drive with age. It is also conjectured that the increased MSNA may result from diminished transmitter release per pulse and/or reduced postjunctional responsiveness.

There are several possible sites at which aging can modulate noradrenergic transmission (Figure 1). It is well established that there is a decreased sensitivity of prejunctional inhibitory α-2 adrenoreceptors with aging (Docherty, 2002). Prejunctional β-2 adrenoreceptors mediate a facilitation of neurotransmitter release, which may become activated when adrenaline accumulates in noradrenergic nerves, and is released together with noradrenaline as a cotransmitter. This facilitation also decreases with aging (Xiao and Lakatta, 1991). A major route of deactivation of noradrenaline released from noradrenergic nerves is by reuptake back into nerve terminals (Figure 1). The effects of aging on the reuptake process has been studied with conflicting results, some reporting reduced and others increased function of the reuptake system. The lack of an age-related tachycardia induced by adrenaline has been explained in terms of diminished reuptake (White and Leenen, 1997). Reduced prejunctional α-2 inhibitory control and reduced noradrenaline reuptake are more likely to outweigh the effects of reduced β-2 adrenoreceptor facilitation. It might, therefore, be expected that evidence of increased release of noradrenaline from adrenergic nerves with aging may be found and reflected in raised plasma levels of noradrenaline.

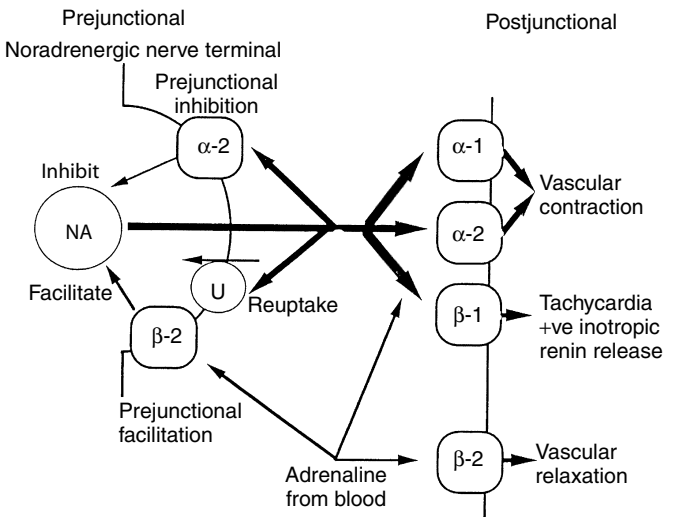

Figure 1 Diagram of the noradrenergic neuroeffector junction to illustrate (1) prejunctional α-2 adrenergic receptor inhibition of noradrenaline release (2) prejunctional β-2 adrenergic facilitation of noradrenaline release (3) neuronal reuptake (U) of noradrenaline, and (4) postjunctional effector actions of adrenergic receptors. (Reproduced from Docherty (2002) by permission of Elsevier)

In fact, one of the most consistently reported changes during aging is an increased plasma level of noradrenaline. Notably, this should not necessarily be simply equated with a basic increase in adrenergic nerve activity in the elderly.

One other important feature of aging in adrenergic neurons is the importance of control by the ion messenger, calcium (Pottorf *et al.*, 2002). Altered calcium homeostasis with age has been suggested to be a fundamental modulator of age-related changes in neuron function. There appears to be a neurotoxic effect of calcium overload in initiating neuron loss. Aging may induce a subtle change in calcium homeostasis through alterations in calcium buffering systems, and this may lead to impaired neuronal performance rather than actual neural loss.

Overall, prejunctional changes tending to increase neurotransmission may be negated by diminished postjunctional responsiveness of the target organs, resulting in little change of adrenergic neurotransmission with aging. However, the downside of these underlying adjustments may be to produce a loss of some of the fine control of neurotransmission.

The Parasympathetic System and Sympathetic Modulation

Compared with sympathetic neurons, less is known about aging changes in parasympathetic neurons, although the impairment of vagal control of cardiac chronotropic responses is well documented. There is considerable variability in findings in different species and tissues, and not always is release of the cholinergic transmitter diminished with age. The major pelvic ganglion in small rodents is unusual in that it contains both sympathetic and parasympathetic neurons and provides a useful model system in which to compare changes in the two efferent pathways. In this model, it has been demonstrated that the population of sympathetic neurons is selectively affected by degenerative changes with aging while the parasympathetic population is spared (Santer *et al.*, 2002).

Many functional and structural aspects of parasympathetic neurons are regulated by the presence of sympathetic innervation (Smith *et al.*, 2002). In addition to being postjunctional to parasympathetic axons, sympathetic varicosities frequently are postjunctional to parasympathetic nerve varicosities, which suggest that parasympathetic neurons could be a target of sympathetic innervation. NGF is one influence promoting sympathetic innervation, and parasympathetic neurons appear to be among a variety of neuron types that apparently synthesize NGF, with the level of NGF protein being modulated by adrenergic transmission. Sympathetic nerve activity is itself important for normal expression of NGF in parasympathetic neurons and may provide a mechanism for reinforcing sympathetic-parasympathetic associations. Sympathetic innervation thus appears to play a crucial role in determining the structural and functional properties of coprojecting parasympathetic neurons.

The Enteric System

There has been considerable growth of interest in recent years in the intrinsic and extrinsic innervation of the gastrointestinal tract. This has included recognition that far from involving only classical autonomic neurotransmitters, acetylcholine and noradrenaline, the autonomic nervous system of the gut employs many transmitters or cotransmitters including amines, γ-aminobutyric acid, adenosine triphosphate, nitric oxide, and a variety of other peptides. The neuropeptides are probably the most abundant neurotransmitter type in the gut. The major inhibitory innervation comes from the intrinsic nerves playing an essential role in most gastrointestinal reflexes. They are noradrenergic, noncholinergic neurons for which there is now a wealth of information that the neurotransmitter is nitric oxide (Keef *et al.*, 1993). It is worth recording also for interpretation of future studies that the conventional view, which holds that the extrinsic parasympathetic and sympathetic innervation is largely composed of motor efferent fibers, is now thought to be erroneous. Recent investigations have shown that the majority of fibers are afferent (Aziz and Thompson, 1998), revealing the fact that the extrinsic innervation continuously transmits information on the functional state of the gastrointestinal tract to the central nervous system (CNS) in a functional gut-brain-gut axis.

The enteric nervous system is complex and capable of mediating semiautonomous reflex responses for gastrointestinal motility, absorption, and secretion. These reflexes are controlled independently through intrinsic sensory neurons, interneurons, and motor neurons interconnected in microcircuits. More studies are required in order to understand the paradox that gastrointestinal function often remains largely intact while the enteric nervous system suffers neuronal loss with age. The neurodegeneration with aging does not consistently change from one organ to another along the length of the tract. Neurodegenerative changes in the enteric nervous system and their functional correlates have been reviewed in investigations in mice, rats, and guinea pigs (Wade, 2002), and the clinical literature seems to indicate similar structural and functional age-related changes in humans. Through combinations of electrophysiology, nerve tracing, and immunocytochemistry, distinct classes of neurons are recognizable and age-related changes in specific neuron components can be identified.

AUTONOMIC DYSFUNCTION AND DISORDERS OF THE NERVOUS SYSTEM

Autonomic dysfunction may arise as a specific feature of certain primary degenerative disorders of the nervous system including multiple system atrophy (MSA), pure autonomic failure (PAF), and autonomic failure in Parkinson's disease (PD) (*see* **Chapter 66, Parkinson's Disease and Parkinsonism in the Elderly**). Dysfunction may also arise as a secondary consequence of more general disorders involving the nervous system such as diabetic neuropathy. Diabetes mellitus is overwhelmingly more commonly associated with autonomic disturbances than other forms of disease involving the autonomic nervous system (Table 1). There are other large groups associated with autonomic symptoms such as parkinsonian patients, those taking drugs affecting the autonomic system, and especially the elderly in whom some progressive decline in autonomic control is thought to result from aging processes.

Table 1 Autonomic dysfunction associated with diseases of the central and peripheral nervous systems

Central
Primary autonomic failure (PAF)
Multiple system atrophy (MSA) (Shy–Drager syndrome)
Cerebrovascular disease
Trigeminal zoster
Parkinson's disease (PD)
Wernicke's encephalopathy
Brain tumors
Alzheimer's disease
Hypothalamic degeneration
Traumatic brain or cord lesions
Multiple sclerosis
Transverse myelitis
Syringomyelia
Tabes dorsalis
Holmes–Adie syndrome
Peripheral
Diabetes mellitus
Guillain–Barré syndrome
Acute inflammatory neuropathies
Amyloidosis
Alcoholism
Vitamin B complex deficiency
Vitamin B_{12} deficiency
Rheumatoid arthritis
Chronic renal failure
Chronic liver disease
Malignancy
Chemical toxicity

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Primary Autonomic Failure

Virtually all patients with primary autonomic failure in PAF, MSA, and PD are found at postmortem to have severe loss of intermediolateral column cells (Bannister and Mathias, 1999). There is widespread involvement of the autonomic system in MSA, which, although a comparatively rare disease, presents with many classical features of autonomic failure including orthostatic hypotension, defective sweating, visual disturbances, and bladder, bowel and sexual dysfunction. There is increasing evidence that neurochemically defined neuronal groups in the brain stem are selectively affected in MSA to a much greater degree than in PD (Benarroch, 2002). However, MSA may have a prevalence rate of 10 per 100 000 compared with 100 to 150 per 100 000 for PD. The neurological changes in MSA are accompanied by marked depletion of dopamine, noradrenaline, and tyrosine hydroxylase-containing dopaminergic neurons projecting primarily to the putamen. Magnetic resonance imaging may

show abnormalities in the cerebellum, brain stem, and putamen. In elderly patients with MSA, dementia is uncommon and it is surprising to find preserved intellectual function in a patient who is almost completely incapacitated in terms of motor control, orthostatic hypotension, and bladder disturbances. This is in striking contrast to the neuronal degeneration in Alzheimer's disease in which there is degeneration of cholinergic ascending projections from the reticular system and with the intellectual impairment that is a feature of PD.

The degree to which autonomic nervous involvement occurs in classical PD has been debated for many years. Autonomic involvement can be defined as measurable sympathetic or parasympathetic dysfunction (Bannister and Mathias, 1999), but few parkinsonian patients have clear autonomic failure. The primary autonomic syndrome associated with PD is rare and much less common than autonomic failure with MSA. Many patients with classical PD have mild orthostatic hypotension. However, such patients do not have the abnormalities of cardiovascular reflex control associated with baroreflex defects or intermediolateral column loss. Because cardiovascular reflexes and Valsalva tests are usually normal, it is concluded that there may be changes in the midbrain or hypothalamus associated with classical PD pathology that affect the input to the autonomic nervous system, and these might be the reason for the relatively mild autonomic abnormalities in PD.

Secondary Autonomic Failure

A variety of disorders including diabetes mellitus, amyloidosis, alcoholism, and a wide range of acute and chronic peripheral neuropathies cause secondary damage to autonomic fibers. Secondary autonomic failure can also be a complication of renal failure and various autoimmune and collagen or connective tissue diseases. Orthostatic hypotension results from damage to the small-diameter myelinated and unmyelinated fibers in efferent and afferent nerves in the baroreflex pathways and in the splanchnic outflow. Diabetes and amyloidosis in which the small fibers degenerate are often associated with orthostatic hypotension. This occurs also in the Guillain–Barré syndrome in which segmented demyelination affects the myelinated autonomic fibers in the vagal and sympathetic pathways. Impaired sweating, bladder dysfunction, impotence, and pupillary abnormalities are other clinical manifestations of autonomic dysfunction in peripheral nerve disease.

Autonomic function declines with age, but in diabetes it deteriorates on average faster than in healthy people. Most patients who develop abnormal autonomic function do become symptomatic. Early small-fiber damage is indicated by impairment of vagally controlled heart-rate variability, while diminished peripheral sympathetic tone leads to increased blood flow, which is detectable before there is clinical evidence of neuropathy. It is possible that immunological mechanisms might underlie symptomatic autonomic neuropathy. Autoantibodies to cervical sympathetic ganglia, vagus nerve, and adrenal medulla are present in 20 to 28% of patients with insulin-dependent diabetes mellitus (Watkins, 1998). NGF, as previously noted, regulates sympathetic nerve development, plasticity, and maintenance of transmitter levels. Antibodies to NGF can both change autonomic nerves and cause pronounced atrophy of sympathetic ganglion cells.

Peripheral neuropathy may be present in alcoholism and in cases of Wernicke's encephalopathy. Thiamine deficiency induces a "dying back" neuropathy as shown in beriberi, the most distal parts of the longest fibers in the vagus nerve appear to be affected earliest. Shorter, more proximal fibers of the sympathetic system are affected later when the peripheral neuropathy becomes severe. Strong evidence of vagal damage has been demonstrated by impaired heart-rate responses to Valsalva maneuver, deep breathing, postural change, neck suction, and atropine tests.

Pupillary Abnormalities

Pupil dysfunction is involved in a number of autonomic disorders. Ocular deficits in the parasympathetic system may be seen most commonly in Adie's syndrome, while increased parasympathetic activity occurs in Argyll Robertson pupils. Sympathetic deficits in Horner's syndrome result in ptosis and miosis, whereas sympathetic overactivity causes large pupils in oculosympathetic spasm. Pupillary changes are important signs of autonomic dysfunction, and small pupils with age are also characteristic in diabetic autonomic neuropathy. Sympathetic dysfunction appears to be partly responsible, but there is also evidence for parasympathetic dysfunction. As small pupils with normal light reflexes are found to be more common than larger pupils with reduced reflexes, it appears that the sympathetic pupillary innervation is more susceptible. Reduced pupil size, diminished darkness reflex amplitude and velocity, and prolonged recovery time of light reflex are consistent with a sympathetic deficit in old age (Bitsios *et al.*, 1996).

CARDIOVASCULAR AUTONOMIC CONTROL

Autonomic syndromes involving altered function in the cardiovascular system with aging are components of both hypertension and hypotension in the elderly population. A systematic increase in sympathetic activity in older subjects, as has been identified in a previous section, would be expected to cause or exacerbate hypertension. Autonomic abnormality with aging is implicated in the well-recognized orthostatic and postprandial hypotensive syndromes as well as other vaso-vagal causes of syncope. Blood pressure homeostasis becomes impaired with age and cardiovascular reflexes such as the arterial and cardiopulmonary baroreflexes, chemoreflexes, facial cooling bradycardia, and sympathetic cold pressor reflexes may be affected (Eckberg and Sleight, 1992; Collins *et al.*, 1996). The main factors contributing to different response patterns include reduced compliance of the vasculature, impaired vagal activity, decreased sympathetic

nerve responses, reduced baroreflex sensitivity, and changes in the integrative role of the central autonomic network.

Essential Hypertension

Hypertension in most elderly patients is primary, or essential, with atherosclerosis and increased peripheral resistance being the underlying causes (*see* **Chapter 48, Hypertension**). Local endothelial vascular factors play a role, as well as central autonomic control. In elderly patients there is a loss of arterial compliance with higher systolic pressure and left ventricular hypertrophy. Secondary hypertension is most often due to renal or reno-vascular factors. There is an important interaction between the sympathetic nervous system and the renin–angiotensin system. Angiotensin II acts on the sympathetic nervous system at the central, ganglionic, and nerve terminal levels, as well as at the adrenal medulla, to increase sympathetic nerve activity. It may also influence the relative balance between vagal and sympathetic drives. Neurochemical studies on regional and whole-body catecholamine release show that sympathetic activation at rest is evident in the elderly, probably originating in excitatory noradrenergic suprabulbar projections from the brain stem (Esler *et al.*, 2002). In contrast to sympathetic nerve activity, tonic adrenaline secretion from the adrenal medulla is markedly reduced with age. It is often not well reflected in plasma adrenaline concentration because of reduced plasma clearance. Despite a widely held belief to the contrary, sympathetic responsiveness to acute stress is not exaggerated with age in healthy adults. Indeed, the adrenaline response to acute stress is reported to be substantially decreased in older men.

Endothelial cells produce a variety of relaxing and constricting substances; some of which, for example, endothelin, are known to influence signaling and central baroreflex modulation. The role of endothelin in the control of hemodynamics is not limited to a direct action on the vascular smooth muscle. Endothelin-1 modulates peripheral neurotransmission with both prejunctional inhibiting and postjunctional stimulating action for cholinergic and adrenergic neurotransmission. Chronic elevations of endogenous endothelin in humans can result in hypertension. In patients with essential hypertension there is an increased venoconstrictor response to local endothelin-1 and sympathetically mediated venoconstriction of capacitance vessels is potentiated (Haynes *et al.*, 1994). Endothelin may contribute to blood pressure control by contraction of the vascular smooth muscle, potentiation of α-adrenergic vasoconstriction, and activation of angiotensin-converting enzyme. Investigations of the baroreflex response to head-up tilt in elderly and young normal volunteers show an increase in circulating levels of vasoactive hormones such as endothelin and noradrenaline and smaller heart rate increases in the elderly (White *et al.*, 1997). The aging kidney reacts to adrenergic stimulation with a more pronounced and prolonged vasoconstriction that is thought to be caused by a defect in prostaglandin modulation of endothelial activity (Castellani *et al.*, 1998).

Orthostatic Hypotension

Orthostatic hypotension is defined as a 20 mmHg or more fall in systolic blood pressure (SBP) and/or a 10 mmHg fall in diastolic pressure on assuming an upright position from supine. The prevalence varies between 4 and 33% among elderly persons living in the community, some of the variation depending on the investigative technique. Higher prevalence and longer falls in systolic pressure have been reported with increasing age and in association with other pathological conditions, such as those listed in Table 1. Comorbid conditions and concurrent medications are more common in the elderly, and are contributory factors. The compensatory response to orthostasis involves stimulation of the sympathetic system and inhibition of the parasympathetic system, reflecting the integrity of the baroreflex arc.

Orthostatic and postprandial hypotension are distinct conditions that may occur together in the same person. Both result from a reduction in venous return to the heart due to blood pooling (in the lower extremities or in the splanchnic region, respectively) and to inadequate baroreflex compensation. Reduction in venous return results in unloading of cardiopulmonary and arterial baroreceptors, which reduce the tonic inhibitory input to brain-stem vasomotor centers in the nucleus tractus solitarius and, thus, to sympathetic activation and parasympathetic withdrawal. In elderly people, the early baroreflex-mediated cardioacceleration response shown by younger adults is blunted, probably due to reduced cardiac β-adrenoreceptor responsiveness to sympathetic activation. To compensate for reduced cardioacceleration on standing, most normotensive elderly people are probably protected from orthostatic hypotension by α-adrenergic vasoconstriction. Data currently available suggest that α-adrenoreceptors show less age-related functional alteration than β-adrenoreceptors (Lipsitz, 1999). Even normotensive elderly may be susceptible to orthostatic hypotension if hemodynamic stress is also present, for example, when blood volume is reduced. Orthostatic hypotension can be asymptomatic when cerebral autoregulation is able to maintain normal cerebral blood flow.

There are three main modes of presentation in the elderly: falls or mobility problems, acute or chronic mental confusion, and predominantly cardiac symptoms. Medications are important in the etiology and have been found to be responsible for orthostatic hypotension in 66% of elderly patients in one study (Craig, 1994).

Postprandial Hypotension

Elderly people often show a fall in blood pressure postprandially with maximum pressure changes occurring within 30 to 90 minutes of meal ingestion. The response seems to be related to meal energy content as well as nutrient composition. The decrease in blood pressure is greater in patients with autonomic failure and in hypertensives. A large increase in splanchnic blood flow occurs after eating a meal. Insulin can lower blood pressure substantially in autonomic failure,

and it has been proposed that this may cause the splanchnic vasodilatation. However, the results of much experimental work make it unlikely that changes in insulin are directly responsible for postprandial hypotension in the elderly (Potter, 1996).

The somatostatin analog octreotide prevents the rise in insulin, neurotensin, and a range of other hormones in response to food ingestion. Octreotide is a synthetic long-acting peptide release inhibitor and effectively reduces postprandial hypotension even in low doses (25–50 μg a day subcutaneously). It has some adverse effects such as diarrhea and abdominal colic, but it has no effect on cardiac output or muscle and skin blood flow, suggesting that it exerts its effect largely on the splanchnic vasculature. Marked symptomatic reductions in blood pressure in elderly patients with pathological postprandial hypotension may result in syncope. These patients show an initial increase in plasma noradrenaline following a meal, but a subsequent inappropriate decline at a time when blood pressure is falling. Measures such as reducing the content of carbohydrate of meals are often effective in preventing postprandial hypotension.

Syncope

Transient loss of consciousness from temporary reduction in cerebral blood flow is usually preceded by an increased sympathetic activity, maintained or sometimes increased blood pressure, and increased heart rate and vascular resistance. This is followed by a profound fall in arterial blood pressure, inadequate cerebral perfusion, and loss of consciousness. Often syncope is accompanied by widespread vasodilatation and a bradycardia – the "vaso-vagal" attack. Excessive vasodilatation also occurs during thermal stress and in response to certain reflex stimuli triggering vagal reflexes during micturition, defecation, or even swallowing. Vasoactive medications may sometimes be the underlying cause and, in addition, vasoconstrictor responses may be impaired in autonomic neuropathies. Syncope can result from cerebral dysfunction due to causes other than hypoperfusion, for example, in epilepsy, hypoglycemia, Addison's disease, or hypopituitarism.

The mechanisms for the sudden switch from the apparently appropriate responses of vasoconstriction and tachycardia to inappropriate vasodilatation and bradycardia are not established. Abnormal baroreflexes, the stimulation of cardiac receptors, emotional stress, central release of opioids, and changes in blood volume have all been considered. Hypovolemia seems to be an important factor and procedures that increase blood volume are of benefit in increasing orthostatic tolerance and prevent fainting (Hainsworth, 1996). In the physically untrained healthy elderly, there is a decline in cardiac output, and even in the absence of apparent cerebrovascular disease, there is a decrease in blood flow to the brain. Baroreflex sensitivity is also decreased in many elderly people. Despite these changes, healthy old people do not appear to have a greater susceptibility to vaso-vagal syncope, though the control of blood pressure does appear to be more variable.

Carotid Sinus Syndrome

Carotid sinus hypersensitivity (syndrome) represents an exaggerated response to stimulation of the carotid sinus area, for example, following carotid sinus massage or effects of a stiff wing collar. Carotid sinus syndrome (CSS) is principally a disease of the elderly, rarely occurring before the age of 50, and it is recognized increasingly as a potential cause of unexplained falls. As expected, there is a strong association between CSS and other hypotensive syndromes such as the neurocardiogenic (vaso-vagal) and dysautonomic syncopes. There is good reason to envisage a common underlying pathophysiology of the disorders. The condition is usually diagnosed by excessive bradycardia or even asystole in response to carotid massage. Many patients diagnosed as having CSS may actually have poor orthostatic tolerance associated with brisk baroreflex responses. Thus, patients treated successfully to improve orthostatic tolerance consistently showed a decrease in baroreceptor sensitivity (El-Sayed and Hainsworth, 1996).

Sick Sinus Syndrome

As a cardiac cause of syncope, sinus node bradycardia is common in the elderly, though in most cases, it does not cause symptoms (*see* **Chapter 45, Arrhythmias in the Elderly**). A sinus node rate of less than 60 beats per minute conventionally defines sinus bradycardia. Sinus bradycardia is accepted as a normal physiological finding in trained athletes who not uncommonly have heart rates of 40 to 50 beats per minute while at rest and awake. Characteristically, in athletes, this is due to increased vagal tone. However, when sinus bradycardia is marked (<40 bpm), and particularly if persistent and with little diurnal variability, it is indicative of sinus node dysfunction. About 40 to 60% of patients with symptomatic sinus node dysfunction (i.e. sick sinus syndrome) have syncope at their initial diagnosis (Brignole, 1996). The condition is frequently associated with autonomic disease since autonomic reflexes play a major role in the genesis of syncope and greatly influence sinus node rhythmicity. The sinus node becomes more fibrotic with age, but apparently not more so in patients with sinus dysfunction. A proportion of patients with sick sinus syndrome have altered autonomic tone. Parasympathetic tone is predominant in younger patients and sympathetic tone predominant in elderly patients with sinus dysfunction.

Analysis of Blood Pressure and Heart-Rate Variability

Dysfunction in cardiovascular autonomic control has been investigated in greater depth in recent years by use of computerized methods. Employing spectral techniques, it has been possible to assess different rhythmicities hidden in R–R interval time series. Since the baroreflex is an important modulator of blood pressure and heart-rate variability, a

joint analysis of these variables by computer can be used to measure sequences of slopes of the regression between them. The slopes, in effect, can be taken as an index of the sensitivity of baroreflex control. In this case, the computer technique clearly is far less invasive than the commonly used test that employs vasoconstrictor drugs such as phenylephrine. Parati *et al.* (1995) have identified linearly related long pulse interval/hypertensive (+PI/+SBP) and linearly related short pulse interval/hypotensive (−PI/−SBP) sequences. In 24-hour ambulatory monitoring records in young adults and elderly volunteers, a reduced number of these sequences were found in the elderly indicating reduced baroreflex sensitivity (Figure 2).

Heart-rate analysis has been used to quantify the relative contribution of sympathetic and parasympathetic systems to heart-rate variability. The power spectrum can be divided into low (LF) and high (HF) frequency components, LF in normalized units possibly as a marker of sympathetic modulation of sinus node activity in some physiological circumstances. On the other hand, there is practically no debate about interpreting HF components both in absolute and normalized units, as a marker of vagal modulation. Spectral analysis techniques have confirmed that "healthy" aging is associated with a reduction both in baroreflex and vagal modulation of heart rate, with a relatively greater loss of the HF parasympathetic component. As has been previously suggested, the loss of vagal input may protect some elderly individuals from the development of "vaso-vagal" syncope.

TEMPERATURE REGULATION

Homeothermy is achieved in humans by the coordinated responses of autonomic, metabolic, and behavioral activities integrated within the CNS. Autonomic vasomotor and sudomotor adjustments are crucial for heat loss mechanisms and vasomotor and metabolic functions for heat gain. Autonomic disorders in human thermoregulation, particularly in the more vulnerable elderly, can lead to the development of abnormal thermal states such as poikilothermia, hypothermia, and hyperthermia (Collins, 1999). Behavioral thermoregulation provides a powerful first line of defense to changes in environmental temperature though it may hinder recognition of autonomic thermoregulatory failure.

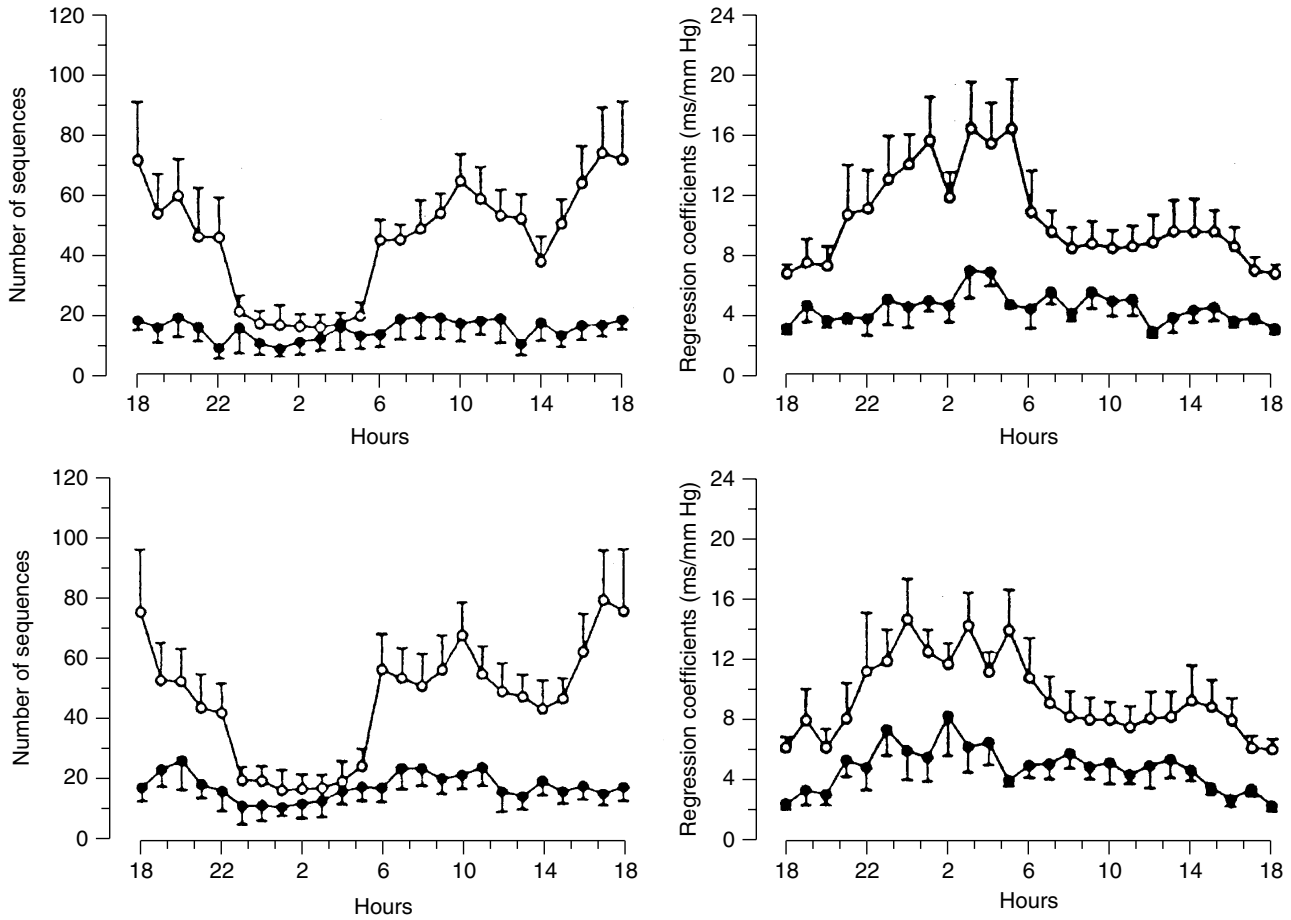

Figure 2 The number (left) and regression coefficients (right) of +PI/+SBP (top) and −PI/−SBP (bottom) sequence slopes (i.e. slopes of pulse interval and systolic blood pressure occurring in hypertension-bradycardia or hypotension-tachycardia sequences) in young (○) and elderly (●). Mean values ± S.E. for each hour of the recording. (Reproduced from Parati *et al.* (1995) by permission of The American Physiological Society)

Thermoregulatory Effector Mechanisms

In cold conditions, shivering and nonshivering thermogenesis operate to maintain deep body temperature in addition to vasoconstriction. Shivering is mainly controlled by somatic motor nerves, and sympathetic thermoregulation of metabolic heat gain in humans is basically concerned with the control of nonshivering thermogenesis. Nonshivering thermogenesis in the adult human can be produced by the calorigenic action of catecholamines and other hormones such as thyroid hormone. The sympathetic system plays a major role in stimulating heat production from brown adipose tissue, but this is only important in the newborn and not the adult. The thermogenic effect of food intake is a relatively small but potentially important part of total daily energy turnover. The facultative component of the thermogenic reaction depends on sympathetic nervous control and it has been shown to be significantly lower in elderly people. Noradrenergic vasoconstrictor neurons probably represent the largest group of sympathetic nerves supplying the skin and their dysfunction plays an important role in thermoregulatory lability of the elderly in cold conditions.

Vasodilatation in hot conditions is brought about by inhibition of sympathetic vasoconstrictor tone, release of colocalized transmitters from sympathetic cholinergic sudomotor activity, and possibly by active vasodilator systems. The degree of thermally induced vasodilatation attained by the elderly is usually less than in younger people and corresponds to a reduced cardiac output. Some of the most striking neurotrophic actions between nerves and target organs have been shown in the aging sudomotor system. Immunohistochemical studies on sweat glands from forearm biopsies in young adult and 80-year-old subjects have demonstrated marked regression of secretory coils with age, together with a significant decrease in the number of immunoreactive sympathetic nerve varicosities and nerve bundles (Figure 3).

Only traces of normally strongly acetylcholinesterase-positive sudomotor nerve fibers were found in the elderly skin biopsies, together with diminished content of cotransmitters VIP (vasoactive intestinal polypeptide) and CGRP (calcitonin gene related peptide) (Abdel-Rahman *et al.*, 1992). The immunohistochemical changes correspond closely to the functional deficits in sweating.

Poikilothermia

Few studies have been made on changes in the brain centers in humans with aging. Indirect evidence from investigations on thermal comfort, behavioral thermoregulation, circadian temperature rhythms, and sleep–wake cycles have implicated changes in the integrative function of the CNS in older people (Collins *et al.*, 1995). Poikilothermia signifies a lack of regulated constancy of body temperature and is diagnosed by abnormal fluctuations in deep body temperature of more than 2 °C when ambient temperature changes. The condition usually relates to a lack of central thermoregulatory control, and it may occur in extremes of hyperthermia and hypothermia. Although there appears to be a heterogeneity of brain lesions responsible for the condition (MacKenzie, 1996), it is claimed that it is principally caused by lesions in the posterior hypothalamus and midbrain leading to autonomic dysfunction. Relative poikilothermia in the absence of acquired hypothalamic lesions is most frequently encountered in the newborn and in old age. Lack of thermal discomfort and failure of behavioral thermoregulation plays an important part by an absence of compensation for autonomic thermoregulatory dysfunction.

Hypothermia

Hypothermia, defined as the condition in which deep body temperature falls below 35 °C, commonly arises as the result

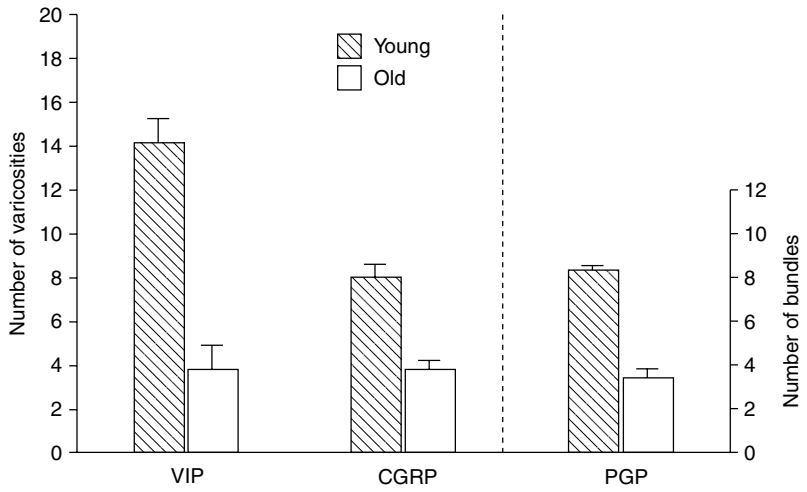

Figure 3 A histogram showing the number of nerve varicosities around each sweat gland secretory coil stained for VIP and CGRP (mean ± S.D.) and the number of nerve bundles around each secretory coil stained for PGP (protein gene product) (mean ± S.D.) in young and elderly subjects. *t*-test for each comparison by age, $P < 0.001$. (Reproduced from Abdel-Rahman *et al.* (1992) by permission of Elsevier)

of accidental and excessive exposure to cold. It occurs in the elderly, in neonates, in undernutrition, and in a number of clinical settings involving central, peripheral, or metabolic failure with disturbances in autonomic nervous control. Primary hypothermia involves abnormalities in the CNS. Persistent hypothermia associated with hypothalamic damage is well recognized, and periodic hypothermia has been observed with agenesis of the corpus callosum, central abnormalities affecting thermoregulatory brain structures, and, rarely, without an associated systemic disease or recognized brain lesion. Most of the latter cases appear to defend a lowered temperature set point by active body heat dissipation through vasodilatation and sweating and by decreasing heat generation by behavioral mechanisms (MacKenzie, 1996).

Secondary hypothermia is by far the most common presentation (Table 2). Low deep body temperature is then associated with existing pathological conditions such as diabetes mellitus, Parkinson's disease, or the effects of medications.

Elderly people are susceptible to cold because of lower thermogenesis, reduced sympathetic vasoconstrictor activity, and blunted temperature perception and behavioral response to temperature change. Phenothiazines, hypnotics, anxiolytics, antidepressants, and alcohol can greatly increase this susceptibility. In hypothermia, there is often a marked deterioration in vital functions in the elderly patient. A spontaneous fall in deep body temperature can occur during the course of overwhelming general infection, and there may be a common link between hypothalamic dysfunction and the infectious disorder. Though once considered to be a significant cause of winter mortality in the elderly, the incidence of hypothermia is not high in the United Kingdom. Only a few hundred death certificates each year mention hypothermia as a cause. Of the annual figures of 20 000 to 40 000 excess winter deaths in England and Wales, perhaps only about 1% is associated with hypothermia.

Table 2 Conditions commonly associated with secondary hypothermia

Metabolic
Hypothyroidism
Hypopituitarism
Hypoglycemia
Diabetic ketoacidosis
Protein calorie malnutrition
Uremia
Adrenocortical insufficiency
Central nervous dysfunction
Cerebrovascular accident
Brain tumor
Head injury
Wernicke's encephalopathy
Spinal cord lesions
Multiple sclerosis
Parkinson's disease
Confusional states
Dementia
Cardiovascular
Myocardial infarction
Congestive heart failure
Shock
Severe hemorrhage
Peripheral vascular disease
Skin disorders
Erythroderma
Extensive burns
Infections
Severe generalized infections
Miliary tuberculosis
Endocarditis
Severe gastroenteritis
Drug induced
Alcohol
Anesthetics
Hypnotics
Vasodilators
Psychotropics
Tranquillizers
Hypoglycemics
Antithyroid agents
Ganglion-blocking agents
Other
Steatorrhea
Paget's disease
Malignant disease
Osteoarthritis
Rheumatoid arthritis
Systemic lupus erythematosis

Hyperthermia

Elevation of deep body temperature above 38.4 °C is arbitrarily considered to represent a hyperthermic state. Heat stroke is characterized by a deep body temperature of 41 °C or more accompanied by CNS disturbances leading to convulsions and coma and anhidrosis, which is often present but is not pathognomic of the condition. Heat-related deaths during urban heat waves, especially in the elderly population, are generally not directly due to thermoregulatory failure but due to existing cardiovascular disease worsened by heat strain. Central nervous dysfunction leading to hyperthermia originates from many of the central nervous lesions listed in Table 2 for hypothermia.

Thermoregulatory autonomic impairment resulting in diminished sweating and peripheral vasodilatation is likely to be one of the factors that may lead to heat stroke in older people. In addition, factors controlling fluid balance, the secretion of vasopressin and its renal response, and the control of sodium balance are adversely affected by age and are important in the response to heat stress. Commonly prescribed medications, anticholinergics, diuretics, and psychotropics, in particular, increase the risk of heat intolerance in the elderly. To a large extent, the physiological deficits in autonomic function can be compensated for by appropriate conscious behavior in hot conditions, but even this avenue becomes less trustworthy because of a thermal perception deficit in the elderly. Mortality in heat waves is significantly higher among the elderly on "heat stress days" (Smoyer *et al.*, 2000) when a heat stress index similar to the WBGT index (wet bulb globe temperature) exceeds 32 °C.

GASTROINTESTINAL FUNCTION

Dysphagia, constipation, diarrhea, and irritable bowel syndrome are more commonly experienced by the elderly, but little is known of the underlying changes in the gastrointestinal tract. Compared with the rapid advances in the neurobiology of the CNS, understanding of age-related changes in the enteric nervous system is also poor (Wade, 2002). Conventional wisdom holds that gut function changes with age though much of the clinical literature suggests that the gastrointestinal tract continues to function adequately despite loss of enteric neurons. Age-related changes in esophageal physiology often appear to be minimal when objective criteria are employed. For example, dysphagia and gastroesophageal reflux are relatively common complaints in the elderly, and morphological studies have shown an age-related loss of enteric neurons in the human esophagus (Meciano Filho *et al.*, 1995). Quantitative manometry suggests that esophageal contractile wave amplitude and velocity and the duration of lower esophageal sphincter relaxation are not different in elderly and younger adults (Ferriolli *et al.*, 1998). However, there is some evidence of reduced amplitude of peristaltic contraction in the lower esophagus of the elderly (Nishimura *et al.*, 1996). The rates of gastric emptying and small intestinal transit are seemingly unchanged with age in humans (Wade, 2002). Gastric myoelectrical activity recorded by electrogastrography (EGG) may be used to indicate the influence of aging on autonomic activity in healthy volunteers 20 to 71 years of age (Thor *et al.*, 1999). It was deduced that changes in dysrhythmia of gastric slow waves in the EGG accompanied measured decreases in cardiac sympathetic and parasympathetic activity from heart-rate variability analysis. There is evidence of both increased and reduced colonic transit in the elderly, discrepancies that may be due to difficulties in assessing normal changes in motility and to the presence of chronic disease and the use of medications. With advancing age, however, there appears to be a reduction in the total population of neurons in human colonic submucosal plexuses. Much of the evidence of autonomic dysfunction in the gastrointestinal tract with aging comes from animal studies on loss of enteric neurons and altered motility and secretory states, but the position appears now to have moved to addressing the mechanisms by which neuronal loss or dysfunction applies to surviving enteric neurons.

UROGENITAL FUNCTION

Normally, basal efferent sympathetic nerve activity appears to be too low to be of major influence on renal hemodynamics. Above baseline, however, the effect of renal sympathetic activity can be profound. Renal nerve stimulation decreases single-nephron glomerular filtration rate and single-nephron plasma flow. In investigations of renal sympathetic nerve activity associated with aging, there is a greater increase in sympathetic activity than would be expected from impairment of arterial and cardiopulmonary baroreflexes (Hajduczok *et al.*, 1991). The increase in renal sympathetic nerve activity, however, appears to represent a true increase in central sympathetic drive. It may partly account for the diminished glomerular filtration rate and renal blood flow observed with aging. Similarly, it could account for reduced plasma renin and reduced responsiveness of juxtaglomerular cells to neural stimuli.

Autonomic function due to aging or due to existing neuropathology commonly causes micturition disturbances. Patients suffering from progressive autonomic failure show a characteristic inability to contract the distal urethral sphincter. Detrusor instability can be due to abnormalities of detrusor muscle activity and/or neural control. The autonomic innervation of the lower urinary tract displays remarkable plasticity (Lincoln and Burnstock, 1993). The number of autonomic axon profiles in detrusor muscle decreases with age and is matched by a linear decrease in the density of acetylcholinesterase–positive fibers in the bladder. There are changes in transmitter or receptor expression leading to rearrangement of nerve pathways and altered function.

Erectile dysfunction, principally a disorder of older men, arises from disturbances in the integration of vascular, endocrine, and neurological mechanisms including lumbar sympathetic, sacral parasympathetic, and somatic nerves. Diabetes mellitus is one of the most common causes of erectile failure. Several processes may contribute, including large vessel disease, microangiopathy, autonomic neuropathy as well as psychogenic factors.

KEY POINTS

- Changes in autonomic neuron form and function occur during "normal" aging and in association with other disease states in the elderly.
- Autonomic function is maintained and modified in the elderly by neurological nerve-target plasticity.
- Diabetes mellitus is the most common secondary degenerative disorder associated with autonomic dysfunction.
- Failure in autonomic nervous control is an important component of hypertensive and hypotensive syndromes in the elderly.
- Thermoregulation in the elderly becomes less efficient because of autonomic nerve–target degenerative changes.

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Control of Chronic Pain

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INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP, 1994). It is always subjective. There is no way to objectively validate the patient's pain report. The role of the clinician is to evaluate the factors contributing to pain and suffering to gain an understanding of pathogenesis and potential therapeutic options.

Chronic pain is defined as pain persisting beyond the period of normal recovery (Bonica, 1953). By consensus, this has been taken to be 3 months if pain has an ongoing cause. However, such persistent pain need not necessarily lead to psychological, social, and functional consequences. Chronic pain can be defined as persistent pain that has accompanying physical, psychological, and social consequences. It is in patients with chronic pain that multidisciplinary strategies are required. There is a tendency, however, to "medicalize" pain and insist on prolonged investigations and treatments, often with an over emphasis on pharmacological and anaesthetic approaches. Once it is clear that curative approaches are not feasible, or acceptable to the patient, then a symptom management approach should be adopted, aiming to reduce pain to tolerable levels, enhance the individual's coping strategies, and minimize any pain-related handicap.

Although we have progressed in our understanding of the pathophysiology of experimental pain in older individuals, there are limitations to our understanding of the management of chronic clinical pain in this age group. This chapter summarizes pertinent data in this field and presents a model for the assessment and management of chronic pain in older people.

The Biopsychosocial Concept of Chronic Pain

Pain is never a consequence of age alone and it is very rare for it to have an entirely psychological genesis in older people. In nearly all situations where chronic pain occurs there is evidence of either nociceptive or neuropathic activity, often associated with maladaptive attitudes or beliefs and inappropriate behaviors. The current concept of chronic pain is that cognitions (appraisal of the situation and beliefs about pain and its treatment) are interposed between stimulus and outcomes. Some beliefs, such as that pain is due to ongoing damage from disease, that physical activity will make the underlying condition worse, that only medical interventions can make the pain go away, that the individual has no control over the pain, or catastrophic interpretations of the situation, can be particularly counterproductive. Conversely, other beliefs, such as that the patients who believe they are able to cope despite pain, lead to better outcomes. Thus, an approach that targets only the pain stimulus and its nociceptive pathway, without taking into consideration the individual's appraisal of the situation may lead to suboptimal outcomes.

Pain and Aging

Acute pain affects about 5% of older people at any point in time (Crook *et al.*, 1984) and management is usually integrated with treatment of the underlying cause. The prevalence of persistent pain increases with age and peaks at about 65 to 69 years in males and 80 to 84 years in females (Helme and Gibson, 2001). Between 25 and 50% of community-dwelling older people 65 years and above have persistent pain. Amongst nursing home patients, the prevalence ranges between 27 and 83% (Weiner *et al.*, 1999). This wide range, especially in residential care settings, indicates the difficulty in addressing a subjective experience in a population with a high prevalence of comorbidities, particularly those associated with cognitive and communication difficulties. There are also methodologic differences that partially explain these variations. Thus, high prevalence studies use surrogate measures such as carer opinion and analgesic use to support

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the contention that the person is in pain. In community samples, the variation may be the result of using biased samples, different time windows for pain (e.g. pain in the last week vs all-of-life pain), or summing-pain at different body sites. However, most of the variability is more convincingly explained by using different criteria for determining the effect of pain in interfering with desired functional outcomes for the individual.

Chronic pain is frequently associated with mood disturbance. Epidemiological data based on community samples suggests that mild depression with symptoms affecting older people's lives ranges from about 10 to 20% (Chiu *et al.*, 1999). The prevalence of anxiety is less well defined as the instruments used to determine affective disturbance overlap on these domains. However, in pain clinic samples, older patients generally express less anxiety than their younger counterparts. Other mood states, which are rarely pursued during clinical assessment, include frustration, anger, and demoralization. There are validated psychometric instruments that may be used to explore these other facets of mood disturbance in older people such as the Profile of Mood States (Gibson, 1997), but they have not been used in epidemiologic studies. The physical impact of chronic pain alone is often difficult to differentiate from the physical disability associated with other comorbid medical conditions common in the older population. In a recent epidemiological survey among community-dwelling Australians, around 60% of the sample aged 65 years and above expressed that pain interfered with their daily activities (Helme and Gibson, 1999).

The belief systems that modulate the effects of nociceptor inputs are diverse in the psychological literature. The commonest approach is to consider coping strategies, or their converse, catastrophic, with feelings of despair, fear, or helplessness. Other concepts, however, may also be explored such as stoicism and fear avoidance. There are instruments validated for these constructs in older people but they have rarely been reported in the clinical literature.

The relationship between pain and gender has not been clearly defined in the elderly, although certain conditions occur more commonly in elderly females, such as joint pain, chronic widespread pain, and fibromyalgia. Chronic pain is more likely in widows living alone. The effects of ethnicity on pain in older people is not known.

AGE-RELATED CHANGES IN THE NOCICEPTIVE SYSTEM

The trend of psychophysical studies suggests that the sum of physiological changes in older persons results in higher pain thresholds, but lower pain tolerance (Gibson and Helme, 2001). The pain threshold is the level of stimulus intensity (mechanical, thermal, chemical, or electrical) that the subject first perceives as being noxious. Pain tolerance is the maximal amount of a noxious stimulus that a subject can bear.

In the peripheral nervous system, A-δ primary afferents associated with nociceptors are essential for the transmission of noxious input to the central nervous system following noxious stimulation (e.g. the sharp sting of a hot object). There is impairment of A-δ nerve function in the elderly (Chakour *et al.*, 1996) suggesting altered and, possibly, less pain. Conversely, in the elderly, noxious stimuli delivered at low frequencies of around 0.2 Hz are capable of showing temporal summation, meaning that for the fifth repeated stimulus a noxious stimulus is rated to be more painful when compared to the first stimulus. This phenomenon only occurs in the young at higher frequencies (Gibson *et al.*, 2002), suggesting amplified pain in older people once stimulation is underway. In addition, it has also been demonstrated that after prolonged noxious stimulation endogenous pain modulation mechanisms in the older person are not activated to the same degree as in younger adults (Washington *et al.*, 2000). The effect of these functional changes in experimental pain on the experience of clinical pain in older people is not yet completely understood, but will become clearer as further studies of these phenomena are undertaken. Making clinical deductions from this information is therefore somewhat premature. However, the experimental data does suggest that damage is perceived by the older person only when it is more severe. Pain may also not be as effectively "dampened" by the body's endogenous pain modulating systems. When it is perceived, it rapidly becomes intolerable in the elderly. Repeated acute pain stimuli, or continued peripheral noxious input from injury or inflammation, may have greater potential to cause more widespread and severe chronic pain in the elderly than in the younger adult.

The clinical literature is, in general, supportive of the notion that the older person feels less pain for a given level of nociceptor stimulation, but it is difficult to control for severity of disease, as attested in a largely anecdotal surgical literature in conditions as varied as fracture, peritonitis, and ischemic heart disease. There is also support for the view that severe clinical pain is less well tolerated in older people.

The clinical impact of these changes is speculative. Once an older person reports pain, they should be believed and managed appropriately. However, the converse may not be true. The absence of pain in an older person should not be interpreted as absence of pathology.

ASSESSMENT

When an individual initially presents to a health practitioner with pain, it is appropriate for the focus to be on the pathology putatively causing the pain, and on the provision of symptomatic relief. The focus shifts, however, when pain becomes chronic.

Persistent pain may be only one of the factors that modulate the well-being of the patient. The aging process is associated with multiple social, personal, and health-related losses. Establishing how persistent pain affects overall "quality of life" is important in planning treatment. This often

necessitates a multidisciplinary approach. In practice, the skills of a doctor, a psychologist, and a physiotherapist, all experienced in care of older people, are complementary and allow for a broad multidimensional picture to be assembled on each patient. A nurse clinician, occupational therapist, and pharmacist may often contribute other aspects of the assessment. The total time commitment in a complex patient may be several hours. Special attention is required to differentiate the impact of pain on the individual, their social interaction, and functional ability from that due to other factors.

Domains of Assessment

Assessment of chronic pain in the older person is similar to that in the younger person. Common problems in the elderly making the assessment more difficult are visual impairment, deafness, cognitive impairment, and multiple comorbid medical conditions.

The assessment should encompass:

1. The medical aspect: what is the pathological process that resulted in the present pain syndrome and are there other pathologies maintaining the pain (see Table 1)? Is the pain primarily nociceptor in origin, neuropathic, a combination of the two, or unexplained? How many medical comorbidities are there and do any of them, or their treatment, affect the management of pain? Is specific disease management or a symptom management approach required, or both? Are there features to suggest more sinister pathology? Is polypharmacy an issue complicating the management of the pain problem? What factors are likely to limit compliance?
2. The functional aspect: what functional implications are there for the patient because of the pain? This may be in terms of activities of daily living, instrumental activities of daily living and effects on discretionary and vocational activities, and even the ability to attend to health care.
3. The social aspect: what impact does the pain have on social relationships and are aspects of the relationship maintaining the chronic pain syndrome?
4. The cognitive aspect: what are the patient's beliefs about the cause, prognosis, and treatment options of the pain? How are these interacting with their pain?
5. The affective aspect: is the pain associated with depression, anxiety, anger, or other mood disturbance?
6. Is general cognition failure interfering with assessment, coping, or management?

The Medical/Physical Assessment

A thorough pain history should include information on the onset, duration, site, radiation, severity, character, and temporal characteristics of the pain, particularly precipitating, aggravating, and relieving factors. The history should include exploration of previous treatments, and why they may have been ineffective, for instance, incorrect "dosing", inadequate duration, poor tolerance, or poor compliance. There may frequently be multiple sites of pain. A pain diagram may give a better representation of the type and distribution of pain.

The physical assessment should focus on the site and type of pathology; as well as posture, flexibility (range of movement), dexterity and gait, evidence of neural involvement with altered sensory perception (hypoalgesia, hyperalgesia, hyperpathia, and allodynia), and the ability to perform everyday activities, perhaps best assessed in the individual's usual environment. The ability to perform specific activities should also be measured to monitor progress, for example, by measuring the distance walked and the time taken. The best outcomes are usually those that improve function. Wide varieties of instruments have been validated for this purpose in older people and should be used to assess progress and reassess goals at appropriate intervals. Other considerations include assessment of autonomic activity and myofascial trigger points, although these aspects are generally less helpful in older people. A full physical, functional, and environmental assessment may need to be undertaken over more than one appointment, particularly for more frail individuals.

Table 1 Mechanisms of chronic noncancer pain

Type of pain	Definition	Examples
Nociceptive pain	Pain derived from stimulation of pain receptors. It may arise from tissue inflammation, cancer mechanical deformation, and ongoing injury or disease.	Low back disorders (vertebral compression fractures, facet arthropathies, vertebral canal stenosis).
		Degenerative joint disease (osteoarthritis)
		Rheumatoid and other inflammatory arthritides
		Visceral pain, e.g. intraabdominal pathology
Neuropathic pain	Damage to the peripheral and/or central nervous system	Poststroke pain syndromes diabetic neuropathy, postherpetic neuralgia, carpal tunnel syndrome, trigeminal neuralgia, surgery
Pain related to psychological or psychiatric disorders	Psychological/psychiatric factors are judged to play a major role in the onset, severity, and maintenance of pain	Pain Disorder (DSM4)
Pain of uncertain pathogenesis		Recurrent headaches, fibromyalgia
		Complex regional pain syndrome type 1

The severity of the pain should ideally be measured and monitored using some form of pain scale. Examples of some of the many available instruments include numerical rating scales, visual analog scales, verbal rating scales, and pain relief scales. These focus on the sensory dimension of pain. Unpleasantness scales have never been validated in older people. The McGill Pain Questionnaire (Melzack and Katz, 1994) evaluates the sensory, affective, and cognitive aspects of pain. It has been validated for use in older people. It contains a five-point severity scale, the Present Pain Intensity, and a variety of descriptors in sensory, affective, and evaluative domains, which are most useful in building a picture of the pain type. Examples of word descriptors include aching, burning, shooting, cruel, and exhausting. Another multidimensional instrument is the Brief Pain Inventory (Cleeland *et al.*, 1994), which is a shorter instrument than the McGill Pain Questionnaire, and has been translated into many languages.

Pictorial pain scales, such as the faces scale, have not been shown to be superior to other more simple scales. The intensity of color has also been used to rate the intensity of pain. The authors' preference is for the Gracely Box Scale (GBS) (Gracely *et al.*, 1978) as it combines a numerical rating scale, a verbal rating scale, and anchor points directly based on psychophysical experiments matching words to the intensity of physical stimuli, although its efficacy in older people has not been formally documented and the verbal rating intervals have only been validated psychophysically in young adults.

The initial screen should exclude organic causes of pain that need urgent or specific interventions. If the exact pathology cannot be accurately ascertained, however, it should not be relentlessly pursued if there are no features to suggest a deleterious outcome. Often a long history without progression of symptoms, or underlying pathology becoming apparent is reassuring. "Red flags" indicative of severe underlying disease include weight loss, chronic ill health and a history of other systemic illness such as malignancy, progressive neurological deficit, progressively worsening pain, and increased intensity of pain at rest. The recurrence of severe pain in an individual whose pain was previously well controlled warrants a reassessment. Where there is good correlation between the clinical findings and radiological studies specific management of the underlying pathology may be considered, for example, joint arthroplasty. Age *per se* should not be taken as an excuse to withhold beneficial surgical management. If a curative approach is not feasible or is declined by the patient, then the focus should be on control of symptoms.

Another *caveat* operative in chronic pain is that functional and clinical severity may not correlate with the severity of pathology on imaging. This applies to radiographic assessment of osteoarthritis of the knees and magnetic resonance imaging of lumbar back pain. Lumbar spondylosis and vertebral canal stenosis are common findings in the aged spine, even in asymptomatic individuals, and these findings should not become the focus of treatment unless the clinical assessment correlates with the radiologic findings.

Advancing age is associated with an increased likelihood of multiple medical comorbidities. The number of medical comorbidities has been shown to affect outcome. Drug–illness interactions are also important considerations. Some medications can also exacerbate common geriatric syndromes. For example, opioids can increase constipation, delirium, or somnolence, and tricyclic antidepressants can worsen obstruction-related lower urinary tract symptoms and postural hypotension. The selection of pharmacological agent is often based more on suitability and tolerability for the individual being treated than on the efficacy of the particular agent for the condition being treated.

The Psychological Assessment

The psychological assessment should take into account affect, pain-related cognitions, and pain-related behaviors.

The assessment of depression and anxiety must take into consideration the changes associated with normal aging, frailty, and the effects of comorbidities. These symptoms often overlap with those observed in depressed patients, such as altered sleep and appetite. Taking this into account, the Geriatric Depression Scale (Yesavage *et al.*, 1983) largely focuses on attitudes rather than somatic symptoms. Again, the Profile of Mood States gives an overall view of mood and has been validated in older people. Establishing the temporal relationship between the pain problem and the mood disorder is important. Treating a primary affective disorder requires a different approach.

Adaptive and maladaptive pain-related cognitions, in the form of beliefs, thoughts, and appraisals, must be identified. These may relate to beliefs surrounding the meaning of the illness, the types of treatment that are available, the amount of control one has over pain, and the type of strategies that one can use to cope with pain. Some cognitive factors that can lead to poor outcomes include beliefs that the severity of pain correlates with the severity of the underlying illness, and perhaps therefore severe ongoing pain represents an undiagnosed cancer or severe ongoing damage. Other maladaptive beliefs are that only medications or an operation will resolve the pain, or that all physical activity should be limited till the pain resolves. Pain-associated behaviors include expressions of pain such as grimacing or rubbing, lying down in company, and avoidance of activities. This may include pain-related fear of movement (kinesiophobia) and avoidance of everyday activities. Reducing the frequency or intensity of activities may also represent a form of avoidance. An undue emphasis on passive strategies (e.g. massage, traction, and heat) and over-reliance on others to bring the pain under control is maladaptive. Some individuals have unrealistic beliefs regarding the efficacy of doctors or of prayer. Catastrophising, for instance, feelings of fear and helplessness, is the most maladaptive behavior.

Conversely, cognitive factors that can lead to better outcomes include high self-efficacy (a person's positive appraisal of their ability to undertake coping behaviors), a belief that active strategies (relaxation exercise) are helpful,

and a belief that the patient is able to control their own pain. The first and last factors represent an internal locus of control as opposed to an external locus, which is generally maladaptive.

The Social Assessment

The concern and support of relatives is often helpful in the rehabilitation of chronic pain sufferers. However, excessive solicitous behavior by relatives and carers can result in a worsening of chronic pain. For example, if a spouse insists on undertaking activities for the patient, deconditioning may occur associated with exacerbation of musculoskeletal pain. An expectation of solicitous behavior on the part of the patient can also result in social conflicts. The evaluation should also consider the possibility of carer stress, which may contribute to the severity of the patient's symptoms or their impact.

Assessment of Pain in Dementia

Given the high prevalence of chronic pain and dementia among older people, these two problems are likely to coincide. There are many different types of dementia, and even within a single diagnostic group individuals differ with regard to their cognitive and communication abilities. Dementia is associated with impairment of memory, affecting the ability to give a history of pain. Cognitive impairment is often associated with language impairment; for example, aphasia in vascular dementia and increasing paucity of vocabulary in advanced Alzheimer's disease. Multiple observations may be required for accurate and reliable diagnosis and an informant history should be sought. The inability of an individual to report pain does not exclude the possibility that they have pain of a severity warranting treatment.

The problem of severity assessment increases as the dementia worsens. For patients who are communicative, the scales listed above are still relevant. There is no consensus as to which scale is the most appropriate. There is some suggestion that word descriptor scales are able to be completed more frequently than numerical rating scales in communicative individuals with moderate to severe dementia. It is best to try a number of different scales, and select the instrument the person appears to manage best. In this way, most people with moderate to severe dementia are still able to have their pain assessed.

In noncommunicative patients, observer interpretation of pain behavior is used. Some features include facial expressions, such as brow lowering, orbit tightening, upper lid raise, and eyelid closure, and others relate to vocalizations, guarding or protective posturing, and change in motor activity. Measures for these behaviors continue to be described in the literature. The first was the Assessment of discomfort in Advanced Alzheimer patients. More recently this has been refined as the Pain Assessment In Advanced Dementia or PAIN-AD scale (Warden *et al.*, 2003). In most experimental studies, patient behavior has been observed in situations of acute pain, such as venepuncture and mobilization. The validity and reliability of these observations do not necessarily apply in situations of chronic pain. Nevertheless, with a consistent history obtained from family and professional carers, and an examination looking for consistent responses to movement of the affected body part together with examination for hypoalgesia, hyperalgesia, hyperpathia, and allodynia, a picture consistent with nociceptor or neuropathic pain can be assembled. Other factors such as hunger, constipation, urinary retention, and urinary tract infection must be considered. This then requires patient discussion of potential treatments with family and carers and consensus on outcome measures for trials of treatment undertaken for predetermined periods of time. These treatments will include medications, physical therapies, environmental modification, and limited exercising when appropriate. The measures will include functional outcomes important for activities of daily living as well as a selection of pain measures as described above.

MANAGEMENT STRATEGIES

The General Treatment Strategy

In most cases, the cause of acute pain is apparent following assessment and the pain is in most cases self limited. Where possible the underlying cause of the pain should be identified and, if possible, rectified, although in practice a short course of symptomatic treatment with modified activity, analgesia, and physical rehabilitation is often adequate. A more comprehensive management approach is required if initial measures fail to treat the pain, and it has become chronic. The aim is to promote self-management by the patient, in active empirical collaboration with the health-care team and carers. The focus is maintenance of functional independence. A multidisciplinary approach to the management of chronic pain is recommended if a good response is not achieved by a single clinician. For convenience, we have divided the management into the individual modalities, although frequently the management programme is multifaceted from the beginning.

Pharmacological Management

Despite the fact that pharmacological management has become the mainstay of pain management in older people, there is limited data specifically regarding the pharmacological treatment of chronic pain in the elderly. Principles of management are based on clinical practice, which is often extrapolated from data available in the young and patients with malignant pain. These data should be interpreted with caution. Published studies tend to be based on highly selected populations quite atypical of the patients seen on a day-to-day basis. Positive trial outcomes are often achieved over short

time frames at doses much higher than that are able to be tolerated by frail older individuals.

Analgesia may be administered as pain-contingent (as required), time-contingent, or prophylactic, that is, just prior to an activity known to exacerbate pain. Efforts to ensure good compliance are often as important as the selection of the medication itself. Side effects are common in this age group and in many instances predictable. Tolerance to side effects may be achieved by commencement at a low dose with slow titration, as tolerated. Explanation of benefits and disadvantages of treatments need to be openly discussed with patients and carers, particularly as in the management of chronic pain the goal is to optimize pain relief without causing intolerable side effect. Attempts to eradicate pain entirely, however, often results in unacceptable drug side effects. These may be as troublesome as the pain itself. Side effects can usually be managed effectively by dose adjustment or added medication that does not compromise analgesic benefits as, for example, with opioid related constipation treated with laxatives. Where there is doubt, a short trial off a medication, or at a lower dose, may help determine whether the medication is of benefit in relieving pain, or causing side effects.

1. Simple Analgesia

Paracetamol remains the first line of treatment for mild to moderate chronic nonmalignant pain. Full dosing can begin immediately at 1 g four times a day if necessary. Efficacy is not significantly different to ibuprofen. It is a relatively safe drug. The risk of liver failure with paracetamol toxicity is increased in alcoholics and malnourished individuals. It is still probably a safer option than opioids and antiinflammatory agents in this population, provided that the maximum daily dose of 4000 mg/day is not exceeded.

Nonsteroidal antiinflammatory drugs (NSAIDs) are effective analgesics and represent one of the most widely used classes of medication. The introduction of the selective cyclo-oxygenase-2 enzyme (COX-2) inhibitors was met with enthusiasm as a safer alternative than conventional NSAIDs in terms of upper gastrointestinal toxicity. There is now concern about the safety of COX-2 inhibitors, particularly in older individuals. Further evaluation of the gastrointestinal safety from the CLASS study reveals that nearly all of the new gastric ulcer complications beyond six months occurred in the subjects treated with celecoxib (Juni *et al.*, 2002; Juni and Dieppe 2004). This rate was similar to subjects treated with conventional NSAIDs. The VIGOR study, comparing rofecoxib with naproxen in subject with rheumatoid arthritis, did show sustained benefit of the COX-2 inhibitor in terms of gastrointestinal side effects, but an increase in the number of serious thrombotic cardiovascular events, beyond that which could be explained by naproxen's cardioprotective potential (Bombardier *et al.*, 2000). Rofecoxib has now been withdrawn from the market because of these concerns. There is no evidence to date that the increased cardiovascular complications observed with rofecoxib represent a class effect of the COX-2 inhibitors. COX-2 inhibitors appear to affect renal function in a similar fashion to nonselective NSAIDs. Particular caution is required in patients with renal impairment, or prescribed diuretics and angiotensin converting enzyme inhibitors. Antiinflammatory agents should be reserved for use in transient or subacute musculoskeletal pain which is thought to have an inflammatory pathogenesis. The coadministration of a proton pump inhibitor with a conventional NSAID should be considered in high-risk patients. Prolonged use of NSAIDs should be avoided.

2. Other Analgesics

For patients with pain not adequately controlled with simple analgesia, there is an intermediate step before embarking on treatment with conventional or strong opioids. The medications in this group include codeine, tramadol, and dextropropoxyphene. They may be used in combination with paracetamol. As a group their efficacy is not always predictable and side effects are common.

Codeine (methylmorphine) is an opioid analgesic with a short half-life often given in fixed combination tablets with paracetamol or with aspirin. Its analgesic effects require transformation to morphine. Recommended for incident, predictable, short lasting, and infrequent pain, its role for chronic pain management is less clearly defined. The starting dose is 8 mg in most preparations and the maximum used in older people should be kept under 60 mg four times a day, although many frailer individuals will only tolerate 30 mg. About 8% of Caucasians and 2% of Asians have a congenital absence of the enzyme responsible for this conversion and therefore obtain little pain relief. Codeine can cause constipation, nausea, and confusion.

Tramadol (hydrochloride) is an atypical centrally acting analgesic with weak action on the μ-opioid receptor. It has additional pharmacological actions, inhibiting noradrenaline and serotonin reuptake. For this reason, it is usually classified separately from the opioid analgesics. Short acting and sustained release oral preparations are available. It is often used for acute pain, and may be used for chronic pain. Dose reduction may be required when used in the elderly. The starting dose is 50 mg of the short acting preparation. Once a daily maintenance dose has been determined, tramadol can be prescribed in a twice-daily slow release preparation. The maximum recommended dose in the elderly is $300\,\mathrm{mg\,day^{-1}}$. Up to one third of patients are unable to tolerate tramadol, experiencing symptoms such as nausea, vomiting, sweating, dizziness, tremors, and headaches. Serious side effects include delirium and hallucinations. Serotonergic syndrome is another possible side effect that can be precipitated when other serotonergic medications are used concurrently, including selective serotonin reuptake inhibitors and tricyclic antidepressants. Serotonergic syndrome features include delirium, confusion, agitation, hypomania, hyperactivity, restlessness, fever, sweating, tachycardia, hypertension, ataxia, and tremor. It may occur dramatically or insidiously. Mild forms should resolve within 24 hours of ceasing the medications.

Dextropropoxyphene should be used with great caution in the elderly. Its major metabolite has a long half-life and has

the potential for causing central nervous system side effects including hallucinations and seizures. The usual dose is 32.5 to 65 mg four times a day.

The analgesic properties of codeine, tramadol, and dextropropoxyphene are limited by a ceiling effect. Further dose increases may cause toxicity without conferring additional analgesia. It is our preference to use a low dose of a strong opioid rather than these agents if additional analgesia is required.

3. **Opioid Analgesia**

Opioids have an established role in the treatment of severe malignant pain in the elderly. Opioids are increasingly gaining acceptance for the management of severe nonmalignant pain in this age group as well. This trend is seen as positive, in the sense that individuals should not be left to suffer uncontrolled pain. The potency of this class means that additional precautions are required. It is possible to mask the symptoms of pathology where specific treatment is more appropriate. Furthermore pain control may occur at the expense of intolerable side effects such as impaired cognition, falls, or severe constipation. Care is needed with selection of the most appropriate opioid analgesic, dosing, and management of side effects. All opioids have the tendency to produce constipation, nausea, sedation, cognitive impairment, and respiratory depression, necessitating commencement at a low dose with gentle titration. Tolerance to these side effects occurs over time, apart from constipation, which tends to persist. Prophylactic treatment of constipation is generally required.

Initiation of opioid analgesia for chronic nonmalignant pain is usually commenced with a small dose of a short acting opioid administered orally, for example, 5 mg of oxycodone or 10 mg of morphine. The dose is titrated according to response. Once the maintenance dose has been determined, a long acting oral preparation can be used with allowance for a short acting preparation for breakthrough pain. The breakthrough dose is usually in the order of one sixth to one third of the daily maintenance dose.

Long acting preparations of morphine and oxycodone are available in a large range of doses and are appropriate for use in the elderly. Methadone has a long half-life, with a potential to accumulate and should only be used with caution. Accumulation of a long acting metabolite may cause agitation, tremor, or seizures. Alternative routes of administration of opioids may be considered for patients who cannot tolerate oral preparations. The use of pethidine for chronic pain is not recommended because of the potential for neurotoxicity associated with the accumulation of the metabolite norpethidine. Transdermal fentanyl patches offer the advantage of infrequent application every 72 hours. However, even the smallest dose patch is too potent for opioid naïve patients. Transdermal fentanyl is indicated for patients with high opioid requirements who are intolerant of oral preparations.

The use of opioid analgesia in nonmalignant pain raises other issues. Maier *et al.*, (2002) demonstrated that only approximately one third of patients responded well to opioid analgesia, one-third responded partially, and one-third did not respond; of the responders, only half continued to benefit in the long term. This compares poorly with their use in malignant pain, where 90% of patients will have opioid-responsive pain. The risk-benefit ratio in older patients is currently unknown. In general, older patients respond to lower doses of opioids where fewer side effects are expected, but have a greater tendency toward adverse effects.

4. **Adjuvant Analgesics**

Commonly used agents for neuropathic pain include tricyclic antidepressants and antiepileptic drugs. Some antiarrhythmic are used, but they generally have a limited therapeutic window in older people.

Amitryptiline remains the most commonly used antidepressant for neuropathic pain. No other antidepressant drug has been shown to be superior to amitryptiline although other tricyclic antidepressants such as nortriptyline have fewer side effects (Backonja, 2001). The tricyclic antidepressants can be used for any form of neuropathic pain. As with any other medication used in older people, the clinician is advised to initiate therapy at a low dose and titrate slowly according to response. Amitryptiline and nortriptyline are usually commenced at 10 mg one hour before retiring and increased every few days by a similar dose until a benefit is achieved or side effects preclude further use. A dose of 50 mg is usually considered to be enough to achieve an analgesic effect if one is going to occur. Common side effects include dry mouth, postural hypotension, drowsiness, and urinary retention. Newer selective noradrenaline or serotonin reuptake inhibitors have not been shown to be effective for pain relief outside their antidepressant effects.

The widespread use of antiepileptic drugs for neuropathic pain is based on clinical experience rather than large numbers of placebo-controlled trials. Carbamazepine is the drug of choice for trigeminal neuralgia. A starting dose of 50 mg is suggested, as some older people are very sensitive to the adverse effects of this medication. The best-studied antiepileptic drug at present is gabapentin. It has been proven to be useful in the management of postherpetic neuralgia (Rowbotham *et al.*, 1998) and diabetic neuropathy (Backonja *et al.*, 1998), but its use in other syndromes is by extrapolation. It can produce somnolence, giddiness, and ataxia in the elderly at therapeutic doses, which can result in falls. The usual starting dose in the frail elderly is 100 mg at night increasing every few days, aiming for 300 mg three times a day. Further increases above this dose are associated with therapeutic benefit but the side-effect profile also increases. Maximum doses of up to 4800 mg day^{-1} are rarely achieved in older people. Other antiepileptic agents may occasionally be of benefit in neuropathic pain.

In summary, there are now good studies confirming the benefit of tricyclic antidepressants, antiepileptic agents, and opioids for the management of chronic neuropathic pain. Their efficacy appears to be similar. The number of patients that need to be treated to achieve a 50% reduction in pain severity compared with placebo treatment is in the order of two to three in all cases. In the absence of head to head

comparative studies, the selection of medication to initiate therapy is based on the likely tolerability of the medications for the individual being treated, and availability and price of the medication.

5. **Other Pharmacological Measures**

Antidepressants and anxiolytics should be considered in patients where the mood disorder precludes the use of cognitive behavioral therapy (CBT) and physical measures for the management of the pain. However, they are best used in the context of a multidisciplinary management program rather than as a sole modality of treatment, unless the disorder is primarily affective in nature. The physician must be alert to the potential for drug interactions and toxicity from over-the-counter preparations as well as prescribed medications for comorbidities. Topical agents are also widely used by older people. The most common are those containing capsaicin, NSAIDs, local anaesthetics, and the rubifacients methyl salicylate and nicotinate. Although of limited efficacy, they are relatively free of systemic side effects. Lignocaine patches have been demonstrated to be of benefit in postherpetic neuralgia but are not widely available.

Psychological Modalities of Management

Most modern chronic pain management programs are based on the CBT model. Such programs consist of patient and family education, contingency management, relaxation training, training in goal setting and problem-solving skills, and training in effective communication, behavioral reactivation, and cognitive restructuring. The last requires attention to specific constructs identified in individual patients. These might include a fear of increased damage from activity or increased pain levels, or excessive reliance on "powerful others" such as doctors and medications.

The efficacy of CBT in the general population has been shown to have unequivocal benefit. However, there have been limited studies in older people. Cook (1998) did demonstrate that 10 weekly sessions of CBT were effective in the institutionalized elderly. Puder (1988) has also shown that age was not a factor in determining the success of a CBT programme. CBT is also useful in the treatment of depression in the elderly.

Physical Modalities of Management

Exercise therapy has been used as a part of CBT programmes. It is most effective if it has a specific goal orientation. Exercise therapy should include stretching, strengthening, aerobic exercise, and postural correction where feasible. Weight loss can help in painful conditions involving the weight bearing joints and can assist in slowing the progression of degenerative arthritis. Other techniques such as bracing, trigger point deactivation, massage therapy, acupuncture, transcutaneous electrical stimulation (TENS), heat, and cold have also been used. Hydrotherapy and use of an exercise bike may promote range of movement and confidence. TENS is useful in subacute injury and postherpetic neuralgia. Controlled trials of TENS using experimental pain models are usually only effective at high intensities of stimulation. TENS has the advantage of being able to be used for long periods at a time, but poststimulus effects are short-lived. The clinician should be aware of the dangers of an over-reliance on passive therapies especially if the patient tends to have an external locus of control. Advice on simple maneuvers for lifting and walking may be of great functional benefit; for instance, leaning on the supermarket trolley in patients with vertebral canal stenosis may increase their walking distance.

The use of assistive devices, such as walking sticks and wheeled frames, can be useful in patients to improve function and reduce pain. However, such measures should be applied judiciously so as not to promote over-reliance or promote deconditioning. Physiotherapists can also counsel patients in approaches to avoid exacerbations of musculoskeletal pains.

Management of Social Circumstances

The patient's family must be educated about the nature of chronic pain. Firstly, they must be assured that the problem is real and the patient is not in any way trying to "fake the pain" to obtain some advantage. Secondly, they must be educated that the aim is to decrease pain and maintain function. The nature of how solicitous behavior can modify the patient's function should be explained to carers. The family should also be educated about the need to maintain a paced level of physical activity and be taught the same methods of nonpharmacological pain management as the patient. Such measures may increase the sense of mastery of both patient and family. The family may play an important role in the management of patients with dementia, who may not be able to maintain a therapeutic approach without ongoing prompting and supervision. Frequently, loneliness and meaninglessness can present as somatic complaints, including pain. Pain management in these instances may be helping the patient source social or meaningful activities.

Procedural Modalities of Management

Ongoing pain may warrant consideration of anesthetic or surgical interventions. Joint arthroplasty of the hip or knee are good examples of interventions that improve pain and function in appropriately selected older individuals. The place of vertebroplasty in vertebral collapse is not yet fully established. Other interventions such as epidural injections of local anaesthetics and steroids may give short-term relief. Most studies of anesthetic interventions have not included older subjects, and in particular those in residential care. Assessment needs to be undertaken on an individual basis. Referral to a multidisciplinary pain clinic or pain specialist should be considered when planning procedures in frail patients.

KEY POINTS

- Chronic pain is a common complaint among older people.
- Older people have higher pain thresholds and lower pain tolerance than young adults in studies of experimental pain. This is probably also true in chronic pain syndromes.
- Chronic pain requires meticulous multidimensional assessment and properly planned and monitored interventions using pharmacologic, physical, and psychologic modalities.
- Empowerment is a key factor in ensuring satisfying and durable outcomes; the patient and their carers must be active participants in therapy at all times.
- Although there is limited high quality information about the management of chronic pain affecting older people in the literature, this is likely to be rectified in coming years as chronic pain is increasingly recognized as an important geriatric syndrome.

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Cervical and Lumbar Spinal Canal Stenosis

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CERVICAL SPINAL CANAL STENOSIS

Anatomy

The cervical spinal canal is triangular in shape. The intervertebral discs in this region are thicker anteriorly than posteriorly and this is responsible for the anterior convexity of the neck. The anterior boundary of the canal is formed by the posterior surface of the body of the cervical vertebrae and by the posterior longitudinal ligament, which in this region is broad and almost uniform in width and is attached to the upper and lower margins of each vertebral body and to the intervertebral discs. The pedicles project laterally and backwards. The posterolateral and posterior canal boundaries are formed by the relatively long and narrow laminae and by the ligamentum flavum, which is attached to the laminae. The capsules around the articular facet joints are longer and looser than in other parts of the spinal column. The atlas (C1) has no body which is replaced by the odontoid process (dens) of the axis (C2). The articulation of the atlas with the axis has three synovial joints: one joint is on each side between the inferior mass of the atlas and the superior facet of the axis and the third is situated between the odontoid process and the anterior arch of the atlas. The normal cervical and lumbar spine has a lordotic alignment. The spinal cord has two enlargements, cervical and lumbar. In the cervical region, the enlargement extends from C2 to T2.

Cervical spinal stenosis is a condition of narrowing of the spinal canal Verbiest (1954). The normal adult diameter of the cervical spinal canal at C3–C6 is approximately 17 to 18 mm when determined by radiographs (Pavlov *et al.*, 1987; Torg *et al.*, 1996) or computed tomography (CT) scans (Herzog *et al.*, 1991; Stanley *et al.*, 1986). Measurement data have been mainly derived from young male athletes who have a larger vertebral body size than nonathletes with possible exaggeration of the prevalence of developmental stenosis. When MRI is used in average young adults, Tierney (Tierney *et al.*, 2002) found a cervical canal diameter 1 to 2 mm less than noted above. The area of the cervical spinal canal and of the spinal cord is influenced by both the saggital and the transverse diameters although the former dimension is more significant (Herzog *et al.*, 1991; Torg *et al.*, 1996, Prassad *et al.*, 2003). The Torg ratio (Pavlov *et al.*, 1987; Torg *et al.*, 1997), also referred to as the Torg–Pavlov ratio and the Pavlov ratio, is derived by dividing the cervical spinal canal saggital diameter by the saggital diameter of the corresponding vertebral body. A ratio of less than 0.80 is indicative of significant spinal stenosis (Pavlov *et al.*, 1987) and it avoids the technical measurement variables associated with cervical spinal radiographs. Tierney compared the Torg ratio with the "Space Available for the Cord" (SAC) derived by the subtraction of the sagittal diameter of the spinal cord from the corresponding spinal canal sagittal diameter (Herzog *et al.*, 1991; Torg *et al.*, 1997) in normal young adults (Tierney *et al.*, 2002). The measurements varied between 2.5 and 10.4 mm (Tierney *et al.*, 2002). These investigators found that the relationship between the Torg ratio and the SAC was significant ($r^2 = 0.53$). However, Prassad *et al.* (2003) found a zero correlation between the area of the cord and the Pavlov (Torg) ratio. In Asians, the Torg ratio is not a reliable indicator of sagittal developmental diameter and the larger vertebral bodies in men give a lower Torg ratio than in women (Lim and Wong, 2004). The SAC reflects both spinal cord and canal sagittal dimensions. Because head position influences spinal cord size, Tierney *et al.* (2002) stressed the importance of a standardized head position in comparative studies of the SAC.

Cervical spinal stenosis is commonly associated with degenerative changes in the surrounding structures usually at the C5 or C6 interspace. With aging, the water content of the nucleus pulposus diminishes with reduced elasticity, loss of disc height, and subsequent bulging of the annulus fibrosus into the cervical canal. Aggrecan is the principal proteoglycan of the nucleus pulposus and it appears that its reduction in the nucleus plays a significant role in disc changes. Reduced disc height alters the relationship of the superior and inferior surfaces of the facet joints

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and stimulates osteophyte formation within the joints. The position of the degenerated discs gives rise to osteophytic changes in the posterior margins of adjacent vertebral bodies. Thinning of the cervical discs leads to a concertina effect on the thickened ligamentum flavum with bulging into the posterior canal space. Spondylosis of the cervical spine is common in elderly people; by age 65 radiographic evidence of this change can be demonstrated in over 75% of subjects (Connell and Wiesl, 1992). Osteophyte development at the facet and uncovertebral joints, degenerative changes of the intervertebral disc margins with spondylotic bars and thickening of the posterior longitudinal ligament, and ligamentum flavum and developmental canal narrowing may all contribute to symptomatic canal stenosis in later life. Usually two or more factors predominate.

Ossification of the posterior longitudinal ligament (OPLL) may be a singular cause of cervical canal stenosis (Matsunaga *et al.*, 2004); in their series of 323 patients without myelopathy when first seen, 17% developed myelopathy when followed up for at least 10 years. The developmental size of the spinal canal can be a significant contributor to myelopathy in OPLL (Koyanagi *et al.*, 2004). The association of OPLL with advanced rheumatoid arthritis is not uncommon (Trojan *et al.*, 1992); however, rheumatoid arthritis may produce anterior and posterior canal encroachment by pannus formation without the presence of ligamental ossification (Kroft *et al.*, 2004). OPLL is predominantly a condition of elderly Japanese but there may be a lack of awareness of this development in Caucasians (Trojan *et al.*, 1992). Calcification may rarely occur in the ligamentum flavum and it is virtually confined to elderly Japanese but the condition has been reported in a Caucasian (Uggariza *et al.*, 2001).

Paget's disease of the cervical bodies may produce canal stenosis as may pseudohypoparathyroidism (Okada *et al.*, 1994). Laron's Syndrome (Laron *et al.*, 1966, 1993; Laron, 1999; Kornreich *et al.*, 2002) is not uncommon, particularly in Middle Eastern populations, and is due to an in-born failure to produce insulin-like growth factor-1 (IGF-1) due to an inherited autosomal recessive defect in the growth hormone receptor gene. The IGF-1 deficiency leads to dwarfism and failure of growth in the upper cervical vertebrae with narrowing of the cervical spinal canal. The development of degenerative disc changes and spondylosis in later life may lead to cord compression (Kornreich *et al.*, 2002). The condition may be associated with the os odontoideum (Kornreich *et al.*, 2002).

A congenital narrow cervical spine is usually asymptomatic until the development of substantial degenerative changes in later life. However, trauma to the head and neck with paraparetic symptoms commonly follows sports related injuries, particularly rugby football (American football). Congenital narrowing of the cervical canal may be associated with achondroplasia or multiple hereditary exostoses. Developmental spinal stenosis due to hypoplasia of the atlas may cause myelopathy (Phan *et al.*, 1998)

Atlantoaxial or cranioatlantoaxial instability may be due to rheumatoid arthritis, trauma, os odontoideum, congenital anomalies or to Down's syndrome associated with ligamentous laxity and increased cervical movement. In rheumatoid arthritis, involvement of the synovial joints and the transverse ligament leads to progressive atlantoaxial subluxation. Involvement of the synovial joint around the dens (odontoid process) with granulation and pannus formation causes pressure on the anterior aspect of the cord and often, eventual arterial compression which accentuates cord damage.

Crystal arthropathy with the deposition of calcium pyrophosphate in the atlanto-occipital region may cause sufficient canal narrowing to produce cord damage and is a condition of late old age.

Symptoms

Radiological and MRI (Golash *et al.*, 2001) evidence of spinal stenosis may be found in elderly people in the absence of symptoms and mild myeloplastic features may be detected clinically when MRI evidence of cord compression is uncertain (Golash *et al.*, 2001). Involvement of the lateral region of the cervical spinal canal may lead to radiculopathy but to myelopathy if the stenotic compression is central.

Radiculopathy

Osteophyte formation with chronic anterolateral disc protrusion with spondylosis may be initially characterized by posterior neck or scalp pain but pain in the neck and arm with a radicular distribution develops sooner or later. There is a variation in the radicular distribution of symptoms depending on the affected dermatome. Radicular pain and/or sensory disturbances usually progress gradually and in many patients intermittently. Trauma in a spondylotic spine may result in the acute onset of symptoms. Acute flexion or hyperextension injuries may be the symptom-precipitating factor, but in older persons a central cord syndrome is more likely to occur. Symptoms due to the level of spinal cord compression:

1. C8 involvement is associated with pain down the medial aspect of the forearm to the medial half of the ring finger and the little finger.
2. C7 compression gives rise to pain in the back of the neck and down the back of the upper limb to the middle finger.
3. C6 compression is associated with pain in the back of the neck and down the outer aspect of the arm to the thumb and index finger.
4. C5 compression gives rise to pain over the top of the shoulder and side of the neck.
5. C4 involvement produces pain in the upper lateral aspect of the neck.
6. C3 compression gives pain in the posterolateral region of the neck. Compression of C4 and C3 is uncommon.
7. C2 and C1 compression may produce pain in the side of the neck and the pinna.

As narrowing in the axialatlanto-occipital region is predominantly due to rheumatoid arthritis and developmental stenosis, myelopathic features overshadow any radicular complaints.

Spondylotic stenosis of the cervical canal may involve more than one dermatome and compression of more than one cervical nerve. Motor weakness and sensory impairment to pin prick and touch may occur over the affected dermatome/s. Loss of biceps (C6) and triceps (C7) reflexes may be found on examination. Symptoms and signs may reflect a combination of radiculopathy and myelopathy.

Cervical Myelopathy

This condition results from central cord compression and its frequency increases with age and it is more common in men than in women. The pathophysiology has been well reviewed by Fehlings and Skaf (1998). Symptoms vary from minimal to severe, but chronic pain in the back of the neck almost always precedes the development of neurological features except when hyperextension injuries complicate a spondylotic spine and acute myelopathic features rapidly develop. The clinical picture depends to some extent on the dermatomal level/s compressed. Motor weakness is more marked in the upper limbs than in the lower limbs as the corticospinal tract is crucial for functional activities of the hand (Eidelberg, 1981; Levi *et al.*, 1996); Impairment of hand dexterity for tasks such as buttoning up a shirt, tying shoe laces or writing may be early manifestations of the disorder. Llermitte's sign, a generalized electric shock-like sensation or tingling, on flexing the neck may be reported by patients. Muscle wasting and weakness in the hands and forearms often occurs as the condition progresses. An early feature in older people may be the gradual progressive onset of a clumsy gait, which tends to be ignored until symptoms and disability are more florid.

Clinical Examination

Sensory changes form part of the clinical picture and include impairment of pain and temperature, joint position sense, tactile sensation, and vibration depending on the dermatome affected. Dysdiadochokinesia is a common feature. Muscle wasting in the hands and forearms can usually be demonstrated. A positive Hoffman's reflex and inverted radial reflex are significant diagnostic findings. In the lower limbs, the principal findings are proximal muscle weakness with spasticity and hyper-reflexia and a positive Babinski reflex. Gait is spastic and ataxic and often on a broad base. The Brown–Sequard syndrome may complicate cervical spine injury or a herniated cervical disc (Kobayashi *et al.*, 2003) but Lunsford *et al.* (1980) found the syndrome in 10% of their 32 cases of spondylotic cervical myelopathy. The characteristic presentation of the syndrome is a hemiparesis with impairment of joint position and vibration on the same side and contralateral impairment of pain and temperature sense.

Clinical diagnostic difficulties are accentuated by multiple level canal compression, asymmetrical signs of myelopathy, and the presence of concurrent cervical and lumbar canal stenosis (LaBan and Green, 2004).

Investigations

It is critical to appreciate the importance of a detailed clinical history and neurological examination in association with radiographic and MRI studies in the diagnosis of spinal root and cord compression due to the frequency of asymptomatic radiological changes in the elderly cervical spine. Initial radiographic investigation should be anterior, lateral, and oblique views of the cervical spine. As indicated above, the frequency of spinal degenerative changes in an elderly population limits the diagnostic value of plain radiographs but an oblique view demonstrates osteophytic encroachment into the neuroforamina and lateral views provide an indication of canal size. A lateral radiograph with patient's right arm above the head may give a more discriminative view of the lower cervical spine (swimmer's view).

Despite the reported unfavorable comparisons with MRI, Yue *et al.* (2001) found the Torg–Pavlov ratio to be significantly lower in patients with cervical spine spondylotic myelopathy than in normal controls.

Magnetic Resonance Imaging

Increasingly, this technique is becoming the investigation of choice for identifying cervical spinal cord and nerve root changes that give rise to myelopathy or radiculopathy. This technique is contraindicated in patients with most types of metal implants but not titanium. MRI identifies soft tissue abnormalities including pressure effects on the cord and spinal roots. Multiple level cord compression is most suitably demonstrated by sagittal T-2 weighted images. Compressive cord changes are seen on axial MRI scans. Calcified bulging intervertebral discs and osteophyte development can be seen as dark images on T-2 fast spin echo and T-2 weighted imaging. The ability to image the degenerative changes in the cervical spine in the upright position and to study the weight bearing and dynamic flexion and extension influences using a recently developed MRI unit has been reported (Jinkins and Dwarkin, 2003). This development allows determination of specific compressive structures in the vertebral canal and will provide precise information for medical or surgical intervention.

Computed Tomography (CT)

This technique demonstrates the size of the spinal canal and osteophyte encroachment into the canal and neuroforamina but does not demonstrate soft tissue changes including cord compression. However, MRI and CT should be regarded

as complimentary to each other. CT–Myelographic imaging provides the best picture of the presence of cervical spondylotic compressive changes but myelography is currently less frequently used with advances in MRI techniques.

Other Investigations

(i). A block in the cerebrospinal fluid (CSF) flow in compressive myelopathy is associated with an elevated CSF protein level. (ii). The results of electromyography (EMG) are highly specific for spinal radiculopathy and the somatic evoked potential from the tibialis posterior muscle has a high degree of specificity for spinal myelopathy (Serrano Castro, 2001). (iii) Use of the ultrafine flexible fibroscope has diagnostic value for some spinal disorders but at this early stage this technique appears to offer no diagnostic benefit in spinal canal stenosis (Tobita *et al.*, 2003).

Os Odentoideum

Plain radiographs of the upper cervical spine – anteroposterior, open-mouth odontoid and lateral views – may demonstrate an odontoid process close to the anterior arch of the atlas. Lateral x-rays taken in flexion and extension will provide evidence of C1, C2 instability. CT of the craniocervical junction, particularly in combination with MRI, demonstrates atlanto-odontoid degenerative changes (Zapetal *et al.*, 1995). MRI will identify relevant soft tissue changes especially in the odontoid bursae (Zapetal *et al.*, 1999). A raised arch-odontoid ratio and a narrowing and interdigitation of the atlantoaxial joint on midsagittal CT reconstruction imaging provides reliable and sensitive evidence of os odentoideum (Fagan *et al.*, 2004); 17 of these investigators cases had no history of trauma and the condition was considered to be due to developmental changes.

Management of Radiculopathy

Where symptoms are mild and stable, pain relief using a combination of analgesics, short-term nonsteroidal anti-inflammatory drugs (NSAID's), but not COX 2 NSAID'S, due to the risks of untoward cardiac events. Tricyclic antidepressants have been used for over 20 years for pain management, especially neuropathic pain; their mode of action is possibly the prevention of norepinephrine reuptake at the presynaptic neurone. Duloxetine is both a balanced selective serotonin and norepinephrine reuptake inhibitor and appears to be beneficial in neuropathic pain; however, until sufficient controlled trials are undertaken, it is too early to assess its potential benefit in pain control. The neuropathic pain of spinal cord injury often responds to gabapentin and it should be considered in the early stage of pain in a titrated dose of 900 mg to 2500 mg. Alleviation of pain may follow periods of rest for the neck, local cold using ice (cryotherapy) or heat using hot packs, or cold followed by heat. Transcutaneous nerve stimulation (TENS) or ultrasound may contribute to pain relief. Skilled physiotherapy involvement is critical for successful conservative management. Safe pain-free movements are to be encouraged and painful movements restricted or prevented to allow reduction of any associated joint inflammatory changes. Graded movement to gently mobilize and stabilize the neck by building up muscle power is useful once pain is reduced. Painful muscle spasm may be relieved by certain massage and/or graded pressure techniques and by structured muscle stretching or traction. A firm cervical collar provides some symptom relief but it is essential that it is removed at regular intervals for structured exercises. Faulty posture often aggravates symptoms and expert physiotherapy advice on both posture and positioning of the head and neck when supine, sitting or standing is very relevant. Prolonged neck flexion as when reading should be modified. None of these interventions will influence the foraminal osteoarthritic changes other than encourage the reduction of associated inflammation, improve cervical spine stability and limit some of the movement factors, which aggravate neural damage. Skilled occupational therapy assessment of activities of daily living (ADL) functions and a home assessment are necessary to maximize independence.

Transforaminal injection of corticosteroids using a precise fluoroscopic guided technique appears to give better results than less advanced methods of root injections for radiculopathy due to cervical spondylosis or focal disc herniation (Slipman *et al.*, 2000; Slipman and Chow, 2002). CT guided nerve root block has been reported to reduce pain in over one-quarter of patients with cervical spinal stenosis but in over half of patients where radiculopathy was due to foraminal disc protrusion (Strobel *et al.*, 2004).

If cervical radiculopathy is unresponsive to conservative measures or to local steroid or nerve block techniques and pain is disabling, or if progressive motor weakness and/or significant sensory impairment develops, surgery is usually indicated depending on the presence and severity of any comorbid conditions. Clinical, radiographic, and MRI must identify the precise site of nerve root compression so that the appropriate surgical procedure can be undertaken. Where posterolateral nerve root compression is due to osteophyte encroachment or associated disc protrusion, keyhole foraminectomy via the posterior approach gives excellent results with minimal patient disturbance or morbidity (Henderson *et al.*, 1983; Davis, 1996). With anterior osteophyte involvement, particularly if there is evidence of a degree of cord compression, anterior foraminectomy and fusion produce satisfactory results with low morbidity and mortality (Sampath *et al.*, 1999). Epstein *et al.* (1969) emphasize the importance of removing osteophytes.

Cervical Myelopathy

Conservative management is appropriate in patients with mild nonprogressive neurological complaints and a stable

nonkyphotic spine. The general thrust of nonoperative management is essentially the same as for cervical radiculopathy with the exclusion of manipulative extension of the spine. The use of a firm cervical collar to prevent further cord damage is considered essential, but the true benefits are yet to be proven. Several factors such as duration of symptoms and severity of cord damage need to be taken into account before embarking on surgical intervention. Laminectomy, either with or without fusion, has been standard surgical treatment for spondylotic myelopathy. Choice of the anterior or posterior approach depends on the site of major compression but more usually on the views of individual surgeons. Both methods give similar rates of improvement (Ebersold *et al.*, 1995; Carol and Decker, 1988). If the anterior approach is adopted, discectomy is followed by corpectomy, and one of the three commonly used fusion techniques provides spinal stability. The anterior approach produces immobilization of multiple spinal segments and the procedure may be complicated by injury to the carotid or, more commonly, to the vertebral artery (Tumialan *et al.*, 2004; Daentzer *et al.*, 2003). Posterior decompression may lead to instability. Laminectomy usually requires the removal of at least the lamina above and below the area of greatest cord compression. Where radiculopathy accompanies myelopathy, facetectomy, with or without fusion, may be indicated. In the presence of severe spinal canal stenosis with substantial myelopathic features, posterior followed a week later by anterior cord decompression achieving a 360 degree arthrodesis gives favorable neurological improvement (Mazel *et al.*, 2002). Multilevel spondylotic myelopathy has been treated by "skip laminectomy" in which a standard laminectomy is undertaken in selected areas and partial laminectomy where anterior cord compression is of minor significance (Shiraishi, 2002). This technique has the advantage of conserving spinal musculature and maintaining cervical spine mobility.

Laminoplasty was initiated in the Asian region and open-door laminoplasty was first described by Hirabayashi *et al.* (1983), but the various modifications are becoming more popular in Western countries. Wang *et al.*, (2004) report the result of open-door expansive hinge laminoplasty (greenstick laminal osteotomy on one side of the canal with laminal division and bone graft insertion on the opposite side) to relieve cord compression. This procedure has the benefits of short surgical duration, low risk, and maintenance of cervical mobility. Even late or severe cases of myelopathy may benefit from this surgical technique (Agrawal *et al.*, 2004). Comparable outcome benefits are obtained in middle-aged and elderly patients as in younger adults (Handa *et al.*, 2002; Wang *et al.*, 2004). To provide good bilateral exposure and decompression, modified forms of myeloplasty involving a complete laminectomy followed by the attachment of stabilizing titanium miniplates (Casha *et al.*, 2004) or bilateral insertion of hydroxyapatite between the cut ends of the laminae and the attachment of titanium miniplates (Goro *et al.*, 2002). The development of the oblique (view) angle microendoscope allows a minimal invasive posterior approach surgical treatment of myelopathy and radiculopathy due to spondylotic cervical canal stenosis (Yuguchi *et al.*, 2003).

Degenerative changes associated with os odontoideum, with or without rheumatoid arthritis, may give rise to instability in the craniocervical territory and to myelopathy. A number of techniques have been adopted to stabilize the atlantoaxial and atlanto-occipital junctions: an atlantoaxial posterior fixation system (3XS System) consisting of a transverse unit, rods and hooks together with insertion of an iliac bone graft stabilizes this junction with good cervical alignment (Nishizawa *et al.*, 2004); a titanium mesh cage filled with autologous cancellous bone and sited between the C1 posterior arch and the C2 lamina gives stability and less donor site morbidity than with autologous iliac crest grafts (Matsumoto *et al.*, 2002); percutaneous transarticular C1-C2 insertion of self-drilling cannulated screws using computed navigation gives good clinical results and effective stabilization (Borm *et al.*, 2004); stabilization of the craniocervical junction has been achieved using a titanium pre-contoured implant (Ohio Medical Instruments Loop), halting the progress of myelopathy (Singh *et al.*, 2003). In the presence of unstable multilevel stenosis, an expanding laminoplasty combined with interspinous iliac bone graft appears to be an effective method of managing this difficult condition (Matsumura *et al.*, 2003).

LUMBAR SPINAL CANAL STENOSIS

Anatomy of the Lumbar Spinal Canal

The anterior aspect of the spinal canal is formed by the posterior surface of the vertebral body and associated spinal discs and the posterior longitudinal ligament; the vertebral body pedicles are the main component of the lateral wall. The posterior and posterolateral boundaries comprise the vertebral laminae and their right and left synovial zygapophyseal facet joints and the ligamentum flavum; the latter forms part of the anterior aspect of the facet joint capsule. These convex facet joints are aligned sagitally as well as obliquely.

Lumbar spinal stenosis, a term first coined by Verbiest (1955), is a narrowing of the lumbar spinal canal. He described two types: congenital, characterized by short pedicles and a sagittal diameter of 10 mm or less, and acquired; in 1977 and 1990 he noted that a diameter of 10–12 mm may cause neurogenic symptoms if other conditions reduced the canal space. Eberi *et al.*, (2003) found no correlation between the degree of sagittal stenosis and neurological deficits in thoracolumbar spine fractures; however, the ratio of the sagittal to the transverse diameter of the lumbar spinal canal at the site of thoracolumbar spinal burst fractures is reported as being smaller in patients with neurological deficits (Vaccaro *et al.*, 2001). Lumbar stenosis may be asymptomatic even in old age. A congenitally narrow spinal canal may be associated with conditions such as achondroplasia but, most commonly, symptoms only occur with superimposed degenerative changes in late middle or old age. Acquired lumbar stenosis is the predominant form of the syndrome and is usually due to degenerative changes

in structures affecting the central or lateral or both canal dimensions and is often associated with encroachment of the lateral recesses and neuroforamina. L4–L5 and L3–L4 are the most frequent sites of stenosis but often more than one level is affected. The condition is more common in men except when degenerative subluxation (spondylolisthesis) is a significant contributory factor; this is largely seen in elderly women and L4/5 is the predominant level to be affected. Lane (1893) described a 35-year-old woman with symptomatic spinal canal narrowing due to degenerative spondylolisthesis.

Degenerative loss of height of the intervertebral discs leads to bulging into the anterior part of the spinal canal and the associated concertina effect on the thickened ligamentum flavum produces posterior bulging; these factors, often with osteoarthritis and osteophytosis of the facet joints may compress the cauda equina and spinal roots. As the spinal cord terminates at L1, this is rarely affected. However, traumatic thoracolumbar burst fractures in older subjects may be associated with acute spinal stenosis. Very small and repetitive abnormal movements at the intervertebral joint surfaces may be responsible for hypertrophy of the ligamentum flavum and reactive bony and cartilaginous changes (Jane *et al.*, 2004). Van Gelderen (1948) described symptomatic narrowing of the spinal canal considered to be due to hypertrophy of the ligamentum flavum and confirmed by myelography. In 1956, Verbiest detailed the cardinal symptoms of lumbar spinal canal stenosis; he opined that congenital narrowing of the canal played a significant role in this condition. Debate continues as to the relative importance of compressive ischemia of the spinal nerve roots and cord and mechanical compression without ischemia. Hall *et al.* (1985) provided autopsy evidence to suggest that nerve root symptoms are due to direct compression; however, in animal experiments (Sekiguchi *et al.*, 2004) found that administration of a 5-hydroxytriptamine receptor (5-HT) antagonist prevented the reduced blood flow following experimental nerve compression. Experimental lumbar nerve root compression induces a reduction in the number of substance P and somatostatin positive fibers in the dorsal horn of the spine suggesting that impairment of neurotransmitter flow may be responsible for the decline in nerve function (Kobayashi *et al.*, 2005). Calcium pyrophosphate deposits may decrease the space in the spinal canal (Jane *et al.*, 1996). Both rheumatoid arthritis (Magnase and Hauge, 1978) and lumbar scoliosis (Simmons and Simmons, 1992) may play a role in magnifying the degree of canal encroachment. The spine is involved in about 50% of patients with Paget's disease producing a variable array of features including spinal stenosis (Saifuddin and Hassan, 2003). Acromegaly may compromise the canal space. Hypertrophy of the posterior longitudinal ligament is a rare cause of stenosis in the lumbar canal but is more common in the cervical spinal canal (Matsumoto *et al.*, 2001).

Clinical Features

The onset is usually gradual; chronic back pain may be the only feature and diagnosis is commonly missed at this stage. Because the narrowing of the canal may be asymmetrical and involve one or several levels, the clinical presentation is variable. Symptoms may be precipitated by trauma. The classical picture is of a patient with chronic back pain who complains of pain with a burning, tingling or numb quality in the legs spreading to the thighs and, although not invariably, to the buttocks on walking, particularly down hill, and relieved by resting (pseudo or neurogenic claudication) in the stooped or sitting or squatting position. Lying supine also eases symptoms as the lumbar spine is relatively straight in this position in contradistinction to the lumbar lordosis which is present in the erect position. Indeed, standing erect may fail to ease exercise-induced pain. Extension of the spine is a pain-inducing position. Initially, neurogenic pain may be in only one lower limb. Numbness and weakness on walking are common features, sometimes accompanied by dysaesthesia in the perineum. With continued walking, limb pain may become so severe that further activity is unbearable. Pain relief on resting may take as long as twenty minutes. Often, no difficulty is experienced in bicycle riding because of the flexed position of the spine (Dong and Porter, 1989). Coughing or sneezing may exacerbate symptoms. Gait abnormality is sometimes observed and this finding has been used to demonstrate quantitative gait improvement following surgery (Suda *et al.*, 2002).

Intermittent neurogenic claudication may be confused with intermittent vascular claudication. A detailed history and vascular and neurological examination (after walking) will usually differentiate the two conditions. Acquired spinal canal stenosis and comorbid peripheral vascular disease are common in later life and may produce clinical diagnostic difficulties (Dodge *et al.*, 1988; Stansby *et al.*, 1994).

In more severe degrees of stenosis with cauda equina compression, urinary symptoms may occur. Intermittent priapism is associated with severe neurogenic claudication and usually responds to surgical decompression measures (Baba *et al.*, 1994).

Clinical examination may elicit few or no neurological findings particularly if the patient has been resting. Lasèque's sign – straight leg raising with dorsiflexion of the foot – is usually absent. Upper motor neuron signs are typically absent. The ankle jerks may be diminished or absent; less common is an absent knee jerk. Neurogenic unilateral calf hypertrophy has been described possibly due to S1 dysfunction (Swartz *et al.*, 2002). Evidence of weakness in the lower limbs may be present in a third of patients (Hall *et al.*, 1985). Neurological deficits are more common when tested after walking, and Jensen and Schmidt-Olsen (1989) used this phenomenon of altered neurological status after walking downhill as a clinical screen for canal stenosis.

Investigations

The EMG frequently shows neurogenic changes indicative of nerve root injury but normal EMG does not exclude canal stenosis.

Plain radiographs of the lumbar spine are not diagnostic of stenosis but they show degenerative changes of the bony structures and narrowing and bony sclerosis of the facet joints. Spondylolisthesis, usually L4 on L5, affects about a third of patients and is most frequently seen in women.

Computed Tomography (CT), particularly using three-dimensional reconstruction, demonstrates the subarachnoid space, bony pathology including fractures, osteophyte formation and hypertrophy of the laminae, facets or pedicles. Post-CT myelography is reserved for patients undergoing surgery.

Magnetic Resonance Imaging (MRI) is now the investigation of choice demonstrating soft tissues in the spinal canal, changes in the intervertebral discs and normally provides adequate information for surgical intervention without the need for invasive studies.

Treatment

At present, there are no adequate randomized long-term studies of the outcome of medical versus surgical management of lumbar spinal canal stenosis. Benoist (2002) has reviewed the current literature on the natural course of this condition and concludes that "at the present time no scientifically based recommendations can be made to lumbar spinal stenosis patients at diagnosis" due to the absence of satisfactory randomized control trials. The benefits of surgical treatment to stabilize spondylotic changes (Grobler *et al.*, 1993), progressive neurological deficits and intractable pain unresponsive to conservative measures are more certain (Snyder *et al.*, 2004). Age is not a barrier to successful surgical management (Arinzon *et al.*, 2003) but medical management may be a reasonable option (Houédakor *et al.*, 2003; Wünschmann *et al.*, 2003).

Conservative Management

Essentially, conservative management of lumbar spinal stenosis parallels that for cervical canal stenosis. Obesity may add to gait difficulties and requires a planned weight-reducing program. Identification and management of comorbid conditions often improve functional competence. Pain is an almost invariable symptom and analgesics and short-term nonsteroidal anti-inflammatory agents should be prescribed. If pain is severe, the limited use of tramadol can be helpful as may the other drugs noted in painful cervical spine stenosis. Local heat treatment or cryotherapy or short wave or microwave diathermy may provide symptomatic pain relief. Therapeutic exercises improve symptoms in almost 50% of patients (Houédakor *et al.*, 2003). Physiotherapy to stabilize the trunk in a flexed position (Wünschmann *et al.*, 2003) should include strengthening of the abdominal muscles. The use of a walking aid lowered to below the standard height can be useful in facilitating mobility in a flexed gait. Improvement of walking distance and enhancement of activities of daily living are essential objectives but require the skilled input of physiotherapy and occupational therapy professionals.

Two randomized control trials of calcitonin injections (Porter and Miller, 1988; Eskola *et al.*, 1992) reported improved walking distance except in the most severely impaired.

Gene therapy has been studied in experimental animals and appears to have the potential to influence biological processes in the degenerative intervertebral disc (Sobajima *et al.*, 2004).

Fluoscopically guided periradicular injections of local anesthetics and steroids at the site of root compression reduce radicular pain to a greater extent in disc protrusion than in spinal stenosis (Ng and Sell, 2004). Breaking down adhesions with injected saline followed by the injection of steroids/local anesthetics via epiduroscopy have also reduced symptoms of radicular pain in degenerative lumbar spinal stenosis in elderly patients (Igarashi *et al.*, 2004).

Microsurgical decompression without laminectomy has been found to be a safe and effective procedure (Nystrom *et al.*, 2001).

Laminectomy and laminoplasty remain the main surgical treatments for symptomatic canal stenosis unresponsive to conservative measures and the overall mortality from these procedures is as low as 1% (Tuite *et al.*, 1994). If multiple stenotic levels are present, as is often the case, or if the degree of stenosis is severe, the outcome may be less favorable. Severe comorbid medical conditions may be a barrier to decompression surgery. With lateral recess stenosis with osteophyte formation, hemifacetectomy or bilateral facetectomy is performed with foraminostomy. Instability at the level of intervention may occur following bilateral facetectomy; to reduce this risk, unilateral bony fusion is also performed with local removal of the ligamentum flavum. If concomitant spondylolisthesis is identified preoperatively, simultaneous fusion of the spondylolisthetic vertebrae is performed to prevent instability. In a 10-year follow-up of the surgical treatment of lumbar spinal stenosis (Rillardon *et al.*, 2003), 21% of patients required revision surgery with a 10% risk at the end of the follow-up period; overall satisfaction was reported in 71% with residual backache being the predominant complaint. Osteoinductive recombinant human osteogenic protein 1 (used as OP-1 Putty) has been successfully compared with autogenous iliac crest bone graft for posterolateral lumbar spine fusion following decompressive laminectomy (Vaccaro *et al.*, 2004).

A new interspinous implant (X STOP Interspinous Process Distraction System) for lumbar spinal stenosis patients whose symptoms are increased by spinal extension and relieved by flexion has been available since 2002 (Zuckerman *et al.*, 2004). The outcome with this technique is comparable to decompression laminectomy at one year but with greatly reduced morbidity.

The importance of cervical spine alignment and the maintenance of cervical lordosis following surgery for chronic cervical disc degeneration has been emphasized by Johnson and his colleagues (2004). They report the maintenance of overall cervical spine alignment following arthroplasty with one-level and two-level Bryan cervical artificial disc replacements.

KEY POINTS

- Cervical and lumbar spinal canal stenoses are mainly conditions of old age and may be either congenital or acquired. The former is usually asymptomatic until degenerative changes occur in later life but in young adults head injuries – usually sports related – may be complicated by paraparesis or tetraparesis, usually temporary.
- Degenerative changes with disc related bony bars, osteophytes and ligamentum flavum, and posterior longitudinal ligament hypertrophy cause canal stenosis.
- Cervical canal stenosis may be associated with myelopathy or/and arm radiculopathy. Lumbar stenosis may produce lower limb pains on walking aggravated by spinal column extension and relieved by rest in the stooped position.
- Diagnostic radiography, CT, MRI studies must be interpreted jointly with clinical history/neurological findings due to the frequency of asymptomatic spinal degenerative changes in old age.
- Treatment is conservative or surgical. If the condition is progressive or symptoms are uncontrollable surgical intervention is required, commonly laminectomy or laminoplasty. A number of new techniques have been introduced in the last 5 years.

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Spinovascular Insufficiency

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SPINAL CORD VASCULATURE

Spinal cord vascular disease is uncommon in relation to cerebrovascular disease, though its frequency has been underrated. Our basic understanding of the arterial blood supply to the spinal cord is largely based on the anatomical studies of Adamkiewicz (1881, 1882) and his fellow anatomist, Kadyi (1889) in Cracow, and of Tanon (1908) in Paris. Their findings were extended and modified by Suh and Alexander (1939) and Herren and Alexander (1939). The finer details of the spinal cord circulation have been emerging over the last 60 years but appreciation of the precise circulatory hemodynamics does not compare with current knowledge on the cerebral circulation. Ischemic spinal cord hazards of aortic surgery and the potential consequences of aortic aneurysm, dissection, or occlusion have focused attention on the spinal cord blood supply. Experimental techniques that test individual arteries during aortic surgery indicate that it is possible to confirm which of the intercostal or lumbar segmental arteries arise from varying levels of the aorta to supply the cord with blood (Svensson *et al.*, 1992). Demands to increase the safety of the surgical treatments of aortic damage and spinal arteriovenous malformations and arteriovenous fistulae have encouraged increasing sophistication in identifying the precise vascular supply to segments of the spinal cord. Magnetic resonance angiographic techniques have had a major impact in defining the spinal vascular patterns in individual patients.

The early embryonic segmental vascular pattern undergoes drastic modification with fetal development. The 31 pairs of segmental and intercostal arteries provide the blood supply for the spinal column and surrounding structures as well as contributing to the spinal cord blood supply (Gillilan, 1958). The intercostal arteries and their equivalent in the neck and lumbar regions penetrate the exterior surface of the dura and divide into a radicular artery, which furnishes blood to the anterior and posterior nerve roots, and a dural artery supplying the nerve root sleeve and spinal dura. At variable levels, a dural artery becomes a medullary artery, which contributes to the blood supply of either the anterior or posterior spinal artery. The anterior two-thirds of the cord is essentially supplied by the anterior spinal artery, which is formed from branches of the two vertebral arteries inside the skull, runs caudally in the anterior median fissure, and receives reinforcement from 6–10 medullary feeders in adulthood. In the neck, the anterior spinal artery is supplemented by branches from the deep cervical and ascending cervical arteries and in the dorsal region by branches, particularly of the fourth and/or fifth intercostal arteries, and in the thoracolumbar region, mainly by the great medullary artery of Adamkiewicz (MAA), the largest of the anterior medullary feeders. In 80% of subjects, the artery of Adamkiewicz occurs on the left side, and in an autopsy study, Biglioli *et al.* (2004) found the level from which it arises can be anywhere between T9 and L5; however, localization of MAA by preoperative magnetic resonance angiographic imaging (Kawaharada *et al.*, 2004) demonstrated that from the 110 MAA identified, 95% arose from intercostal arteries branching from the left side and 86% originated between T9 and T11. In 10% of patients, two MAAs were demonstrated. A collateral network also supplies the MAA (Akasaka *et al.*, 2004). The predominant source of blood supply to the distal spinal cord is from the lumbar aorta and hypogastric arteries (Figure 1). The level of these anastomoses shows considerable individual variation.

Blood flows in both caudal and rostral directions in the anterior spinal artery and generally in opposite converging directions from adjacent pairs of anterior medullary arteries. The blood supply to the anterior two-thirds of the cord is potentially tenuous where the upper and lower bloodstreams meet to form watershed zones (Henson and Parsons, 1967). About 10% of subjects who have a minimum blood supply of only two or three major anterior medullary arteries have watershed areas that are potentially vulnerable to spinovascular insufficiency, particularly at the T4 level (Zulch, 1976).

The posterior third of the cord is supplied by two posterior spinal arteries that are reinforced by posterior medullary vessels along their length; these two vessels

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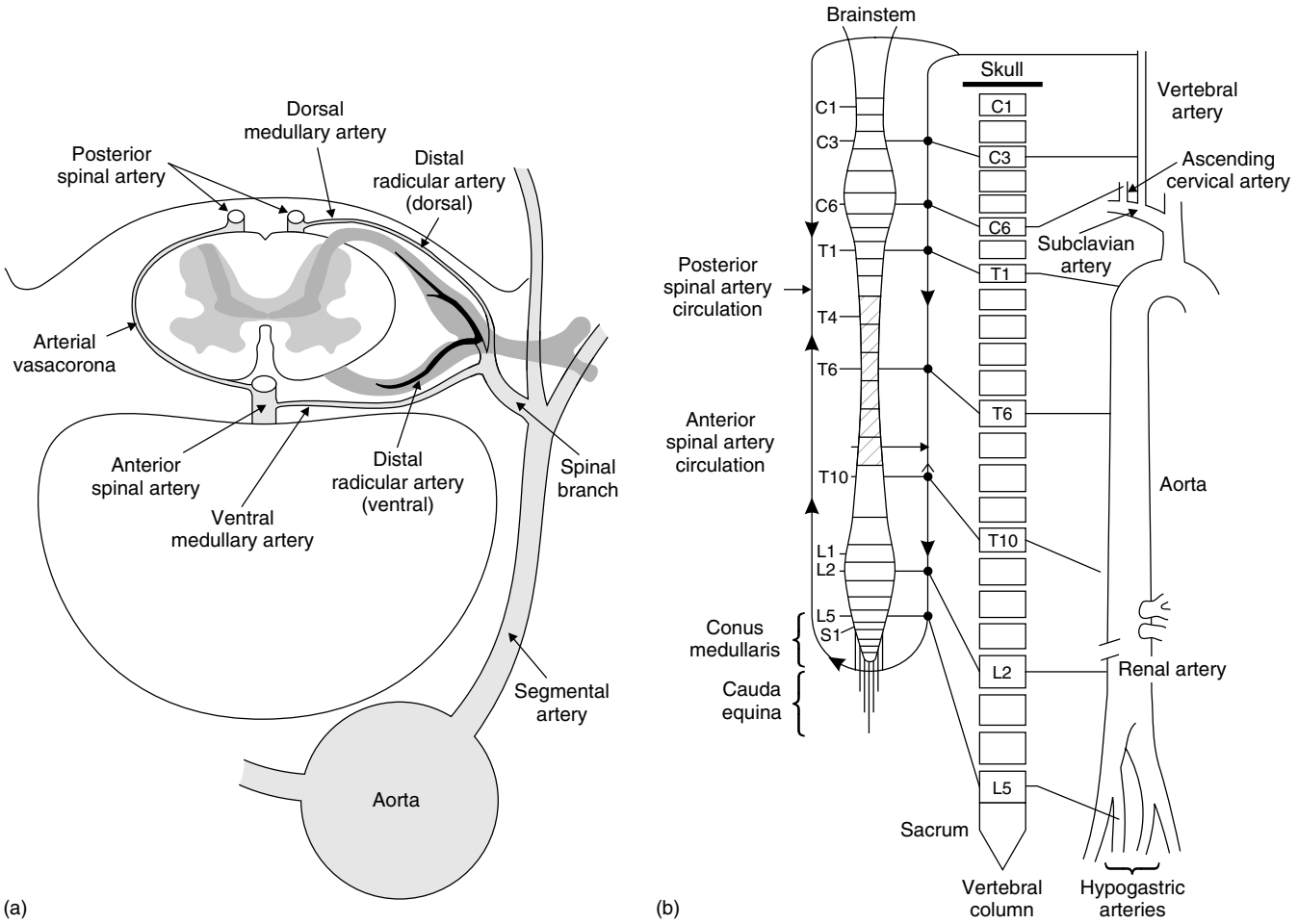

Figure 1 Intrinsic (a) and extrinsic (b) blood supply of spinal cord. (a) In cross-sectional view, shaded region is perfused by posterior spinal arteries while unshaded region is perfused by anterior spinal artery. (b) Ventral medullary "feeder" vessels to anterior spinal artery are shown. Greater medullary artery is shown arising at T10 level. Arrows indicate predominant direction of blood flow in spinal arteries (Reprinted from *Journal of Vascular Surgery*, V3, Picone AL *et al.*, Spinal cord ischemia following operations on the abdominal aorta, pp 94–103, Copyright 1986, with permission from Society for Vascular Surgery)

traverse either side of the cord medial to the dorsal roots. Posterior spinal arteries originate from the vertebral arteries, though occasionally from the inferior cerebellar arteries. Although arterial surface vessels form a vascular ring around the spinal cord, there is, in fact, no effective blood flow between the anterior and posterior vessels. The direction of blood flow in anterior and posterior spinal arteries may be reversed by altered physiological demands or by pathological changes. The blood supply to the cord is kept constant by autoregulatory mechanisms as in the brain. Blood flow changes appropriately in response to alterations in blood pressure and carbon dioxide tension (Kindt, 1972) but the ability to autoregulate may be lost in posttraumatic ischemia (Senter and Venes, 1979) or in hypercarbia.

SPINAL VENOUS SYSTEM

The veins lie parallel to the arteries along the cord but their disposition is substantially more varied than the spinal arteries. The tortuous anterior spinal vein runs posterior to the anterior spinal artery and one or two main posterior veins run longitudinally on the posterior surface of the cord. There are abundant venous connections both within the cord and on the surface, and with the pial plexi and veins of the epidural space. The final drainage is mainly into the azygos, hemiazygos, and jugular systems via segmental intervertebral veins.

VASCULAR DISORDERS OF THE CORD

The experimental findings of Stensen (1669) preceded clinical observations on the interruption of the arterial supply to the spinal cord by almost two centuries. During his study on muscle function in the dogfish, Stensen was able to produce reversible paralysis of the tail of the fish by occluding the descending aorta.

Spinovascular insufficiency may be discussed from a clinical or anatomical viewpoint. Though an anatomical

rubric is used here for descriptive convenience, it will be appreciated that blood flow inadequacy to the spinal cord can be a phenomenon common to or transgressing both intra- and extraspinal arteries, including the aorta.

The site and magnitude of ischemic change in the spinal cord is greatly influenced by the level, number, and size of the medullary arteries that anastomose with the anterior spinal artery. The watershed areas receiving blood from adjacent medullary feeders are particularly vulnerable to ischemia. The neuropathological study of Zivin *et al.*, (1982) throws considerable light on the pathophysiology of spinal cord ischemia. A spectrum of neurological deficits ranging from permanent paraplegia to transient paraparesis with complete recovery could be produced by temporarily ligating the spinal artery of rabbits. From an extensive review of the literature, Brusa *et al.* (1987) suggest that the site of cord softening rarely corresponds with the recognized anatomical distribution of medullary vessels.

Spinovascular insufficiency may be a sequela of many unrelated disorders, which include cervical spondylosis (Pau Serradell, 1994; Weidauer *et al.*, 2002) or cervical disc protrusion (Errea *et al.*, 1991), due to involvement of the vertebral artery or its branches; spinal arterial compression from intervertebral foraminal disease (Ram *et al.*, 2004); acute hypotensive events (Singh *et al.*, 1994; Weidauer *et al.*, 2002); cardiac arrest (Idali *et al.*, 1996; Imaizumi *et al.*, 1994; Bozkurt, 2002) may cause spinal cord ischemia because of varied causes; spinal cord trauma may impact on the arterial or venous component of the cord vasculature; however, Norenberg *et al.* (2004) have emphasized the importance of neuronal and demyelinating changes following spinal cord injury. Posttraumatic myelopathy may rarely develop with a subacute presentation (Visocchi *et al.*, 2003). Trauma may also be responsible for spinal subarachnoid hematomas but lumbar puncture for anesthetic or therapeutic purposes and coagulopathies are substantially more frequent culprits; spinal epidural hematoma may follow the administration of intravenous recombinant tissue-type plasminogen activator (Sawin *et al.*, 1995); vertebral angiography may give rise to spinal cord ischemic damage (Pathak *et al.*, 2000); Paget's disease involving the vertebral column may produce cord ischemia because of competitive demand on the associated blood supply; aortic disease or associated angiography or surgery are the most frequent precipitants of ischemic spinal cord damage; severe anemia (Miyai *et al.*, 1986); the 20210A allele of the prothrombin gene is associated with an enhanced risk of venous thromboembolism. Younger women on contraceptive estrogens who carry this allele have been reported to be at risk of developing anterior spinal artery syndrome (ASAS). A postmenopausal woman using topical estrogen and having the 20210A allele of the prothrombin gene has been reported to have developed spinal cord infarction and recurrent venous thrombosis (Gonzalez-Ordonez *et al.*, 2001). The risk for spinal cord ischemia in postmenopausal women with this gene on treatment with Hormone replacement therapy (HRT) is unknown. It has long been known that venous thrombosis may be associated with ASAS (Kim *et al.*, 1984; Satran, 1988); rarely fibrocartilage embolism (Bert *et al.*, 1995) and intraspinal gouty tophi (Wang *et al.*, 2001) may cause spinal cord ischemia. Other causal conditions reported to produce ASAS include polycythemia; leukemia; spinal tumor; diabetes; tuberculosis; arachnoiditis; meningitis; single segmental embolic infarction; focal vasculopathies; granulomatous conditions; embolic and hemodynamic phenomena; these conditions are among the rare and common disorders that may jeopardize the effective blood supply status of the spinal cord.

The Aorta

La Galois (1830) noted reversibility of motor paresis due to cord ischemia induced by temporary aortic ligation. Experimental occlusion of the aorta of cats for less than 15 minutes gives rise to temporary paraplegia, but aortic occlusion exceeding 20 minutes leads to permanent paraplegia (Tureen, 1936).

Aortic Aneurysm

Increased tangential tension and strain in the aortic wall causes wall thickening, especially with advancing age. Hypertension is a significant factor in producing intimal thickening and altered matrix volume. Sites of rapid intimal thickening are often associated with atherosclerotic plaque formation. Increased intimal plaque size leads to adaptive increase in aortic diameter to maintain the velocity of blood flow. The infrarenal segment of the abdominal aorta has substantially less elastin layers than the suprarenal aorta, and both elastin and collagen layers are arranged to withstand arterial pressure; both of these layers diminish with advancing age. The infrarenal aorta is more susceptible to damage to the medial lamellar architecture and to degenerative obstructive plaque formation and subsequent aneurysmal dilatation. Exercise increases shear stress and flow velocity and has a protective effect on the arterial wall. Reduced exercise levels in old age may therefore also have a role in aortic dilatation.

Abdominal aortic aneurysm (AAA) is held to be primarily associated with atherosclerosis: hypertension, smoking, age, family history, abnormal lipid profile, white race, and gender are the predominant risk factors. Giant cell arteritis is often complicated by an aortic aneurysm. AAA is a condition of old age and the prevalence increases progressively in ages 65 and over. Men are more often affected than women (4–8% versus 0.5–1.5%) (Fleming *et al.*, 2005) and women are, on average, 10 years older than men at the time of disease occurrence (Lederle *et al.*, 2001; Scott *et al.*, 2002). AAA has an increased growth rate in women than in men when measured over a 5-year period (Solberg *et al.*, 2005). Postmenopausal weight gain is a significant risk factor for cardiovascular disease and correlates with increased adventitial diameter of the abdominal aorta and iliac arteries (Patel *et al.*, 2005). In a population screening study in men, Norman *et al.* (2004) defined an aortic aneurysm as an aortic diameter of $\geq$30 mm.

Some small individuals having a normal aortic diameter of less than 20 or 25 mm may be aneurysmal. Modification of the standard CT 14-cm view for male smokers aged 55 and over and female smokers aged 65 and over presenting with back pain (*see* **Chapter 116, Back Pain**) allows incidental identification of aortic aneurysm (Gouliamos *et al.*, 2004); however, more commonly, abdominal aneurysms are detected incidentally during ultrasound examination of the abdomen or even by plain radiographs if there is wall calcification. The major complication is aortic wall rupture and the prevalence of this complication is uncertain as most patients die at home and it is very likely that sudden death is often ascribed to acute myocardial infarction. Mortality associated with emergency surgery of aortic rupture remains high but mortality from elective surgery continues to decline. Evidence is convincing that population screening for men over 65, particularly smokers (Norman *et al.*, 2004; Fleming *et al.*, 2005; Lindholt *et al.*, 2005), and women over 65 (Lederle *et al.*, 2001; Scott *et al.*, 2002; Fleming *et al.*, 2005) reduces deaths from abdominal aneurysms $\geq$50 mm.

Symptoms and Signs

AAA is usually asymptomatic until rupture occurs, but this is a rare complication in aneurysms less than 50 mm in diameter. Vague abdominal or back pain or symptoms arising from compression of intra-abdominal structures may be occasional complaints. The symptom of abdominal pulsation or self-detection of an abdominal swelling may bring a patient to medical attention. An onset with acute paraplegia is one of the catastrophic manifestations of this common condition, but it much more frequently follows dissection or aortic surgery, particularly of the thoracoabdominal segment of the aorta. A peripheral arterial embolic episode requires abdominal ultrasonography to exclude an aneurysm as the potential thrombotic source. A focused search for an AAA should be a mandatory routine in the clinical examination of all elderly patients; however, even a large aneurysm may be clinically undetectable in an obese patient and a tortuous aorta in a thin elderly subject may be misdiagnosed as an aneurysm.

Investigations

B-mode abdominal ultrasonography is the most widely available and least expensive of the imaging techniques; it should be used to establish the diagnosis and as a follow-up screening tool for small aneurysms of 30–40 mm diameter; a diameter of $\geq$50 mm is an indication for considering surgical intervention. Extension of an AAA into the iliac arteries is often not detected by conventional ultrasonography but can be readily recognized by intravascular ultrasonography. Three-dimensional reconstructed spiral CT will precisely delineate the size and extension, if any, of AAA and is the presurgical imaging technique of choice. Volume-rendered reconstructed (on a workstation) CT (3D CT) clearly defines the extent of the aneurysmal change and the size and extent of any intramural thrombus. This technique detects renal and internal iliac artery involvement and the visceral aortic branches (Fukuhara *et al.*, 2004). Magnetic resonance imaging (MRI) is being increasingly superseded by recent developments in CT imaging.

Surgical Treatment

The major risks are comorbid coronary artery disease (Rinckenbach *et al.*, 2004), vascular disease of the kidneys and spinal cord (Minatoya *et al.*, 2002), involvement of the iliac arteries (Maldonado *et al.*, 2004), and chronic obstructive pulmonary disease due to the high frequency of smokers with aortic aneurysms. Protective measures include the preoperative management of hypertension and, as far as is possible, the other comorbid conditions. The basic surgical treatment is endoaneurysmorrhaphy with an aortic tube graft in about 50% of patients. A bifurcated graft repair extending to the iliac arteries is required in the other 50% of recipients. Ischemic cord damage may complicate surgery for AAA but this is predominantly a feature of intervention for thoracoabdominal aneurysms; the risk increases with the duration of aortic cross-clamping. However, other factors such as perioperative hypotension may be significant. Emergency aortic surgical intervention will obviously be associated with greater risk of ischemic cord damage than elective surgery.

Since the introduction of endografting in 1990, improvement in techniques and skills with the procedure has achieved a low mortality and complication rate in early to middle term follow-up (Chuter *et al.*, 2004). The graft is introduced over a guide wire via the femoral artery to an infrarenal position in the aneurysmal sac under radiological control. Bifurcated endografts are now used. The cinematic picture is checked to exclude the extravasation of contrast material suggestive of an endoleak. Regular follow-up is essential as long-term outcome is not known but short-term results are excellent (Towne, 2005) and a 7-year concurrent comparison with open surgery showed a lower perioperative and late aneurysmal mortality with endovascular treatment (Cao *et al.*, 2004). Women derive benefit from the procedure compared to men (Sampaio *et al.*, 2004). Spinal cord ischemia may be an occasional complication of endovascular repair in this region (Maldonado *et al.*, 2004).

Rupture of Abdominal Aortic Aneurysm

Rupture of AAA is closely related to the aneurysmal size. At a diameter of 5–6 cm, rupture is uncommon but the rate of this complication increases rapidly with increasing expansion, particularly if this is acute. Symptoms depend on the site of rupture; if it is anterior into the peritoneal cavity, profound shock, severe hypotension, loss of consciousness, and early death are the common features. Approximately 80% of ruptures occur posteriorly into the retroperitoneum. Hypotension and shock may be transient and the patient may complain of rapid onset of abdominal and upper back pain. If the patient is known to have a preexisting aneurysm, clinical

diagnosis is more certain. Examination may occasionally detect abdominal tenderness but a pulsating abdominal mass is more frequent. Blood pressure may be low but this depends on the degree and speed of containment of blood flow into the retroperitoneal space and the time available for cardiac compensation. Treatment with endovascular stent grafting may be a safe alternative to conventional surgery (Castelli *et al.*, 2005; Doss *et al.*, 2005) in the short term but longer-term complication rates have yet to be established.

Aneurysms of the Thoracic and Thoracolumbar Aorta

Less than 5% of all aortic aneurysms occur in the thoracic and thoracolumbar aorta. Chest and back pain are often severe; the major risk is aortic rupture with a high mortality. Operative mortality depends on the extent of the aneurysmal changes but it is about 10% in experienced centers. The catastrophic potential for paraplegia occurs in 5–40% of patients (Wada *et al.*, 2001; Yamashiro *et al.*, 2003). Prevention of perioperative and postoperative hypotension is an essential factor in reducing the frequency of spinal cord ischemia. To reduce mortality and the risk of complications, a number of additional features have been incorporated into the surgical program: preoperative management of hypertension; perisurgical identification of the spinal arterial system by spinal angiography (Minatoya *et al.*, 2002) or by multidetector row CT (Kudo *et al.*, 2003); spinal fluid drainage during aortic cross-clamping to increase perfusion pressure to the spinal artery blood supply (but meta-analysis of randomized controlled trials provides limited evidence of benefit) (Khan and Stansby, 2004). The use of somatosensory-evoked potential and motor-evoked potential to indicate ischemic cord changes during surgery and extracorporeal circulation each produce improved outcome when compared with patients treated in the previous 4 years without these adjuncts (Schepens *et al.*, 2004). MR angiography allows identification of the MAA and all spinal cord–feeding arteries (Nijenhuis *et al.*, 2004) and reimplantation of critical intercostal arteries and the MAA (Jacobs *et al.*, 2002). A number of pharmacological agents have been used in experimental animals to reduce the risk of spinal cord ischemia during aortic surgery: ATP-MgC12 intravenously (Ulus *et al.*, 1999); tyrphostine Ag556 (Usul *et al.*, 2004); the free oxygen radical scavenger and nitric oxide upregulator, resveratrol (Kiziltepe *et al.*, 2004); adenosine A 2A receptor activation by ATL-146e (Reece *et al.*, 2004) and PJ34, an inhibitor of the nuclear enzyme poly (adenosine diphosphate ribose) polymerase (Casey *et al.*, 2005), to modulate ischemic changes in the spinal cord.

Surgical aortic prosthetic grafting includes reconstruction of the renal and visceral arteries and reattachment of important intercostal arteries feeding the spinal cord. Paraplegia is the dreaded complication of thoracic and abdominothoracic surgery but the risk is becoming less frequent with the use of the above adjuncts. Acute paraplegia after resection of the thoracoabdominal aorta has been documented as responding to hyperbaric oxygen therapy (Yamashiro *et al.*, 2003). Six consecutive patients receiving intraoperative perfusion of the MAA recovered without neurological complications (Ohtsubo *et al.*, 2004). A 4-year (Bortone *et al.*, 2004) and 3-year (Dagenais *et al.*, 2005) follow-up of patients treated with endovascular stent grafting show a low mortality and morbidity rate but until long-term results are available, the overall incidence of complications remains to be determined. The development of anatomical shaping of the straight Nitinol stent may enhance the outcome of endovascular stent procedures (Hyodoh *et al.*, 2005).

Aortic Dissection

Dissection of the aorta occurs as an intimal tear of the vessel wall, allowing separation of the aortic wall layers by an extraluminal extravasate of blood. Several classifications have been proposed, but only two of them are commonly used: DeBakey *et al.* (1965) divided dissections into three types depending on the segment/s of aorta involved; Daily *et al.* (1970) from Stanford University simplified this classification into Stanford type A (involving the ascending aorta) and Stanford type B (absence of involvement of the ascending aorta). Symptoms are usually acute with intense central chest pain, often mistaken for an acute myocardial infarction, and upper back pain. Over time, the pain descends to a lower position in the trunk. Acute vascular damage to the spinal cord presenting as paraplegia or paraparesis is common, and at times, paraplegia may be the initial presentation (Hsu and Lin, 2004; Zull and Cydulka, 1988; Waltimo and Karli, 1980) or the only presentation (Inumasu *et al.*, 2000; Donovan *et al.*, 2000). An initial presentation may be difficulty in walking (Staubli, 2004). Mortality is higher in patients with painless dissection (Park *et al.*, 2004). Neurological deficits have been reported in 22.7% of patients with hypotension at the time of hospital admission as against 12% of cases without hypotension (Tsai *et al.*, 2005). Acute rupture of the aorta in Stanford type A may lead to massive bleeding into the pleural cavity with acute shock and, usually, rapid death. Type B dissection may be asymptomatic and chronic and identified as an incidental finding during radiological investigation of unrelated conditions or as a result of sudden aortic rupture. The rate of increase in the diameter of type B aortic dissection is significantly greater in the presence of persistent blood flow in the false lumen as determined by regular CT follow-up over a mean duration of 49 months (Sueyoshi *et al.*, 2004).

In type B dissection, medical management may be the predominant option, particularly by vigorous control of hypertension, cessation of smoking, and by regular monitoring. Long-term outcome for medically treated patients requires attention to the predictors of patent false lumen and a maximum aortic diameter at onset of greater than 40 mm (Onitsuka *et al.*, 2004). The mortality and morbidity with treatment of type B by surgical graft replacement depends on the extent of the dissection. Mortality is high and, despite current techniques to preserve the arterial blood supply to the spinal cord, neurological sequelae are common and serious (Wada *et al.*, 2001). Acute postoperative

paraplegia following emergency repair of type A dissection with improvement following treatment by hyperbaric oxygen has been described (Yamashiro *et al.*, 2003). Experience is limited on the use of glue aortoplasty since its introduction over 15 years ago. No improvement was found in the mid-term dissection rate after aortoplasty using two strengths of formalin in gelatine-resorcin-formalin glue (Nakajima *et al.*, 2005). Aortic fenestration, a procedure of cutting an opening in the lower extension of the dissection, allows blood to flow back into the aortic lumen thereby reducing the obstruction in the aortic branch arteries and limits ischemic complications; immediate mortality and morbidity rate is low (Hartnell and Gates, 2005).

Endovascular stent graft placement is safe in selected patients who are without serious preoperative comorbidity (Eggebrecht *et al.*, 2005) and in an 8-year retrospective review, Lee *et al.* (2004) found this procedure to be effective, provided that regular follow-up was maintained to identify new complications; however, it is suggested that randomized control trials are required to establish the role of stent grafts in uncomplicated acute type B aortic dissection (Taylor *et al.*, 2004). Early diagnosis is the single most important factor for survival from acute dissection (Mariani *et al.*, 2004).

Aortic Intramural Hematoma

This condition has only become widely recognized as a discrete entity in the last 10 years and the knowledge base remains limited and does not approach that of aortic dissection. Aortic intramural hematoma occurs predominantly in men who are generally substantially older than patients with aortic dissection (Evangelista *et al.*, 2004, 2005). Age, gender, hypertension, and smoking are the major risk factors. Bleeding from spontaneous rupture of the vaso vasorum into the medial layer of the aortic wall with an intact intima is the common underlying pathology. Aortic intramural hemorrhage may result from a penetrating atherosclerotic ulcer, possibly via an intimal microtear (Song, 2004). The two causes should be distinguished from one another (Ganaha *et al.*, 2002; Timperley and Banning, 2003) if a better understanding of outcome and management is to be acquired. Intramural hematomas associated with penetrating atherosclerotic ulcers occur in the descending aorta (type B) and have a worse prognosis than the more stable hematomas without ulcers (Ganaha *et al.*, 2002). Occasionally, invasive procedures during surgery may be causal. The descending aorta is most commonly involved, but bleeding into the ascending aortic wall is associated with a much higher mortality rate (Evangelista, 2004). The common presenting symptom is chest or back pain but paraplegia may occur (Ferguson *et al.*, 1996; Timperley and Banning, 2003). Intramural hematomas are associated with a significant risk of aortic aneurysm, dissection, or rupture (Nienaber *et al.*, 2004).

Ascending aorta involvement has a reported mortality of 55% with medical treatment compared to 8% with surgical aortic graft repair (Nienaber *et al.*, 2004). In type B aortic hematomas, a trial of medical management is justified, particularly if symptoms subside (Dake, 2004). Aggressive management of hypertension is crucial and, at the onset, β-blocking agents may need to be given intravenously often with the addition of sodium nitroprusside (Blanchard and Sawhney, 2004) and subsequent oral β-blocking medication, and regular imaging follow-up until absorption of the hematoma is demonstrated with an absence of complications (Evangelista, 2004). In a 25-year retrospective survey of patients with acute aortic syndrome, Choi *et al.* (2004) found that 85% of penetrating atherosclerotic ulcers of the descending aorta had completely resolved in 1 year. Batt *et al.* (2005) suggest that penetrating atherosclerotic ulcers of the infrarenal aorta may be life threatening.

CT, MRI, and transesophageal echocardiography are the main tools required for the accurate diagnosis of aortic intramural hematoma but transesophageal echocardiography provides the most effective information (Song, 2004). Multiple imaging techniques may be required to exclude aortic risk factors.

Acute Aortic Occlusion

Acute aortic luminal occlusion may be due to thrombosis of an atherosclerotic aorta, thrombosis of an aneurysm, or embolism (Meagher *et al.*, 1991). Embolli are usually from the left atrium in patients with mitral stenosis with or without atrial fibrillation (Chiang *et al.*, 1998). A history of previous embolic events and significant aortic regurgitation are recognized risk factors. Floating aortic thrombi commonly send off peripheral embolli but may primarily occlude the aorta (Choi *et al.*, 2004). Embolic occlusion may be by a saddle embolus from an atrial myxoma (Ali *et al.*, 2004). Acute occlusion may be associated with aortic dissection. The presenting signs are usually acute paraparesis or paraplegia (Meagher *et al.*, 1991; Zainal *et al.*, 2000) accompanied by lower limb ischemia. The vascular paraplegia is often associated with thrombotic occlusion of a major medullary artery and severe hypotension may critically reduce blood flow in the other spinal cord–feeding arteries. Diagnosis is by CT or MRI.

Acute aortic occlusion has a high mortality rate and requires early intervention. Suggested treatment includes aortic embolectomy and, where indicated, femoral embolectomy, aortic bifurcation graft, thromboendarterectomy, and femoropopliteal bypass (Meagher *et al.*, 1991). Reperfusion injury may be a serious complication of thromboembolectomy (Ali *et al.*, 2004). Successful treatment with systemic streptokinase has been reported (Ahmed *et al.*, 2005). Long-term anticoagulation in patients with mitral stenosis and atrial fibrillation is essential in reducing the possibility of embolic phenomena; however, a 6-month transesophageal echo follow-up of anticoagulated patients with left atrial or atrial appendage clots found clot dissolution in appendage clots but infrequently in atrial body clots (Srimannarayana *et al.*, 2003).

Spinal Hematomas

This term includes subdural and epidural hematomas and subarachnoid hematomas/hemorrhages. Domenicucci *et al.*

(2005) suggest that subarachnoid hemorrhages can be distinguished from subarachnoid hematomas and that the former condition is more common than hematomas; at present, any such distinction is ill-defined and the two terms are at times used interchangeably. In subarachnoid hemorrhage, the cerebrospinal fluid (CSF) dilutes the hemorrhage and significantly inhibits coagulation. For the purpose of this chapter, extraspinal cord bleeds are considered together as a group with reference to significant differences. The underlying causes are essentially similar for bleeds in the three sites. A bleeding diathesis (due to systemic diseases or drug therapy, particularly from anticoagulant agents) is the most frequent underlying cause. In a meta-analysis of 613 patients reported in the literature from 1826 to 1996, Kreppel *et al.* (2003) found the etiology to be multifactorial in most cases, and in a third of patients, no cause for the bleeding could be identified; however, diagnostic methods and the relevant premorbid therapeutic agents used have changed dramatically over this period. Seventy percent of subdural hematomas are reported to occur in the lumbar or thoracolumbar spine (Domenicucci *et al.*, 1999). Lumbar puncture is an important precursor, especially in anticoagulated patients. Trauma may be the underlying cause. Spinal dural arteriovenous fistulae usually produce subarachnoid bleeding in the lumbar region but dural fistulae occasionally occur in the cervical spine and may also bleed into the spinal subarachnoid space. Rupture or dissection of spinal artery aneurysms (Berlis *et al.*, 2005) or a radiculomedullary pseudoaneurysm (Yahiro *et al.*, 2004) may produce spinal subarachnoid bleeding; spinal intradural extramedullary cavernous angiomas are among the causes of bleeding into the subarachnoid space. Gender incidence is approximately equal, irrespective of the exact location of the hemorrhage and, in the seven cases of subdural and intradural hematomas reported by Kuker *et al.* (2000), the age range was from 55 to 86, and in the 613 patients reviewed from the literature, Kreppel *et al.* (2003) noted that most patients were between 55 and 70 years old. Spinal subdural and epidural hematomas have an acute or subacute onset and are located in the cervical, thoracic or lumbar regions of the spine, but most often in the thoracic spine. Epidural hematomas are located dorsal to the cord because of the firm fixation of the dura to the vertebral bodies, whereas, subdural bleeds are mainly situated ventral to the cord (Kuker *et al.*, 2000). Subarachnoid hemorrhages/hematomas may extend along the total length of the subarachnoid space.

Presentation with progressive paraparesis or paraplegia is common to all three sites of extraspinal cord bleeding but uncommonly, the neurological sequelae are less profound, particularly if the subarachnoid space is not involved. In peridural hematomas, nerve root compression may be the main neurological deficit. Initial back pain may be present in subarachnoid bleeds but it is often severe in peridural and subdural hematomas. Rapid paraplegia or paraparesis follows the onset of pain.

CT and MRI are used to identify spinal hematomas/hemorrhages, but these imaging techniques are usually unable to distinguish subarachnoid bleeds from those that occur in the subdural space, except when CSF or contrast material is visualized in the subarachnoid space. Where a spinal dural fistula is suspected, a spinal angiogram is indicated.

Mortality rate is high in the absence of prompt decompressive surgical intervention and is higher in spinal subarachnoid hemorrhage than in subdural hematomas; where possible prior correction of coagulopathies (iatrogenic or due to disease) is critical. An extensive spinal subdural hematoma has been successfully treated by irrigation of the subdural space with recombinant tissue plasminogen activator (Little *et al.*, 2004) but the place of this approach has yet to be established.

Large Vessel Vasculitis: Takayasu's Disease

Large vessel vasculitis due to Takayasu's disease and giant cell arteritis was identified using highly effective (18)F-fluorodeoxyglucose positron emission tomography. The 26 consecutive patients with confirmed large vessel vasculitis had a mean age of 70 years with an age range of 17–86 years (Walter *et al.*, 2005). This higher mean age than that noted in most reports may be due, in part, to the sensitivity of the imaging technique or, more probably, to the case mix. Takayasu arteritis is a disorder of unknown etiology predominantly affecting the aorta and its major branches, and most commonly occurring in women. The natural history is unpredictable. Most studies in the Far East have reported cases mainly in young adults although the condition occurs worldwide. Only a brief outline of this type of vasculitis will be considered because of the younger age structure in most surveys.

Infection, genetic factors, and hormonal and autoimmune influences have been postulated but none has been confirmed. The aorta and its major branches are predominantly affected. Older subjects are usually seen in the phase of absent pulses. Hypertension is common, usually due to renal artery stenosis (Mwipatayi *et al.*, 2005). In a study of 104 Italian patients with Takayasu's arteritis, Vanoli *et al.* (2005) reported that stenosis was the most frequent vascular complication being present in 93% of patients. Vascular symptoms of arterial insufficiency are common and peripheral pulses may be absent. Presentation with a pyrexia of unknown origin is common and frequently gives rise to diagnostic difficulties. Aneurysm of large arteries is a common complication but the incidence varies considerably in different countries. Involvement of the whole length of the aorta and the aortic bifurcation was common in the South African study (Mwipatayi *et al.*, 2005).

Medical treatment is aimed at controlling inflammatory changes in the affected arteries and managing associated systemic manifestations. Corticosteroid therapy using the lowest effective dose is the cornerstone of medical support. If response is limited or relapse occurs, low dose methotrexate or cyclophosphamide is indicated but the latter preparation is often associated with serious side effects following long-term administration. Hypertension is common and requires supervised treatment but medical management is often unsuccessful without intervention procedures, usually percutaneous

transluminal angioplasty (PTA), to deal with underlying renal artery stenosis.

PTA is often successful for treating stenosis in limited segments of peripheral arteries with control of active inflammation by immunosuppressive therapy (Min *et al.*, 2005). Balloon dilatation of segmental stenosis of the abdominal aorta is justified but restenosis may occur. Aortic aneurysmal changes may require surgical graft replacement.

Other forms of inflammatory arteritis due to rheumatoid syndromes, sarcoidosis, scleroderma, and polyarteritis nodosa predominantly involve medium or small arteries but may rarely involve the aorta; radiation induced atherosclerotic arteritis also affects small or medium arteries and, uncommonly, the aorta. Patients with giant cell arteritis are 17 times more likely to develop thoracic aortic aneurysm (Launay and Hachulla, 2004). The frequency of aortitis is substantially greater in geographical regions where the level of infection in the community is high.

Arteriovenous Malformations (AVM)

Several classifications have been used to distinguish the different types of arteriovenous malformations (AVM) but that modified by Spetzler and Myers (2004) is the most useful. Intradural AV fistulae are probably congenital and occur in children and young adults and will not be considered here. Dural AV fistulae mainly affect men (Thron, 2001) with a mean age at presentation of 65 years. This type of malformation is situated within the dura of the spinal nerve roots and is believed to be acquired. The arterial supply can be by a single arterial feeder or by multiple feeders depending on the subtype. AV fistulae can occur at any spinal level; in the neck, a single feeder is usually from the left cervical ascending artery, in the thoracic region, the arterial supply is from the left T10 intercostal artery, and in the lumbar region, from the L1 lumbar artery (Mascalchi *et al.*, 2001). Blood flow is directed into the venous plexus encircling the spinal cord and the resulting venous hypertension is responsible for the myelopathic sequela.

The cardinal symptom is that of a myelopathy with a variable, but usually slow, rate of progression. Back pain often precedes neurological features. Symptoms may be accentuated by coughing, bending, or straining. Progressive difficulty in walking is the most common manifestation of venous hypertension; lower limb function is impaired in about 50% of patients and about 10% present with an acute onset (Aminoff and Logue, 1974). Diagnosis is by MRI and spinal angiography.

Traumatic AV fistulae are not considered here as they do not give rise to myelopathy.

Treatment

At present, there is no clear consensus between the case for surgery or for embolization in the management of AV fistulae. There is general agreement that intervention should be offered to all symptomatic patients with a possible exception of cases with prolonged severe myelopathy. It is likely that it is not a choice between two options but between alternatives in individual situations and the availability of appropriate skills for each technique. Steinmetz *et al.* (2004) concluded from a single center 7-year retrospective review and a meta-analysis of a MEDLINE search that microsurgery is superior to embolization in the treatment of spinal dural AV fistulae. In a MR angiographic assessment of patients treated by embolization, 37% of cases showed partial or complete persistence of flow in the perimedullary vessels (Mascalchi *et al.*, 2001). Using neurophysiological testing by cortical somatosensory-evoked potentials and transcranial motor-evoked potentials to monitor the response to provocative testing with sodium amytal and lidocaine injections, Niimi *et al.* (2004) were able to identify which patients would successfully respond to *N*-butylcyanoacrylate embolization.

ANTERIOR SPINAL ARTERY

The anterior spinal artery supplies the anterior two-thirds of the cord and, therefore, all the white matter except the posterior columns, and all the gray matter other than the posterior horns. Occlusion of this artery due to syphilis was first reported by Preobaschenski (1908) and, in the following year, by Spiller (1909) The genesis of the occlusion may be thrombotic or embolic and may occur in the vulnerable vascular watershed areas of the cord following an episode of hypotension. In many of the reported cases of ASAS, no occlusion is demonstrable at autopsy. Reduction of mean arterial blood pressure to 25 mmHg in the experimental animal effectively terminates recordable blood flow (Kobrine *et al.*, 1979). The role of the artery of Adamkiewicz and the segmental arterial supply to the cord have been highlighted as critical in spinal cord ischemia in hypotension. Arteriosclerotic changes in the anterior spinal artery or/and the main feeding arteries appears to be the major cause of compromised blood flow, but vasculitis, angiomas, infection, and trauma can also give rise to spinal artery syndrome, but the predominant factors are aortic disease and its therapeutic intervention. Rarely, the ASAS is due to severe vertebral artery stenosis or follows infrainguinal bypass surgery Mihaljevic and Belkin (2001).

Clinical Picture of Ischemic Cord Infarction

The ischemic event may be heralded by segmental or root pain, or by girdle pain. The pain is often intense and is followed after a variable interval of 1 to several hours by flaccid paraplegia or quadriplegia depending on the level of obstruction. In nonsurgical cases, prodromal symptoms are rarely absent. Initial retention of urine is commonly followed by urinary and fecal incontinence. The paretic muscles exhibit wasting and fasciculation at an early stage due to anterior horn cell destruction. Pyramidal features develop

later, but spasticity is often slight. The motor changes vary from mild weakness to complete paralysis, though the latter is much more common. However, this may in part reflect case reporting bias. Loss of pain and temperature sensation with a defined upper level is an early finding, but proprioception and vibration senses are intact as the posterior columns are supplied by the posterior spinal arteries. The sensory deficits frequently improve with time. Once neurostability is attained, bladder sensation is preserved indicating that this function uses the posterior columns. Cervicomedullary infarction may give rise to Horner's syndrome, vertical nystagmus, and, occasionally, hypoglossal paralysis with ipsilateral paralysis of the tongue.

Spinal cord infarction following aortic surgery usually presents with paraplegia on recovery from anesthesia. Transient ischemic attacks involving the spinal cord may be isolated episodes or events heralding cord infarction and closely parallel the situation in the cerebrovascular system.

The ASAS may be due to vertebral artery stenosis presenting with quadriplegia and sensory deficits (Suzuki *et al.*, 1998) or a sensorimotor stroke.

POSTERIOR SPINAL ARTERY

Isolated occlusion of the posterior spinal artery is rare (Perier *et al.*, 1960; Fukuda and Kitani, 1994) due to an adequate collateral system. The predominant clinical findings are segmental anesthesia, loss of proprioception, vibration, and tactile discrimination; ataxia and areflexia due to posterior column damage. Most commonly, there is involvement of the circumflex collateral arteries with consequent lateral or anterior zone neurological features.

Diagnosis

MRI or diffusion weighted MRI of the spinal cord and vertebral body has proved useful in identifying spinal cord infarction with associated vascular and vertebral body changes.

Prognosis

The outcome of spinal cord ischemia will depend on completeness of the cord damage. The presence of voluntary motor control of the anal sphincter and/or sensory function at the mucocutaneous junction of the anus defines an incomplete cord injury (Waters *et al.*, 1991). Absent motor and sensory function at sacral levels is considered to represent complete injury. Waters *et al.* (1993) found that the prognosis for motor recovery was poor for patients having complete motor deficit persisting for longer than 1 month.

If the brunt of the motor deficit is in one limb, recovery is moderate or less often complete. In transient episodes of paraparesis, recovery is normally complete but the likelihood of a subsequent established spinal stroke exists.

Treatment

Primary predisposing factors will clearly require active treatment. When complete infarction of the anterior two-thirds of the cord occurs, the treatment of the patient will be the management of paraplegia. Care of the bowels, management of urinary incontinence (*see* **Chapter 126, Urinary Incontinence**), and the prevention of pressure sores (*see* **Chapter 136, Pressure Ulceration**) require considerable understanding and skill; posterior cord infarction has a much better prognosis. Physical treatment is directed toward improving upper limb and trunk power and the achievement of wheelchair independence.

SPINAL VEINS

Spinal vein thrombosis is commonly secondary to inflammatory, neoplastic, or traumatic conditions of the vertebral column. Septicemia and thrombophlebitis are significant antecedents and polycythemia may be a predisposing factor.

The white matter of the cord is initially affected and involvement of the gray matter occurs later and, probably, as a secondary phenomenon. In her authoritative study on the veins of the spinal cord, Gillilan (1970) points out that the posterolateral white matter and the lateral cortical spinal tract are involved at the outset, and only as the process extends, do the lateral spinothalamic and spinocerebellar tracts become involved. These findings are in keeping with the clinical descriptions of dissociated or complete sensory loss at or below the level of the lesion associated with progressive paraparesis.

Experimental occlusion of the posterior spinal veins in rhesus monkeys produces gliosis associated with demyelination, confined to the posterior columns (Doppman *et al.*, 1979).

The clinical picture may be dominated in the initial phase by associated disease. Back pain may be intense and signs of rapidly progressive transverse myelopathy are common though it seems likely that evidence of minor localized spinal venous occlusion may pass unrecognized when it is secondary to more florid precipitating disease.

Epidural venous stasis may be associated with spinal canal stenosis and both conditions may be visualized on CT or MRI scanning. Epidural metastases or vertebral venous plexus metastases from carcinoma of the bronchus or lymphoma may cause substantial neurogenic edema due to compression of the vertebral venous plexus.

CHRONIC MYELOPATHY

The possibility that chronic myelopathy may be due to aortic atheroma was mooted by Marie and Foix (1912); further cases were reported by Winkleman and Eckel (1932), Keschner and Davison (1933). The atheromatous change is mainly in the aorta, but may involve the arteries of the spinal cord. In chronic degenerative thoracoabdominal

aneurysm, gradual obliteration of intercostal arteries may allow collateral vessels to slowly develop. Most cases of chronic myelopathy are now thought to be due to undetected dural AV fistulae (Masson *et al.*, 2004). The clinical picture may resemble motor neurone disease with muscle wasting and slowly progressive paraplegia (Skinhoj, 1954).

KEY POINTS

- Rapid advances in surgical procedures for aortic artery disease have accelerated our understanding of the spinal cord vasculature.
- Developments in CT and MRI imaging have played a role in identifying causal disorders responsible for spinal cord ischemia and have increased the safety of interventional treatment.
- Atherosclerotic disease affecting the spinal arteries and their aortic feeders is the major cause of neurological sequelae from spinal cord vascular damage.
- Aortic aneurysm and its complications – dissection, rupture, or occlusion – may have a high mortality depending on the site of aortic involvement; treatment is by surgical synthetic graft replacement or by endovascular stent placement, procedures that may cause myelopathy.
- Dural AV fistulae are an increasingly recognized cause of myelopathy due to spinal venous hypertension.
- Intramural bleeding into the media of the aortic wall and subdural and subarachnoid hematomas/hemorrhages often produce spinal cord ischemia.

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Subarachnoid Hemorrhage

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INTRODUCTION AND EPIDEMIOLOGICAL ASPECTS

Subarachnoid hemorrhage (SAH) is mostly caused by ruptured aneurysms, though some other causes will be considered in this article. Case fatality is around 50%, yet SAH accounts for only 3% of all stroke deaths because other types of strokes are far more common. On the other hand, the rupture of a cerebral aneurysm mostly strikes younger age-groups as compared to cerebral infarction and intracerebral hemorrhage, which usually occur after the sixth decade of life. As a result, SAH is responsible for more than one-quarter of potential life-years lost through stroke, despite its relative rarity (van Gijn and Rinkel, 2001).

Age-groups above 65 years make up around 30% of SAH cases in population-based studies (Anderson *et al.*, 2000). Hospital series are notoriously unreliable in this respect, because of referral bias. In contrast, age-specific incidence rates indicate a continuous upward trend in the risk for SAH with increasing age (Anderson *et al.*, 2000). Overall, the annual incidence in a standardized European and Australasian population is in the order of 6–8 per 100 000 (Anderson *et al.*, 2000; Linn *et al.*, 1996), but in those over 85 years, this rate rises to 20–40 (Anderson *et al.*, 2000; Menghini *et al.*, 1998). Within each age stratum, women have a 1.6 times higher risk than men (95% CI 1.5–2.3) (Linn *et al.*, 1996). The increasing risk of SAH with age is in keeping with the finding that cerebral aneurysms develop in the course of life, although only a small proportion of them will ever rupture.

In summary, the relation between SAH and age is an example of the risk paradox. From the point of view of an entire population SAH is mainly a disease of the middle-aged, whereas from the point of view of a given individual who has lived to the 8th or 9th decade, the risk of SAH is substantially higher than for a younger person. To draw a somewhat unexpected but illustrative parallel: most children with Down's syndrome are born out of mothers under 35 years, but pregnant women over 35 years are aware that for them the risk of carrying a child with trisomy 21 is much higher than for younger women. Relatively large fractions of small groups can be outnumbered by small fractions from a very large group.

RISK FACTORS

Genetic factors are traditionally regarded as important – especially in former times when cerebral aneurysms were erroneously called *congenital*, but this should not be overrated. Between 7 and 20% of patients with subarachnoid hemorrhage have a positive family history. First-degree relatives of patients with subarachnoid hemorrhage have a three- to sevenfold increase in the risk of being struck by the same disease (Bromberg *et al.*, 1995). In certain geographical areas, this risk is high for population at large; in Finland and Japan, incidence rates are in the order of 20 per 100 000 per annum, that is, more than three times higher as compared to other parts of the world (van Gijn and Rinkel, 2001).

Specific heritable disorders of connective tissue may also be predisposed to SAH, but these patients account for only a minute fraction of all patients. Even though autosomal dominant polycystic kidney disease (ADPKD) is the most common heritable disorder associated with subarachnoid hemorrhage, it accounts for only 0.5–2% of all patients with subarachnoid hemorrhage. Ehlers–Danlos disease IV is only weakly associated with SAH and Marfan's syndrome is probably not at all associated with SAH.

Modifiable risk factors for subarachnoid hemorrhage include smoking, hypertension, and heavy drinking, with odds ratios in the order of 2–3. For the use of oral contraceptives, the odds ratio is between 1 and 2 (van Gijn and Rinkel, 2001).

In terms of attributable risk, drinking alcohol 100–299 g/wk has been estimated to account for 11% of cases of SAH, drinking alcohol greater than or equal to 300 g/wk for 21%, and smoking for 20% (Ruigrok *et al.*, 2001). An additional

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17% of the cases could be attributed to hypertension, 11% to a positive family history of SAH, and only 0.3% to ADPKD.

A special group of patients who are at increased risk for SAH is formed by those who have survived an episode of subarachnoid hemorrhage, even if all aneurysms detected at the time of the hemorrhage have been treated, because of its ongoing development during life.

OUTCOME

Case fatality in a published series ranges between 32 and 67%, with a weighted average of 51%. Among the patients who survive the hemorrhage, approximately one-third remain dependent (van Gijn and Rinkel, 2001). Recovery to an independent state does not necessarily mean that the outcome is good. In a study on the quality of life in patients after subarachnoid hemorrhage, only 9 out of 48 (19%; 95% CI 9–33%) patients who were independent 4 months after the hemorrhage had no significant reduction in the quality of life. Reevaluation of this cohort at 18 months after the hemorrhage showed that the outcome had considerably improved in terms of handicap and quality of life, but that still only 15 of the 48 patients (31%; 95% CI 19–46%) had no reduction in the quality of life (van Gijn and Rinkel, 2001). The improvement in the first year and a half shows that long-term follow-up is essential in studies on the effectiveness of new treatment strategies on functional outcome after subarachnoid hemorrhage.

In published series of outcome in patients over 65 years of age, the follow-up period rarely exceeded 6 months (Table 1). However, perusal of these studies allows some tentative conclusions, despite important differences across these studies such as selection criteria (all patients or only operated patients; lower age limit 65, 70, or 80 years). First, the proportion of patients who are dead or dependent after 3 or 6 months is not strikingly different from the outcome mentioned above for the entire cohorts of patients with SAH. Secondly, tabulations in some of the original papers listed in Table 1 suggest that the complications leading to death and disability were mainly of the same nature as those in younger people: rebleeding, delayed cerebral ischemia, and hydrocephalus (see following text). Apparently, general medical complications such as heart failure or respiratory failure are relatively unimportant in determining the outcome after SAH even in older patients.

Although age is a relatively minor factor in determining the outcome after SAH, the sad truth remains that only a small minority of all patients with subarachnoid hemorrhage can continue their life as before.

DIAGNOSIS OF SAH

Clinical Features

The clinical hallmark of subarachnoid hemorrhage is a history of unusually severe headaches with sudden onset. A period of unresponsiveness longer than 1 hour occurs in almost half the patients, and focal signs develop at the same time as the headaches or soon afterward in one-third of patients.

In those in whom headache is the only symptom, it is often difficult to recognize the seriousness of the underlying condition. Classically, the headache from aneurysmal rupture comes on in seconds. It is therefore important to make

Table 1 Studies reporting outcome after subarachnoid hemorrhage in the elderly (≥65 years). Studies were included only if they included at least 30 patients, if patients had been followed up for at least 3 months after the ictus and if outcome had been assessed by means of the modified Rankin Scale (mRS) or the Glasgow Outcome Scale. All studies were retrospective, except that of Muizelaar *et al.* (1988)

Year of publication	First author	Selection according to treatment or condition	Number of patients	Lower Age limit	Length of follow-up	Number dead or dependent (Rankin grade ≥4)	Comments
2004	Agazzi *et al.* (2004)	All patients	33	70 years	1–2 years	15 + 4 (58%)	– outcome poor if WFNS ≥3 – conservative treatment can be rewarding
2004	Johansson *et al.* (2004)	Endovascular	58	65 years	6 months	(59%)	– 4 other patients with incomplete procedure
2004	Lubicz *et al.* (2004)	Endovascular	68	65 years	6–36 months	14 + 14 (41%)	
2003	Ferch *et al.* (2003)	Surgical	100	70 years	6–>44 months	24 + 18 (42%)	– mRS grades not well defined and specified
2003	Yano *et al.* (2003)	All patients	76	80 years	2–6 years	54 + 9 (83%)	– 31 of the 76 patients were operated
2002	Sedat *et al.* (2002)	Endovascular	52	65 years	12 months	12 + 15 (52%)	
2001	Johansson *et al.* (2001)	All patients	281	65 years	1–10 years	87 + 36 (44%)	– results improved between 1981 and 1998
2000	Chung *et al.* (2000)	All patients	89	70 years	6 months	40 + 8 (54%)	
1996	Lanzino *et al.* (1996)	All patients	65	70 years	3 months	23 + 18 (63%)	
1995	Fridriksson *et al.* (1995)	Surgical	98	70 years	6 months	(40%)	
1993	Inagawa (1993)	All patients	131	70 years	6 months	65 + 25 (69%)	– results better in 1986–1990 than 1980–1985
1988	Muizelaar *et al.* 1988)	All patients	61	65 years	3 months	32 + 7 (64%)	

specific inquiries about how quickly the headache developed; patients often complain only about the severity of the headache and do not know that the speed of onset is a pivotal piece of information. But even an accurate history does not reliably distinguish between aneurysmal rupture and innocuous forms of headache, such as benign vascular headache or a muscle contraction headache. First, only half the patients with aneurysm rupture describe the onset as instantaneous, the other half describe it as coming on in seconds to even a few minutes (van Gijn and Rinkel, 2001). Second, patients with an exceptionally rapid onset of common types of headache ("crash migraine") outnumber those with SAH – another example of the risk paradox. Other headache features are equally unhelpful in making the distinction: the severity is rated similarly; vomiting occurs in 70% of patients with aneurysmal rupture but also in 43% of patients with innocuous "thunderclap" headache. Neck stiffness is a common sign in SAH of any cause but it takes hours to develop and therefore it cannot be used to exclude the diagnosis if a patient is seen soon after the sudden-onset headache. Subhyaloid hemorrhages require experience with funduscopy and occur in approximately 17% of patients, at least of those who reach the hospital alive.

Even though the chance of SAH in a patient with explosive headache as the only symptom is only 10% (Linn *et al.*, 1994), the lack of clinical features that distinguish reliably and at an early stage between SAH and innocuous types of sudden headache necessitates a brief consultation in hospital for all such patients. The discomfort and the cost of referring the great majority of patients with innocuous headache is outweighed by the avoidance of the disaster that a ruptured aneurysm causes when not detected.

It is even more difficult to suspect aneurysmal rupture if the patient does not give a history of sudden headache, or if other symptoms seem to prevail over the headache, such as in patients presenting with a seizure or a confusional state, or if there is an associated head trauma. Epileptic seizures at the onset of aneurysmal SAH occur in approximately 10% of patients. Of course, the majority of patients with *de novo* epilepsy above age 25 will have underlying conditions other than subarachnoid hemorrhage, but the diagnosis should be suspected if the post-ictal headache is unusually severe. One to two percent of patients with subarachnoid hemorrhage present with an acute confusional state, and in most such patients, a history of sudden headache is lacking.

The physical examination sometimes provides an indication about the cause of SAH. Monocular blindness may result from an anterior communicating artery aneurysm if it is exceptionally large. Complete or partial third nerve palsy is a well-recognized sign after rupture of an aneurysm of the internal carotid artery at the origin of the posterior communicating artery, less commonly with aneurysms of the basilar bifurcation or the superior cerebellar artery. The pupil may be spared, contrary to conventional wisdom. Sixth nerve palsies, often bilateral in the acute stage, usually result from a nonspecific and sustained rise of cerebrospinal fluid (CSF) pressure, at the time of rupture or later. A combination of visual and oculomotor deficits should raise the suspicion of a pituitary apoplexy.

Investigations: Brain Scanning (CT, MRI)

If subarachnoid hemorrhage is suspected, computed tomography (CT) scanning is the investigation of choice because of the characteristically hyperdense appearance of extravasated blood in the basal cisterns (van Gijn and Rinkel, 2001). The pattern of hemorrhage often suggests the location of any underlying aneurysm. The CT scan should be carefully scrutinized because small amounts of subarachnoid blood may easily be overlooked (Figure 1). If after a thorough review no blood is found, aneurysmal subarachnoid hemorrhage cannot be excluded. Even if CT is performed within 12 hours after the hemorrhage and with a modern machine, studies

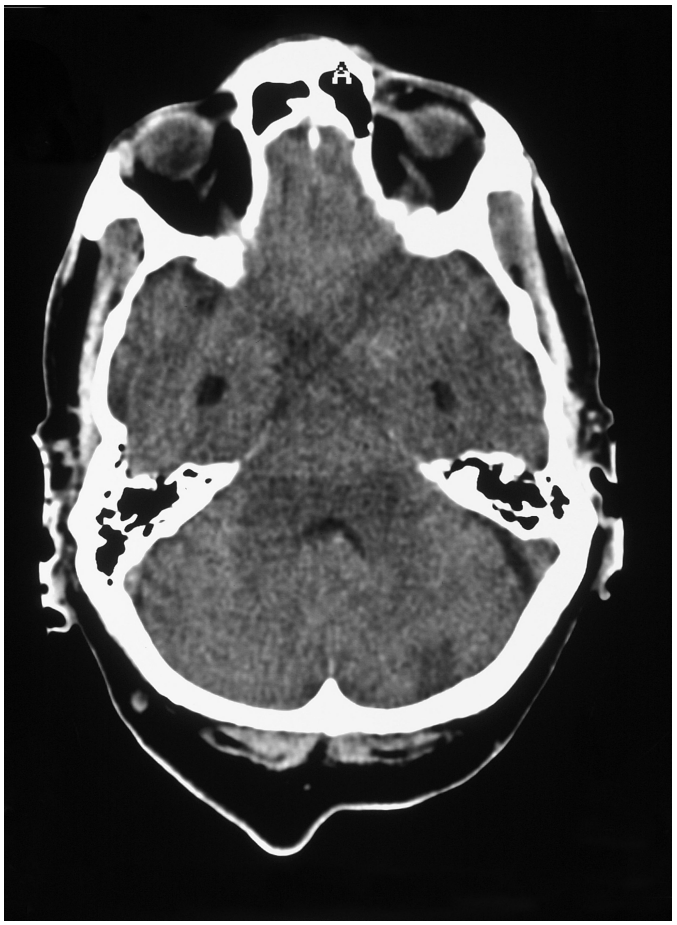

Figure 1 Subtle evidence of subarachnoid hemorrhage. CT scan of the brain of a 43-year-old man, within a few hours of onset of sudden headache, followed by drowsiness and a partial oculomotor palsy on the left side. The suprasellar cisterns are normally visible as a hypodense region (CSF density) in the shape of a five-pointed star in the midline, between the temporal horns. In this case the region is barely visible, especially on the left (the reader's right) because of a mixture of CSF (hypodense) and blood (hyperdense), which has almost the same density as brain tissue (isodense). Angiography confirmed an aneurysm at the origin of the left posterior communicating artery from the internal carotid artery

are negative in about 2% of patients with a subarachnoid hemorrhage.

Brain CT may also help in distinguishing primary SAH from traumatic brain injury, but the aneurysmal pattern of hemorrhage is not always immediately appreciated in patients admitted with head trauma. If trauma is the cause of SAH, the blood is usually confined to the superficial sulci at the convexity of the brain, adjacent to a fracture or to an intracerebral contusion, which findings dispel any lingering concern about the possibility of a ruptured aneurysm. Nevertheless, patients with basal-frontal contusions may show a pattern of hemorrhage resembling that of a ruptured anterior communicating artery aneurysm, and in patients with blood confined to the Sylvian fissure or ambient cistern it may also be difficult to distinguish trauma from aneurysmal rupture by the pattern of hemorrhage alone.

MR imaging with gradient echo T2 sequence or fluid attenuated inversion recovery (FLAIR) techniques demonstrates subarachnoid hemorrhage in the acute phase almost as reliably as CT, but MR is often impracticable because the facilities are less readily available than CT scans, and restless patients cannot be studied unless anaesthesia is given. After a few days, however, MR imaging is increasingly superior to the CT in detecting extravasated blood, up to 40 days later. This makes MRI a unique method for identifying the site of the hemorrhage in patients with a negative CT scan but a positive lumbar puncture (see below), such as those who are not *referred* until 1 or 2 weeks after symptom onset.

Investigations: Lumbar Puncture

Lumbar puncture is still an indispensable step in the exclusion of subarachnoid hemorrhage in patients with a convincing history and negative brain imaging (van Gijn and Rinkel, 2001). Lumbar puncture should not be carried out rashly, or without some background knowledge. A first rule is that at least 6 and preferably 12 hours should have elapsed between the onset of headache and the spinal tap. The delay is essential, because if there are red cells in the CSF, sufficient lysis would have taken place during that time for oxyhemoglobin and bilirubin to have formed. The pigments give the CSF a yellow tinge after centrifugation (xanthochromia), a critical feature in the distinction from a traumatic tap; the pigments are invariably detectable until at least 2 weeks later. The "three tube test" (a decrease in red cells in consecutive tubes) is unreliable, and a false positive diagnosis of subarachnoid hemorrhage can be almost as invalidating as a missed one. Spinning down the bloodstained CSF should be done immediately, although only oxyhemoglobin and no bilirubin can be formed *in vitro*. The specimen should be stored in darkness until spectrophotometry has been performed, because bilirubin can be degraded by ultraviolet light (as in icteric babies).

Keeping patients in an emergency department or admitting them to hospital 6–12 hours after symptom onset may be a practical problem. Yet, it is unavoidable until a scientifically sound method has been devised to distinguish a traumatic tap reliably from blood that was previously present. Even the smoothest puncture can hit a vein and may leave lingering doubts that may negatively influence patients' lives – also in practical matters such as driving licenses and life insurances.

CAUSES OF SAH

The Main Cause: Saccular Aneurysms

Approximately 85% of all spontaneous hemorrhages into the subarachnoid space arise from a rupture of saccular aneurysms at the base of the brain. Saccular aneurysms are almost never congenital, but develop during the course of life. The frequency with which saccular aneurysms are found in the general population depends on the definition of size and the diligence with which the search for unruptured aneurysms has been performed. In a systematic overview of studies reporting the prevalence of intracranial aneurysms in patients studied for reasons other than subarachnoid hemorrhage, the prevalence ranged between 0.4% in retrospective autopsy studies and 6.0% in prospective angiography studies, resulting in a weighted estimate of 2.3% for adults without risk factors (van Gijn and Rinkel, 2001).

Is Catheter Angiography Still Necessary for Demonstrating the Aneurysm?

The gold standard for detecting aneurysms is conventional angiography, but this procedure can be time consuming and is not without risks. Transient or permanent complications occur in 1–2%. Other imaging modalities are magnetic resonance angiography (MRA) and computed tomography angiography (CTA). Three-dimensional imaging is now possible with both these new techniques as well as with conventional angiography. MRA is safe but less suitable in the acute stage, because in the acute stage patients are often restless or need extensive monitoring. A review of studies comparing MRA and intra-arterial angiography in patients with recent subarachnoid hemorrhage, under blinded-reader conditions, showed a sensitivity in the range of 69–100% for detecting at least one aneurysm per patient. For the detection of all aneurysms, the sensitivity is 70–97%, with specificity in the range of 75–100% (White *et al.*, 2000).

CT angiography is based on the technique of spiral (helical) CT. It can easily be obtained immediately after the noncontrast CT on which the diagnosis is first made. It is minimally invasive, because it does not require intra-arterial catheterization. Compared with MRA, it involves radiation and injection of iodine-based contrast, but it is much simpler to perform, especially in ill patients. After the data acquisition, which can be done within 1 minute, postprocessing techniques are needed to produce an angiogram-like display.

There is no doubt that catheter angiography is on its way out for the initial detection of aneurysms in patients with subarachnoid hemorrhage and certainly in patients who are

screened because of a family history or polycystic kidney disease. Currently, catheter angiography with 3D rotational subtraction equipment is often used to decide on the choice of optimal treatment, coiling, or clipping.

Nonaneurysmal Perimesencephalic Hemorrhage

Approximately 15% of subarachnoid hemorrhages are not attributed to saccular aneurysms. It was recognized in the 1980s and subsequently confirmed that two-thirds of patients in this group (10% of the total) are characterized not only by a perfectly and consistently normal angiogram but also by a so-called *perimesencephalic* pattern of hemorrhage, distinct from that in most episodes of aneurysmal bleeding. In this strikingly harmless variety of subarachnoid hemorrhage, the extravasated blood is confined to the cisterns around the midbrain, and the center of the bleeding is immediately anterior to the midbrain (Figure 2). In some cases, the only evidence of blood is found anterior to the pons. There is no extension of the hemorrhage to the lateral Sylvian fissures or to the anterior part of the interhemispheric fissure. Some sedimentation of blood in the posterior horns of the lateral ventricles may occur, but frank intraventricular hemorrhage or extension of the hemorrhage into the brain parenchyma indicates arterial hemorrhage and rules out this particular condition (Rinkel *et al.*, 1991).

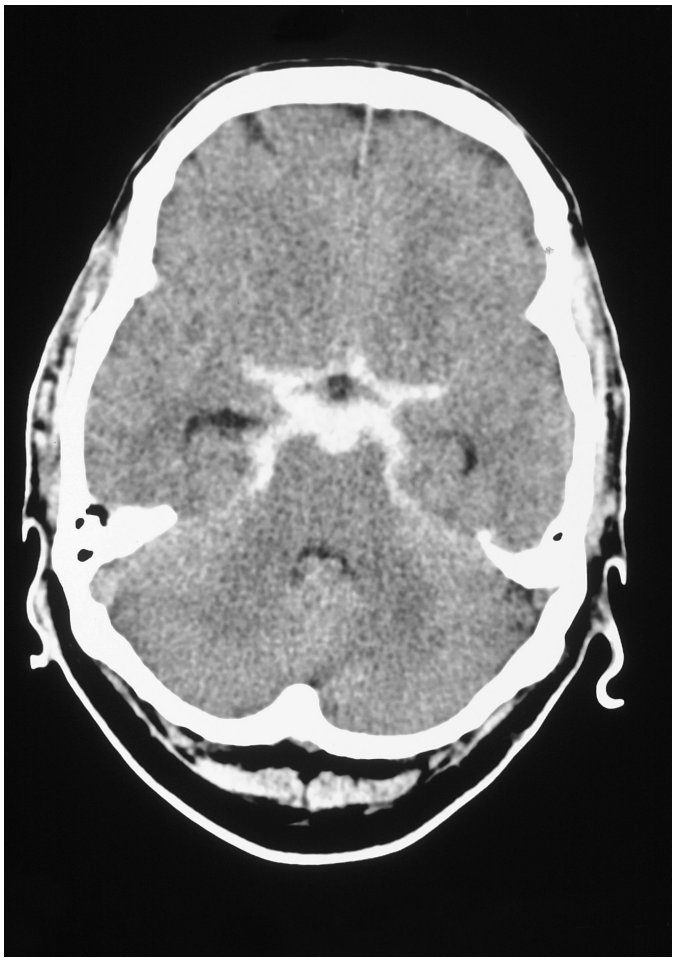

Figure 2 Nonaneurysmal perimesencephalic hemorrhage. CT scan of the brain of a 60-year-old woman, within 24 hours after the sudden onset (within seconds) of an unusually severe headache. There is dense subarachnoid blood in the interpeduncular cistern, ambient cisterns, and chiasmatic cisterns, but not at all in the Sylvian fissures or in the frontal interhemispheric fissure (also not on other slices). This pattern of hemorrhage is unusual for an arterial (aneurysmal) hemorrhage and fairly characteristic for a nonaneurysmal perimesencephalic hemorrhage. The CT angiogram was completely normal, also in the posterior circulation. The patient completely recovered and resumed her usual lifestyle

Clinically, there is little to distinguish idiopathic perimesencephalic hemorrhage from aneurysmal hemorrhage. Perimesencephalic hemorrhage can occur in any patient over the age of 20 years, but most patients are in their sixth decade, as with aneurysmal hemorrhage. Loss of consciousness and focal symptoms are exceptional in idiopathic perimesencephalic hemorrhage, and in those cases only transient; a seizure at onset virtually rules out the diagnosis. On admission, all patients are in fact in perfect clinical condition, apart from their headache. Typically, the early course is uneventful: rebleeds and delayed cerebral ischemia simply do not occur. Only few have symptoms from ventricular dilatation, and even then an excellent outcome can be anticipated. The period of convalescence is short, and with appropriate support almost invariably patients are able to resume their previous work and other activities, without a lasting decrease in the quality of life.

A perimesencephalic pattern of hemorrhage may occasionally (in 2–5%) be caused by rupture of a posterior fossa aneurysm. The chance of finding an aneurysm in 5% of patients has to be weighed against the risks of angiography imposed upon the remaining 95% of patients. A formal decision analysis indicates that a strategy where CTA is performed as the only procedure results in a better utility than a strategy where conventional angiography is performed if CTA is negative or if all patients are initially investigated by conventional angiography (Ruigrok *et al.*, 2000).

Rare Causes of Subarachnoid Hemorrhage

Together these make up 5% of all the first episodes of SAH (van Gijn and Rinkel, 2001).

Arterial dissection tends to be recognized more often in the carotid than in the vertebral artery, but subarachnoid hemorrhage from a dissected artery occurs mostly in the vertebral artery. Rebleeding occurs frequently, within hours of the first ictus or after a few weeks. The second episode is fatal in approximately half of the patients. Intracranial dissection in the anterior circulation is much less common than with the vertebral artery. Reported cases have affected the terminal portion of the internal carotid artery, the middle cerebral artery, and the anterior cerebral artery.

Arteriovenous malformations (AVMs) of the brain may cause subarachnoid hemorrhage, but only less than 5% of all ruptured AVMs rupture only in the subarachnoid space, usually at the convexity of the brain, without intracerebral

hematoma. Saccular aneurysms form on feeding arteries of 10–20% of AVMs, presumably because of the greatly increased flow and the attendant strain on the arterial wall. If bleeding occurs in these cases, it is more often from the aneurysm than from the malformation.

Dural arteriovenous fistulae of the tentorium can give rise to a basal hemorrhage that is indistinguishable on CT from aneurysmal hemorrhage.

Spinal arteriovenous malformations or cavernous angiomas present with subarachnoid hemorrhage in approximately 10% of subjects; in more than 50% of these patients, the first hemorrhage occurs before the age of 20 years. Clues pointing to a cervical or thoracic origin of the hemorrhage are an onset with a sudden and excruciating pain in the lower part of the neck, or pain radiating from the neck to the shoulders or arms. CT scanning of the brain in patients with a ruptured cervical AVM may show blood throughout the basal cisterns and ventricles and may thus falsely suggest a cerebral origin. If a cervical origin of the hemorrhage is suspected, MRI or MR angiography are first line investigations; spinal angiography is impractical as well as hazardous if there are no localizing signs or symptoms.

Septic aneurysms develop if infected tissue debris enter the blood stream and lodge in the wall of cerebral arteries. Most strokes in the context of infective endocarditis are not subarachnoid hemorrhage, but (hemorrhagic) infarcts or intracerebral hemorrhages from pyogenic arteritis. Sometimes rupture of a septic aneurysm is the initial manifestation of infective endocarditis. Aneurysms associated with infective endocarditis are most often located on distal branches of the middle cerebral artery, but approximately 10% of the aneurysms develop at the base of the brain and may show a pattern of hemorrhage on CT that is very similar to that of a ruptured saccular aneurysm.

Pituitary apoplexy is the traditional name for arterial hemorrhage occurring in a pituitary tumor, probably resulting from tissue necrosis involving one of the hypophyseal arteries. The initial features are sudden and severe headaches, with or without nausea, vomiting, neck stiffness, or a depressed level of consciousness. The hallmark of pituitary apoplexy is that most patients have a sudden decrease in visual acuity. In most patients with pituitary apoplexy eye movements are disturbed as well, because the hemorrhage compresses the oculomotor, trochlear, and abducens nerves in the adjacent cavernous sinus. Brain CT or MRI scanning indicates the pituitary fossa as the source of the hemorrhage and in most instances the adenoma itself is visible.

Anticoagulant drugs are seldom the sole cause for subarachnoid hemorrhage; if patients with a ruptured aneurysm are on anticoagulants, the outcome is relatively poor (Rinkel *et al.*, 1997).

EARLY ASSESSMENT OF PATIENTS WITH ANEURYSMAL SAH

In the following sections it shall be assumed that the cause of SAH is an aneurysm, unless specifically indicated otherwise.

Grading Scales

The baseline variable most closely related to poor outcome in aneurysmal SAH is the neurological condition of the patient on admission; two other important factors are age and the amount of subarachnoid blood in the initial CT scan. Several grading systems have been developed for this initial assessment, in most cases consisting of approximately five categories of severity, in hierarchical order. The constituent features of these grading systems are not only the level of consciousness, but also headache, neck stiffness, and focal neurological deficit. These scoring systems have become part of the neurosurgical tradition but they have poor validity and the variation between observers is wide.

A committee of the World Federation of Neurological Surgeons (WFNS) has proposed a grading scale of five levels, essentially based on the Glasgow Coma Scale (GCS), with focal deficit making up one extra level for patients with a GCS score of 14 or 13 (Table 2). In other words, the WFNS Scale takes into account the fact that a focal neurological deficit in patients with SAH rarely occurs with a normal level of consciousness, and acknowledges that the presence or absence of such a deficit does not add much to the prognosis in patients with a GCS score of 12 or less. Although no formal studies of the validity and reliability of the WFNS Scale have yet been undertaken, its face validity is high and it is regrettable that obsolete grading systems are still much used.

Causes of Poor Clinical Condition on Admission and Their Management

It is often tacitly assumed that the initial clinical condition is related only to the impact of the first hemorrhage. This is incorrect, since some complications can occur within hours of the original rupture. Only by exclusion, it should be assumed that the cause is global brain damage as a result of high pressure and subsequent ischemia.

Early rebleeding occurs in up to 15% of patients in the first few hours after admission for the initial hemorrhage, at least in those in whom it is associated with a sudden episode of clinical deterioration. Because such sudden episodes often occur before the first CT scan or even before admission to hospital, a definite diagnosis is difficult and the true frequency of rebleeding on the first day is invariably

Table 2 World Federation of Neurological Surgeons (WFNS) grading scale for patients with subarachnoid hemorrhage

WFNS grade	Glasgow Coma Scale sum score
I	15
II	14 or 13, without focal deficit
III	14 or 13, with focal deficit[a]
IV	12 to 7
V	6 to 4

[a]cranial nerve palsies are not considered a focal deficit for this purpose.

underestimated. Patients with rebleeding should be resuscitated and artificially ventilated if respiratory arrest occurs, because spontaneous respiration can return within a few hours.

Intracerebral hematomas occur in up to 40% of patients with ruptured aneurysms. Not surprisingly, the average outcome is worse than in patients with purely subarachnoid blood. When a large hematoma is the most likely cause of a poor condition on admission, immediate evacuation of the hematoma should be seriously considered (with simultaneous clipping of the aneurysm if it can be identified), often with the aneurysm having been demonstrated only by MRA or CTA. Surgical treatment may be life saving in patients with impending transtentorial herniation, particularly with temporal hematomas.

Acute subdural hematoma is usually associated with recurrent aneurysmal rupture, but can also occur with the initial hemorrhage. It may be life threatening, in which cases immediate evacuation is called for.

Acute hydrocephalus should be suspected in patients with gradual obtundation within 24 hours of hemorrhage, especially if accompanied by slow pupillary responses to light and downward deviation of the eyes (Figure 3). If the diagnosis is confirmed by the CT, this can be a reason for lumbar puncture or early ventricular drainage depending on whether the site of obstruction is in the subarachnoid space or in the ventricular system, but it should be kept in mind that some patients improve spontaneously in the first 24 hours.

Global cerebral ischemia is the most probable cause if neither a supratentorial hematoma nor intraventricular hemorrhage can explain a patient's poor clinical condition. The most likely explanation is a prolonged period of global cerebral ischemia at the time of hemorrhage, as a result of the pressure in the cerebrospinal fluid spaces being elevated to the level of that in the arteries, for as long as a few minutes. This is quite distinct from delayed ischemia, that is focal or multifocal (see below).

COMPLICATIONS OF ANEURYSMAL SUBARACHNOID HEMORRHAGE AND THEIR MANAGEMENT

Patients who survive the initial hours after a subarachnoid hemorrhage from a ruptured intracranial aneurysm are at

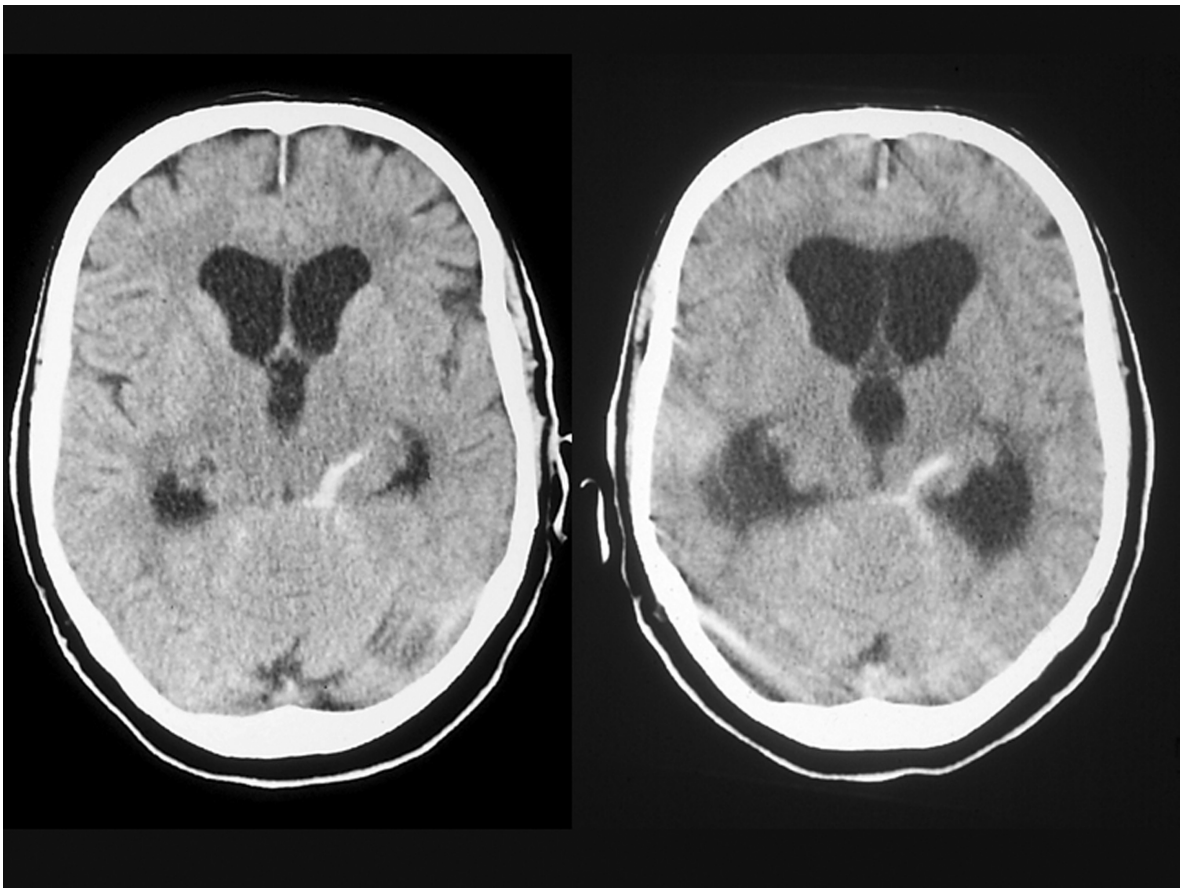

Figure 3 Acute hydrocephalus. CT scans of the brain of a 74-year-old woman admitted because of a severe and sudden headache, 6 hours (a) and 15 hours (b) after symptom onset. Initially she was disoriented but alert, but in the interval her level of consciousness gradually decreased, while the pupils became small and unreactive, with downward deviation of the eyes. The ventricular system is enlarged on the first scan (frontal horns, temporal horns, and third ventricle are visible) but even more on the repeat study

Table 3 General management of patients with aneurysmal subarachnoid hemorrhage

Nursing
- continuous observation (Glasgow Coma Scale, temperature, ECG monitoring, pupils, any focal deficits)

Nutrition
- oral route preferred, but only with intact cough and swallowing reflexes
- if nasogastric tube is necessary:
  - deflate endotracheal cuff (if present) on insertion
  - confirm proper placement by X ray
  - begin with small test feeds of 5% dextrose
  - prevent aspiration by feeding in sitting position and by checking gastric residue every hour
  - tablets should be crushed and flushed down (phenytoin levels will not be adequate in conventional doses)
- total parenteral nutrition should be used only as a last resort
- keep stools soft by adequate fluid intake, magnesium oxide, and restriction of milk content

Blood pressure
- do not treat hypertension unless there is evidence of heart failure or progressive organ damage

Fluids and electrolytes
- intravenous line mandatory
- give at least 3 L day^{-1} (normal saline)
- insert an indwelling bladder catheter if voiding is involuntary
- compensate for a negative fluid balance and for fever
- monitoring of electrolytes (and leukocyte count), at least every other day

Pain
- start with acetaminophen and/or dextropropoxyphene; avoid aspirin
- midazolam can be used if pain is accompanied by anxiety (5 mg intramuscularly or infusion pump)
- for severe pain, use codeine or, as a last resort, opiates

Prevention of deep vein thrombosis and pulmonary embolism
- before occlusion of aneurysm: Apply compression stockings
- after treatment of the aneurysm: fractionated heparin

Medical treatment to prevent secondary ischemia
- nimodipine 60 mg orally every 4 hours, to be continued for 3 weeks

risk for secondary complications, of which rebleeding and secondary ischemia are the most important. General measures for nursing and medical management of patients with ruptured aneurysms have been summarized in Table 3.

Prevention of Rebleeding

The risk of rebleeding within the first 3 weeks is approximately 40% when the aneurysm is not treated; rebleeding results in death or dependence in about 80%. Unfortunately, it is impossible to predict which patients are most at risk of rebleeding. Therefore, all patients will have to be exposed to the complications of the treatment, whereas only a smaller proportion will actually benefit from it. The risk of complications from surgical or endovascular treatment for unruptured aneurysms increases with age and there is no reason to assume that this is different for patients with ruptured aneurysms. An estimated risk of procedural complications of 10–15% for patients older than 70 years is of course lower than a 40% risk of rebleeding with almost invariably a poor outcome, but if intervention is delayed, the balance of risks may shift as time goes on.

Antifibrinolytic Drugs

Medical treatment for preventing rebleeding has not yet been successful; systematic review of the available evidence shows that the treatment with antifibrinolytic agents does reduce the rebleeding rate, but fails to improve the overall outcome. Although the risk of rebleeding is significantly reduced by antifibrinolytic therapy, this is offset by a similar increase of the risk of secondary cerebral ischemia.

Operative Clipping of the Aneurysm

Surgical obliteration of the aneurysm has been the mainstay of treatment for decades. Until the 1980s this was deferred until day 10–12, because of the many complications with earlier operations. Since then, many neurosurgeons have adopted a policy of early clipping of the aneurysm, that is, within 3 days of the initial bleed. The theoretical advantages of early operation have not yet been proven in the few randomized trials on record.

Endovascular Treatment

Since the introduction of detachable platinum coils for the packing of aneurysms with subsequent local thrombosis, endovascular embolization is increasingly used. Indirect comparisons between endovascular and surgical treatment are inappropriate because there are a variety of differences in study design, patients, and aneurysms in the observational studies. Fortunately in 2002, the results of a randomized comparison between endovascular and surgical treatment in 2143 patients were published, in which the proportion of patients who were dead or dependent after 1 year was 30.6% in patients allocated to surgical clipping, versus 23.7% in patients allocated to coiling (Molyneux *et al.*, 2002). This corresponds with an absolute risk reduction of 6.9% and a relative risk reduction of 22.6%. It should be kept in mind that most aneurysms in this trial were at the anterior communicating and carotid artery; and that most patients were in good clinical condition. Patients with aneurysms at the middle cerebral artery were rarely randomized because these aneurysms are often not suitable for coiling, whereas most patients in poor clinical condition and almost all patients with aneurysms in the posterior fossa were preferentially treated by coiling.

The best strategy for follow-up control angiography in the long term after coiling has not yet been established. After surgical treatment, the rate of late rebleeding from the same aneurysms is in the order of 2% after 10 years and 9% after 30 years, but at this stage the rate of recanalization followed by rupture after coiling is hardly known beyond a few years.

Prevention of Secondary Cerebral Ischemia

Delayed cerebral ischemia occurs mainly in the first or second week after aneurysmal subarachnoid hemorrhage, in

about 2% of unoperated patients at risk per day, with an approximately fourfold increase in risk after early operation. Despite many years of intensive research, the pathogenesis of secondary cerebral ischemia following subarachnoid hemorrhage is only partly understood. It is a generally held belief that after the hemorrhage an unidentified factor is released from the blood clot into the subarachnoid space, which induces vasoconstriction and thereby secondary ischemia. Several observations argue against this popular notion. First, the presence of subarachnoid blood, though a powerful predictor of delayed cerebral ischemia, is not in itself a sufficient factor for the development of secondary ischemia, because it does not occur in patients with a perimesencephalic (nonaneurysmal) subarachnoid hemorrhage. Second, in large series of patients, the site of delayed cerebral ischemia does not correspond with the distribution or even the side of subarachnoid blood. Third, many patients with vasospasm never develop secondary ischemia. These observations collectively suggest that not only the presence of subarachnoid blood *per se*, but rather the combination with other factors such as the arterial origin of the blood and the existence of a tear in the arterial wall determine whether and where secondary ischemia will develop.

Despite this lack of pathophysiological insight, some progress has been made in the prevention of secondary ischemia after aneurysmal SAH by changes in general medical care (notably increased fluid intake and avoidance of antihypertensive drugs) as well as by specific drug treatment (van Gijn and Rinkel, 2001).

Management of Blood Pressure

Management of hypertension is a difficult issue in patients with SAH, especially if the blood pressure rises above 200/110 mm Hg. Aggressive treatment of high blood pressure entails a definite risk of ischemia in areas with loss of autoregulation, especially since hypertension after SAH may be a compensatory phenomenon. The empirical evidence for the advice not to administer antihypertensive drugs is sparse. Nevertheless, it seems best to reserve antihypertensive drugs (other than those the patients were on already) for patients with extreme elevations of blood pressure as well as evidence of rapidly progressive end organ deterioration, diagnosed from either clinical signs (e.g. new retinopathy, heart failure, etc.) or laboratory evidence (e.g. signs of left ventricular failure on chest X ray, proteinuria or oliguria with a rapid rise of creatinine levels).

Fluid Balance and Electrolytes

Fluid management in SAH is important to prevent a reduction in plasma volume, which may contribute to the development of cerebral ischemia. Nevertheless, the arguments for a liberal (some might say aggressive) regimen of fluid administration are indirect. Observational studies with historical controls suggest that a daily intake of at least 3 L of saline (against 1.5–2.0 L in the past) is associated with a lower rate of delayed cerebral ischemia and a better overall outcome. A regimen of prophylactic volume expansion, regardless of fluid balance, has not proved effective in a few clinical trials, though these studies were underpowered.

Despite the incomplete evidence, it seems reasonable to prevent hypovolemia. We favor giving 2.5–3.5 L day^{-1} of normal saline, unless contraindicated by signs of impending cardiac failure. Frequent calculation of fluid balance (four times per day until approximately day 10) is the main measure for estimating how much fluid should be given. Fluid intake should be increased proportionally in patients with fever, from whatever cause.

In patients with previous myocardial infarction or other heart disease, supplementation of large amount of fluids carries a risk of inducing congestive heart failure. In them fluid intake is probably best guided by means of central venous pressure measurements.

Calcium Antagonists

Clinical trials have been undertaken with three types of calcium antagonists: nimodipine, nicardipine, and AT877, of which nimodipine is the most extensively studied and used. A systematic review of all randomized controlled trials on calcium antagonists in patients with subarachnoid hemorrhage showed a significant reduction in the frequency of poor outcome, which resulted from a reduction in the frequency of secondary ischemia (Rinkel *et al.*, 2002). The nimodipine trials showed a significant reduction in the frequency of poor outcome, whereas the nicardipine and AT877 trials did not. On the other hand, nicardipine and AT877 significantly reduced the frequency of vasospasm, whereas the nimodipine trials showed only a trend toward reduction of vasospasm, despite an inclusion of a larger number of patients. In brief, administration of nimodipine improves outcome in patients with subarachnoid hemorrhage, but it is uncertain whether nimodipine acts through neuroprotection, through reducing the frequency of vasospasm, or both. Nicardipine and AT877 definitely reduce the frequency of vasospasm, but the effect on overall outcome remains unproved, which again underlines the weak relation between vasospasm and outcome.

The practical implications are that the regimen employed in the dominant nimodipine trial (60 mg orally every 4 hours, to be continued for 3 weeks) is currently regarded as the standard treatment in patients with aneurysmal subarachnoid hemorrhage. If the patient is unable to swallow, the tablets should be crushed and washed down a nasogastric tube with normal saline. There is no evidence for the effectiveness of intravenous administration of nimodipine, which is much more expensive than oral administration and carries a risk of inducing hypotension.

Treatment of Delayed Cerebral Ischemia

Treatment with hypervolemia, hemodilution, and induced hypertension, the so-called *triple H therapy*, has become

widely used, although evidence from clinical trials is still lacking. The risks of deliberately increasing the arterial pressure and plasma volume include rebleeding of an unclipped aneurysm, increased cerebral edema or hemorrhagic transformation in areas of infarction, myocardial infarction, and congestive heart failure.

Few centers have experience with the endovascular approach in the treatment of symptomatic vasospasm after SAH. These reports document sustained improvement in more than half of the cases (the number of patients in these reports ranged between 20 and 50), but the series were uncontrolled and evidently there must be publication bias. Rebleeding can be precipitated by this procedure, and also hyperperfusion injury has been reported. In view of the risks, the high costs and the lack of controlled trials, transluminal angioplasty should presently be regarded as a strictly experimental procedure. The same caution applies to uncontrolled reports of improvement of ischemic deficits after intra-arterial infusion of papaverine, following superselective catheterization.

KEY POINTS

- Although most patients with SAH are below 65 years, the risk of SAH increases with age.
- Outcome after SAH is determined mostly by neurological complications, which are equally common in any age-group.
- CT scanning is the investigation of choice for the diagnosis of SAH, to be followed by lumbar puncture if this is negative (but not earlier than 12 hours after headache onset).
- The risk of procedures to occlude the aneurysm (operation or endovascular coiling) increases with age but the risk of death or dependence from rebleeding is even greater, at least in the acute stage.
- Hypovolemia through loss of sodium contributes to the risk of delayed cerebral ischemia; therefore the fluid balance should be carefully monitored in patients with SAH.

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Acute and Chronic Subdural Hematoma

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INTRODUCTION

The subdural space lies between the inside of the skull and the arachnoid layer of the dura, which contains the cerebrospinal fluid (CSF) and surrounds the brain. Throughout most of life, this is a potential space closed by the inflexibility of the skull and the pressure of the brain. The normal intracranial pressure is about 12–17 mmHg. Thus, for a mass to fill this potential space and to cause pressure on the brain under normal circumstances requires that the pressure applied is greater than the intracranial pressure or that the space for some reason is more capacious and the whole system is under low pressure. It is for the large part empty, but is traversed by both the major arteries to, and veins draining from, the brain.

Bleeding into this space can be either from acute arterial hemorrhage or from a chronic hematoma. While there are some similarities, the two conditions are usually encountered in quite different scenarios and are considered separately. The result of either type of hematoma is raised intracranial pressure. The primary and most important consequence of this is a depression of conscious level, either acutely, as with drowsiness, or rather more slowly with confusion. Other signs are those nonlocalizing signs associated with raised intracranial pressure such as third or sixth nerve palsies or a deficit from pressure on the underlying brain, for example, hemiparesis or dysphasia.

Acute subdural hematomas can occur at any age and are usually associated with significant head injury. At both ends of the age range, bleeding into the subdural space can occur for more innocuous reasons and is usually venous in origin initially; tearing of bridging veins from the brain to the sagittal sinus has been suggested as the commonest mechanism. This is because there is less pressure closing the subdural space. In the neonate and the early infant, this is a consequence of the skull being expansible, and in the elderly it is because the brain is atrophied. In both cases, there is potentially a bigger space within the head than there is brain to fill it. This allows a low-pressure source of bleeding to produce a subdural hematoma. As a rule, venous pressure is less than intracranial pressure and the bleeding usually stops by tamponade once the intracranial pressure reaches the venous pressure. Such a hematoma is thus initially filling a potential space but not contributing to raised pressure; it is therefore normally asymptomatic. As described below, this clot may expand and become space occupying, causing pressure on the underlying brain.

ACUTE SUBDURAL HEMATOMA

Acute subdural hematoma may follow acute head trauma, or far less commonly, may be spontaneous.

Posttraumatic

Acute subdural hematoma is usually encountered in association with major closed head trauma. It is a serious condition carrying a high mortality. In this context, the presence of an acute clot in the subdural space is usually associated with significant trauma to the underlying brain.

The source of bleeding is usually the traumatized brain and is largely arterial in origin. It is often quoted that in acute subdural haematoma just as in chronic subdural haematoma the source of the bleeding is venous. But this is not the case; venous pressure is far lower than the pressure inside the skull in an acute head injury and hence a venous injury would not bleed. Both management and the poor prognosis of the acute subdural hematoma is a reflection of the fact that the underlying problem is a brain injury.

Epidemiology

Overall, more than a third of cases of acute subdural hematoma are in patients over 60 years old; similarly, about a third of cases of admitted head injuries in the elderly

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population will have an acute subdural hematoma (Kotwica and Jukubowski, 1992). While in younger patients these head injuries are associated largely with road traffic accidents, in the older age-group, simple falls are a more common cause (Howard *et al.*, 1989). In this series, both clot volume and brain shift on the CT scan were greater in the elderly groups of patients although the presence of radiological contusion or intracerebral hematoma was similar to that of the younger group. With increasing age therefore it seems that even with minor injury, there is a greater tendency to bleed into the subdural space, to bleed more and for this to cause greater brain distortion. The reasons for this have not been explored but this may be due to a general fragility of elderly vessels.

Presentation

There is a history of a head injury with loss of consciousness in over half of the cases. Occasionally, there will be little initial alteration of consciousness at the time of the injury or a lucid interval followed by deterioration. This may be from delayed brain swelling, either primarily posttraumatic or anoxic or from gradual accumulation of the blood clot. In most cases therefore, there will be depression of the conscious level. About three-quarters of patients with an acute subdural hematoma will lose consciousness at some stage prior to treatment (Bender and Christoff, 1974).

Since there is usually trauma to the underlying brain, this is the source of the bleeding in most cases; there may, in addition, be focal signs. For example, a hemiparesis is seen in over 30% of cases (Bender and Christoff, 1974). The weakness will be usually, but not invariably, on the contralateral side to the hematoma. Nonlocalizing signs associated with raised intracranial pressure and brain shift such as pupillary abnormalities from third nerve palsies, or occasionally isolated sixth nerve palsies are common. Pupillary changes, either unilateral or bilateral are seen in about half of the cases.

Management

The clinical presentation and the management are largely that of a head injury. The latter consists of primary assessment, resuscitation, appropriate investigation, and prevention of complications.

The initial assessment consists of obtaining a history; this can be especially difficult in the elderly patient. It can be difficult to know whether there was a head injury or a spontaneous collapse. It is particularly important to know what medication the patient is receiving and, in particular, anticoagulation therapy. This is a common accompaniment of both severe intracranial bleeding following trivial trauma and of spontaneous intracranial hematoma in the elderly patient.

Examination should include general examination, noting vital signs. The most important neurological observation is of course the coma score but focal signs should be noted. Signs may be from brain shift and can be nonlocalizing or from direct brain trauma.

Resuscitation takes the form of establishing and maintaining the airway with intubation if necessary, achievement of adequate breathing with assisted ventilation, if needed, and maintenance of an adequate circulation of good quality blood. Especially in the elderly patient, excessive intravenous fluids should be avoided in the acute phases and should be restricted to normal saline unless there is a good reason to use other fluids. However, adequate perfusion using colloids or, if available, blood is essential.

The above is, however, essential for the management of any acute head trauma at any age. In the elderly, however, it is important to identify comorbid conditions. Even in the absence of a clear history, evidence should be sought for cardiac, respiratory, or metabolic disease. Furthermore, the presence of a coagulopathy often from medication, anticoagulants, or antiplatelet medication is clearly significant both in the presence of the clot and in the danger associated with any attempt to remove it. Correction of this is important prior to any operation for the sake of improving the safety of the intervention. A major intracranial operation in the presence of disordered clotting is likely to result in serious bleeding and consequent danger for the patient. It is of course a matter of balancing the time taken to correct the clotting problem against the requirement to undertake any operative procedure as soon as possible. However, operating with poor clotting is usually a major disaster and the outcome is almost always poor.

Investigation

Acute subdural hematomas are best seen on CT scanning and are seen as a crescentic high-density mass overlying the surface of the brain. Since the underlying brain is usually also injured and hence swollen, there is often significant shift of the midline structures (Figure 1). Plain X rays are usually unhelpful but a well-centered anteroposterior skull X ray may show the shift of the pineal which is almost always calcified in this age-group. There is really no case for the routine use of MRI scanning in the acute phase of head injury management.

Surgical Management

In the past, early surgical evacuation of the clot was advocated. However, currently there is a rather less proscriptive view to surgical intervention. The decision-making process involved in surgical management involves considering the general neurological status of the patient and the size of the subdural clot. The relevance of the clot itself in the context of the whole picture of an injured brain is often difficult to assess and is of course central to the management. It can be difficult to know whether the patient's condition is from the underlying brain trauma or from the presence of the hematoma. Certainly, the decision to intervene must also to take into account the likely outcome. Aggressive surgery with no realistic hope of survival or a reasonable functional outcome is best avoided. At the other end of the scale are

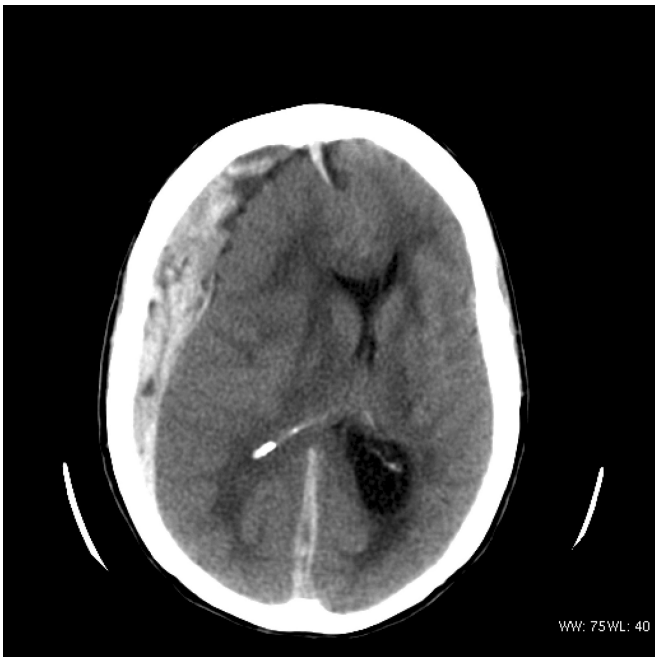

Figure 1 CT scan of an acute subdural hematoma in an elderly patient. Note crescentic shape and mixed density hematoma. This is from a rupture of the arachnoid and CSF mixing with acute hematoma. Note also the large degree of midline shift and distortion of the ventricles

patients in good condition who may be managed conservatively; they should, however, be monitored closely since many will subsequently deteriorate and require intervention (Howard *et al.*, 1989).

Outcome seems related more to the level of consciousness within the first 24 hours. This of course would be a reflection of the severity of the injury and raised intracranial pressure. The age of the patient is also inversely related to outcome. Elderly patients with a Glasgow Coma Score (GCS) of below 12 have a very poor chance of any worthwhile recovery after an operation and have a high mortality of more than 70% (Howard *et al.*, 1989). Those with normal consciousness would be better treated without an operation, as even in this group there is a significant mortality of about 30%. Series of conservative management of minimally symptomatic patients (GCS 11–15) are considered to have a better functional outcome if operation is avoided (Croce *et al.*, 1994). These cases would probably not be considered for operation these days in any case. However, the presence of a large hematoma in a good grade but deteriorating patient would be an unequivocal indication for intervention.

In any other group, there would be a degree of disagreement about the predicted outcome and the advisability of surgical interference. This is to some degree irrespective of the size of the hematoma. What is more significant is the clinical situation and, in particular, the GCS of the patient, the timescale of the history, and the progression of the condition. At any age, a patient with a GCS 3 would be unlikely to survive and would thus often not be subjected to aggressive surgery. Operation in elderly patients presenting with a GCS below 5 would be contraindicated because of the appalling outcome at this level. Others (Kotwica and Jukubowski, 1992) point out that in their series, no patient with a GCS below 13 was a functional survivor. It is therefore debatable whether elderly patients with marked depression of a GCS below 10 should be considered for active intervention.

Surgical intervention is usually a generous craniotomy overlying the thickest part of the clot. While technically this is a relatively straightforward procedure, removing an acute subdural hematoma can be a challenging operation. The reason for this is that under the clot is a very swollen brain, and closure of the dura and replacement of the bone flap may be difficult. For this reason, a wide opening of the dura is generally not practiced; the clot is better evacuated through a number of small dural openings. Removing a generous amount of the skull by providing decompression can be helpful. However, the bulging of the brain through such a skull decompression can obstruct venous drainage and exacerbate brain swelling.

While the decision to operate can be difficult, it is certainly the case that the earlier this is undertaken the better. In conservatively managed patients, it is imperative to keep a close eye on progress so that a review of the management decisions can be made as early in the course of any deterioration as possible.

Outcome

There have been a number of reviews looking specifically at severe head injuries and acute subdural hematomas in elderly patients (Howard *et al.*, 1989; Munro *et al.*, 2002). All of them demonstrate poorer outcome over the age of 65. Indeed, some have found the age at which outcome begins to deteriorate as a function of age to be at about 30 (Harris *et al.*, 2003). This may be a reflection of the higher incidence of concomitant medical conditions, poorer recovery from brain insult, and there being less neurological reserve in the elderly; however, it is also perhaps the case that generally there is a less aggressive management policy toward older patients. It is suggested that triage decisions, level of monitoring, and referral patterns are biased simply because of the age of the patient (Howard *et al.*, 1989; Grant *et al.*, 2000). Thus, it might well be that the perception of poor outcome in the elderly in the minds of the medical staff makes this a self-fulfilling prophecy.

Spontaneous

Occasionally, acute subdural hematomas may present spontaneously as a collapse or acute onset of drowsiness with focal signs. Often, this is in patients taking anticoagulant therapy. However, acute subdural hematoma may complicate acute subarachnoid hemorrhage. Rare causes are tumors and dural arteriovenous malformations. As with posttraumatic hematomas, the favorable prognostic factors are higher GCS

preoperatively, younger age, and early intervention (Missori *et al.*, 2000). The neurological state of the patient at the time of treatment is, however, the most important factor.

CHRONIC SUBDURAL HEMATOMA

While as with acute hematomas, this condition follows injury and is the result of bleeding into the subdural space; the chronic subdural hematoma is seen in quite different circumstances and has a significantly different presentation, outcome, and management. The primary problem with this condition is the indolent presentation, which can be difficult to spot in the early stages. The observed resolution of the condition with sometimes very little therapeutic intervention suggests that this condition may sometimes be asymptomatic throughout the population and undergo spontaneous resolution without treatment in a number of cases. It is a common condition and more so with increasing age. It is also a mysterious condition; the mechanism by which the initial clot becomes bigger to compress the underlying brain is not fully understood. Perhaps even stranger is the fact that the resolution of the chronic clot occurs in most cases merely from a solitary drainage of the fluid part of the hematoma leaving the membranes intact. These membranes are postulated to be the cause of the expanding nature of the chronic subdural hematoma.

Incidence

The mean age at diagnosis is 56–63 years and men outnumber women by 3:1. The true incidence is unknown. While it is not exclusively a disease of old age chronic subdural haematoma is much more common in the elderly. Two-thirds of cases are in the over 65 age-group and in men. The use of oral anticoagulants is associated with this condition in about 40% of cases. (Baechi *et al.*, 2004). A classic study from Helsinki in 1975 (Fogelholm and Waltimo, 1975) suggested an overall incidence of 1.72 per 100 000 increasing to 7.35 per 100 000 in the 70–79 age-group. It should be noted, however, that in this series a third of chronic subdural hematomas were found at postmortem and were presumably asymptomatic, and that this was before the era of routine CT scanning and from a small population in the City of Helsinki. Asghar *et al.* (2002) found a higher rate of 8.2 per 100 000 of over 65-year olds in North Wales of which a third were taking antithrombotic therapy.

Pathophysiology

From the basic considerations of the anatomy of the subdural space, it can be appreciated that if the brain shows some shrinkage as occurs in old age, there are a number of factors which might predispose to bleeding into the space. The brain being smaller has the potential for more movement within the cranium with even minor acceleration/deceleration, and the bridging veins being longer and under more tension owing to their being stretched are more prone to tear. The bleeding from this will be into a low-pressure space and will achieve a significant volume before the increased pressure equates to the venous pressure and tamponade occurs.

The initial bleed is thus easily provoked and the formation of a clot is primarily an *ex vacuo* phenomenon. Just as with blood in the thoracic or pericardial space, the solid clot is subject to pulsation, in this case from the brain, and although it is initially solid it soon becomes liquid and is surrounded by a membrane. Exactly why this clot progresses and enlarges to form a space-occupying lesion and compresses the brain is unknown. Over the years, a number of theories have been advanced. The presence of the membrane led to the initial description of this condition by Virchow in 1857 as *pachymeningitis hemorrhagica interna*, the initial view being that this membrane secreted the fluid and that it was this that caused the progressive enlargement. The osmotic pressure of the breakdown products of blood causing the absorption of fluid into the collection was also suggested. This was refuted by the finding that the osmotic pressure of the fluid was similar to that of CSF and blood. It is currently thought that the membrane is generally unstable and has large friable blood vessels in the wall and that the progression is largely from repeated small bleeds into the collection.

Whatever the cause, there is a tendency for chronic subdural collections to increase in size. This results in the clinical picture of slowly progressive raised intracranial pressure.

Clinical Presentation

There is no history of trauma in about 40% of patients and if any, it usually occurs some weeks previously and is trivial (Fogelholm *et al.*, 1975; Hamilton *et al.*, 1993). Trauma usually occurs more than 3 weeks previously and rarely occurs less than two weeks previously. It is thought that this is the time taken for the hematoma membrane to form and mature. The presentation is usually nonspecific and gradual. The patient may complain of headache, which may be typical of raised intracranial pressure, that is worse on waking or even when the patient is woken during the early hours of the morning. The headache may show no temporal exacerbations and may be nonspecific in nature. There is a tendency for the headache to be a more prominent feature with a smaller size of hematoma in the younger patient.

Further, since confusion and reduced mental facility is the commonest presentation, the absence of a specific history is not uncommon. In the early days, there were generally no specific signs and in many cases there was a fluctuating course. This is a characteristic shared with hydrocephalus and is seen in other conditions of an intracranial fluid filled mass; even cystic tumors have fluctuating histories.

With progression, there tends to be more frank drowsiness and complaints of unsteadiness. There may be evidence of focal deficit with hemiparesis, and dysphasia may present in dominant hemisphere collections. Epilepsy occurs in less

than 7% and can be generalized or partial (Kotwica and Brzeinski, 1991). Eventually, there is marked drowsiness and a significantly reduced conscious level. The specific elements of presentation of chronic subdural hematomas are protean. It has been referred to as *the great imitator* but in practice, there is a progressive degree of neurological failure; this tends to be subacute, over a matter of weeks or even a few months. However, it is often difficult to recognize and this failure to establish the diagnosis until quite late in the clinical course is one of the difficulties in managing this condition. A high index of suspicion is therefore important in older patients.

There is a fairly wide differential diagnosis in chromic subdural hematomas. Other causes of progressive raised intracranial pressure include hydrocephalus and benign space-occupying lesions, although these tend to be even more slowly progressive. More aggressive tumors may present in a similar way over weeks. Dementias can also present surprisingly quickly. The fluctuating and nonspecific nature of the early complaints may even raise the possibility of transient ischemic events.

There are no specific diagnostic clinical signs.

Investigation

CT scanning is the method of choice; however, in the elderly it is often possible to demonstrate a shift of the midline from the position of pineal calcification on a well-centered antero-posterior (AP) skull X ray.

The CT findings seem to undergo a progressive evolution. There is the acute phase where there is some acute hematoma in the subdural space (Figure 2). This is associated with minimal midline shift and usually the patient is either asymptomatic or fully alert and conscious. The hematoma gradually becomes less dense on the scan and isodense with the brain at about 10–14 days (Figure 3). The exact timing of the density change is dependent on a number of factors such as the amount of hemoglobin in the clot. After this time, the clot is hypodense to the brain, and as with the acute hematoma is crescentic over the surface of the brain. The volume gradually increases and there is midline shift. Usually at presentation of a mature chronic subdural hematoma, there is mixed density in the hematoma space, implying acute bleeding within the chronic collection.

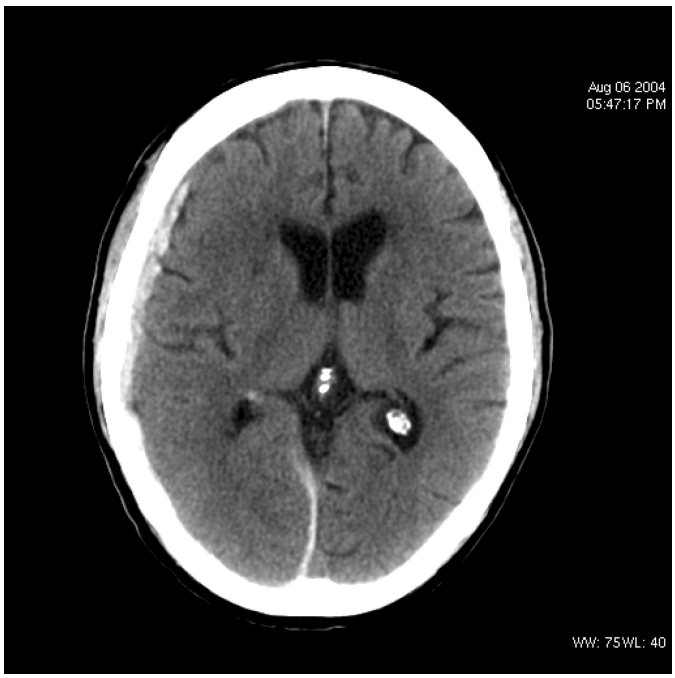

Figure 2 An asymptomatic acute subdural hematoma 5 or 6 days following a fall. Note that there is no midline shift of significance

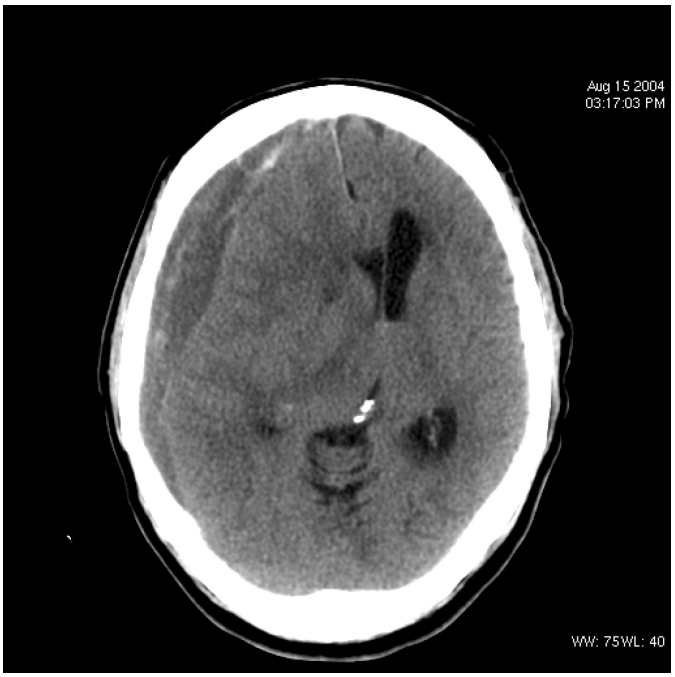

Figure 3 Same patient as in Figure 2 9 days later. The hematoma has become hypodense with some layering of more acute blood. There is now significant midline shift

Treatment

This is directed at decompressing the pressurized chronic clot. At the same time, continued medical management of associated conditions should be maintained. Anticoagulants should be discontinued and normal coagulation status achieved and maintained until after evacuation of the chronic hematoma. It seems widely accepted that the outcome in anticoagulated patients is worse and the recurrence rate is higher. Certainly, with an increase in anticoagulation therapy, there has been an increase in the number of patients with chronic subdural hematoma; some (Gonugunta and Buxton, 2001) have found no adverse effect of warfarin medication on the outcome of treatment.

However, it has to be said that as mysterious as the genesis of this condition, the resolution is even more curious. Some symptomatic chronic hematomas simply disappear with a

short period of bed rest (Bender and Christoff, 1974). These are of course those with the smaller clots. Clearly, during a period of rest, the circumstances for repeated small bleeds are reduced. However, for this usually brief period to reverse, what was until then an inexorable process to increase the size of the clot is remarkable.

This spontaneous resolution of the clot is often assisted by the use of a short course of oral steroids. The dose and duration is not standardized and is usually fairly brief and accompanied by bed rest. This is generally considered to be the more safe treatment but is often ineffective and may be used in poor risk patients.

Other treatments involve the surgical evacuation of the liquid clot. Most commonly, this is through burr holes under a general or local anesthetic. One or more holes may be used. At times, the pressure of the hematoma is quite high and the brain is seen to expand and collapse the cavity. This is, however, not always the case and the clinical outcome does not seem to be related to the observed pressure at operation. A number of measures may be added to attempt to expand the brain and occlude the subdural space. The most common is to nurse the patient head down for a few days. There is, however, no particular evidence that this is entirely necessary (Nakajima *et al.*, 2002). Alternatively, fluid is instilled into the subarachnoid space by lumbar puncture or drain to inflate the brain.

There are modifications of this basic theme. Some advocate the use of twist drill holes in the skull and drains or simple aspirations repeated if necessary (Reinges *et al.*, 2000). Others recommend closed drainage of the subdural collection, the drain being inserted at operation with no irrigation or opening of the membrane below the burr hole (Kuroki *et al.*, 2001). It is suggested that in not allowing air into the hematoma cavity, recurrence of the hematoma is reduced from about 11% to less than 2%. It is suggested that air in the clot cavity reduces reexpansion of the brain and filling the space of the clot with saline is recommended by some (Mori and Maeda, 2001).

In some recalcitrant cases, craniotomy is required to remove the membranes as well as the clot. This was once a commonplace operation but is now not normally part of the mainstream mode of treatment (Lee *et al.*, 2004). However, it remains a viable option even as a primary treatment for the hematoma (Hamilton *et al.*, 1993).

The safest and most effective mode of treatment is a subject of debate (Maurice-Williams, 2001). Furthermore, the fact of there being a number of different modes of treatment suggests that the result of any one of these is variable.

Outcome

What is quite remarkable and not easily explained is the fact that about 80% of cases are effectively cured by the simple procedure of a solitary aspiration of the contents of the chronic clot. Furthermore, that improvement is often immediate while rescanning usually demonstrates that the size of the clot cavity and the degree of midline shift has not altered from the preoperative state. The aspiration has therefore not collapsed the mass or obliterated the space, and the clinical condition does not seem to be related to the degree of shift. Some have suggested that raised intracranial pressure or even cerebral perfusion is not a relevant factor in the clinical picture. Recurrence seems to be in the first few weeks and months and is relatively rare after this period.

There is a recurrence rate perhaps of about 15–30%. This is higher in patients on anticoagulants (Mori and Maeda, 2001), antiplatelet drugs, or with coagulopathies (Stroobandt *et al.*, 1995). Recurrences usually can be treated by reaspiration through the burr holes. The more frequently the subdural space is entered, the greater the risk of infection, and subdural abscess is a very serious complication resulting in high morbidity and death in most cases.

Outcome seems mostly related to the clinical condition at the time of treatment (Van Havenbergh *et al.*, 1996). Therefore, whatever the mode of treatment used, it is clearly important to establish the diagnosis at the earliest opportunity and to institute treatment before significant neurological failure has occurred. Most patients make a very good recovery, however, most large series have a mortality of about 5–10% and a poor outcome of about 15–20%. The major complications of this condition, even with treatment, are seizures, sepsis, and persisting neurological failure. In the elderly group, there is a further morbidity from unrelated medical conditions and those associated with neurological disability, such as chest infections.

Driving After Subdural Hematoma (see Chapter 13, Transportation, Driving, and Older Adults)

Of course residual disability and, in particular, a hemiparesis or significant visual field deficits would present a contraindication to driving because of inability to safely control a vehicle in traffic. However, for the recovered patient, the law requires that the Driver and Vehicle Licensing Authority (DVLA) be contacted and that driving cease until approved by the DVLA. This requirement is of course explicitly included in the licence and failure to do so carries a penalty. It is, however, incumbent on the doctor to inform the patient that this is a condition that requires reporting.

The reason for licence withdrawal is the potential risk of epilepsy. This is dealt with in depth elsewhere in this volume (*see* **Chapter 76, Epilepsy**). However, after an acute subdural hematoma requiring a craniotomy, the recommendation is for a 1-year ban for a group 1 entitlement. If treated with burr holes, an unlikely clinical scenario, the ban is for 6 months. However, in conservatively treated hematomas with less than 24 hours amnesia, the guidelines are less clear and suggest that resumption without notifying the DVLA is appropriate. Probably, notification would in fact be wise with any significant hematoma, even if tolerated without any need for treatment.

Chronic subdural hematomas can be followed by an immediate return to driving on recovery. If a fit occurs, however, there is generally a year's ban. Of course, further fits would extend this time. In this sort of case there really is no room for clinical discretion; if in any doubt, the patient

should be advised to report to the DVLA. The medicolegal implications of a practitioner advising the patient to return to driving and the driver subsequently injuring someone by having a fit while driving is obvious. The legal authority for granting permission to drive is the DVLA and the doctor's responsibility is to advise reporting by the patient.

KEY POINTS

- Early diagnosis is important in the management of acute and chronic hematomas. A high index of suspicion is therefore crucial.
- Outcome in either hematoma is related primarily to the neurological state of the patient at onset of treatment.
- Appropriate resuscitation and management of coincidental medical conditions is essential. Correction of clotting defects is mandatory prior to treatment.
- Outcome is worse in acute subdural hematoma; few recover if below a GCS 9 prior to treatment. Most patients with chronic subdural hematoma make a good recovery.

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PART III

Medicine in Old Age

Section 7

Dementia and Cognitive Disorders

89

Communication Disorders in Dementia

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THE NORMAL COMMUNICATION PROCESS – A MODEL

Communication is the process through which an "idea" or "thought" is passed from one person to another. Ideas commonly are expressed through the use of words, and nonverbally, for example, through body language, gesture, or facial expression. The generation of an idea in the mind and its expression, or the appreciation of ideas received from an external source requires a complex interaction of many cognitive systems and processes. In order to account for the pattern of breakdown of communication in dementia, it is important first to consider some of the components that underlie verbal communication.

Three long-term memory stores are fundamental to the communication process. *Semantic memory (conceptual or "meaning" memory)* is knowledge of the environment that is common to everyone within that environment. For example, the concept "champagne" would be represented in long-term memory in a similar way from one person to another. It could be represented with "visual memories" of context (in a bottle, glass, party, bar, wedding), color (white, pink), and movement (within a glass, poured from a bottle), "gustatory memories" of how it tastes, "olfactory memories" of how it smells, "nonverbal acoustic memories" (cork popping), "emotional memories" (joy, celebration), "kinaesthetic memories" (lifting glass, pouring action), "tactile memories" (feeling of gaseous liquid in the mouth), and so on. These memories in combination form the concept of "champagne" represented in semantic memory.

Episodic memory is an individual's memory of the world that is personal to that individual. For example, whereas basic knowledge of what champagnes is common knowledge (stored in semantic memory), the fact that *you* drank champagne *yesterday* is personal knowledge which is stored in episodic memory. Episodic memory is therefore probably built up of elements of semantic memory with a personal context attached.

Lexical memory (word memory) is a mental dictionary or lexicon. The label "champagne", which represents the concept of champagne would be stored here. The label in itself is meaningless without reference to conceptual knowledge in semantic memory.

Working memory is a buffer that holds information in consciousness – it is in effect what you are thinking right now. Information stored in long-term memory is brought back into consciousness in working memory as and when it is needed – this creates an internally generated "thought". Information received into working memory from an external source is matched to information previously stored in semantic, episodic, and lexical memory in order to be "understood". If the information is new to the individual, for example, a new concept, word or event, it is transferred into semantic and/or episodic and/or lexical memory for long-term storage and future reference. Working memory incorporates executive functions, attention, concentration, extraction, reasoning, and so on.

The relationship between thought and language (lexical memory) is complex. An information-processing model of the normal communication process can provide a helpful framework for understanding how they may relate (Figure 1).

Thinking refers to the formation, generation, and manipulation of memories, concepts, and ideas in the mind. Semantic, episodic, and working memories are fundamental components. Thinking is heavily dependent on efficient working memory. We are all aware of times when we have trouble with thought – when our ideas are not well organized, when we have only vague, hazy, or wooly knowledge about something or when we lose track of what we are thinking.

The relationship of language to thought has been the subject of debate for centuries. Understanding some of the complexities of this relationship is important in order to understand communication breakdown in dementia. In considering the link between thought and words, it is helpful here to consider three subcomponents within lexical

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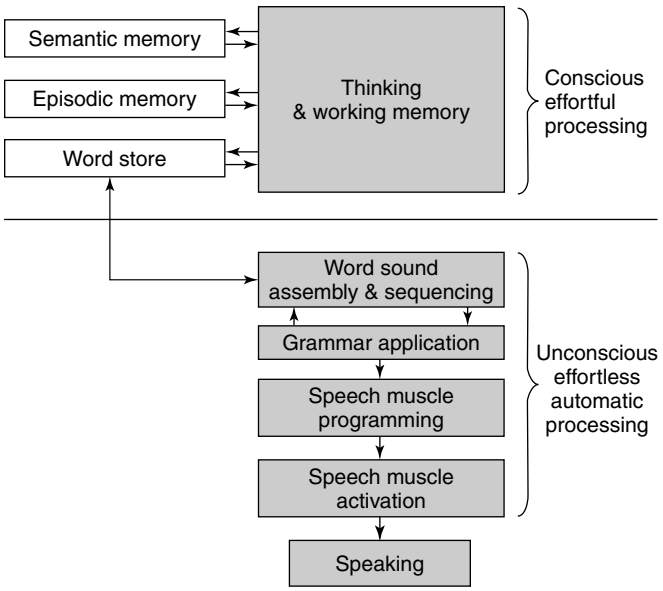

Figure 1 A model of the communication process – from internally generated thought to speech

memory – *word store, word sound assembly and sequencing, and grammar (syntax) application*.

The *word store* is the actual store that contains word memories. Semantic memory, thinking, and word store are closely intertwined. Concepts weakly established in semantic memory can give rise to "word-finding" difficulties in the normal person. For example, when first encountering a new exotic fruit, its name may not be recalled on a second occasion if the concept is too weakly represented in semantic memory. Further encounters with the fruit (its taste, texture, appearance, uses, etc.) help establish and strengthen the concept in semantic memory. Hearing and using the word strengthens the label of its name in the word store. Selection and retrieval of the name of the item is easier if its concept representation in semantic memory, its word memory representation in the word store and the connections between the two types of representations are strong.

A second subcomponent of lexical memory is *word sound assembly and sequencing. This* refers to the selection and sequencing of word sounds (phonemes) to form words. A third subcomponent of lexical memory is *grammar (syntax) application*. This is the ordering of words into meaningful phrases and sentences according to an internalized set of rules. It includes the application of morphemes (minimal grammatical units), for example, the addition of "ed" after "walk" to denote the past tense.

Speech muscle programming is the process of planning the pattern and sequence of movements to be made by the speech muscles. Finally, *speech muscle activation* refers to the physical enactment of the motor program.

Communication is, in reality of course, not a linear process – there is considerable overlap and interaction between its various components. Words loop back into thinking, thereby facilitating thought and becoming a part of thought in themselves. In addition, impairment within one component can give the impression of impairment within another component that is, in fact, intact. For example, when there are problems within thinking with holding onto and organizing ideas, grammar is consequentially affected with the use of half sentences as the person loses their train of thought. In reality, the grammar system may in itself be fully intact. Clinically, it can be a challenge to identify the primary locus of a presenting impairment. However, doing so can help in differential diagnosis of the dementias.

BREAKDOWN OF THE NORMAL COMMUNICATION PROCESS IN DEMENTIA

The concept of "*conscious effortful processing"* versus "*automatic processing"* is fundamental to understanding communication breakdown in dementia. Degree of effort required for each of the components in the communication process varies. *Thinking,* including accessing episodic, semantic, and lexical memory requires conscious effortful processing, whereas *word sound assembly and sequencing, grammar application, speech muscle programming*, and *speech muscle activation* are all normally automatic, unconscious, and effortless. Whereas we can be consciously aware of thinking of what to say and the words to say it, we are not normally aware of choosing word sounds or grammar or of programming and activating the speech muscles – these skills are, in effect, akin to "procedural memory" tasks like walking or riding a bicycle.

As a general rule, in dementia the more conscious and effortful a process is, the more likely that it will be affected. Unconscious, automatic processing is least affected.

Thinking in Dementia

In most dementias, the biggest problem is with thinking. Thinking requires highly effortful, conscious processing. It also involves a large number of cognitive components and processes spread over a wide area of the brain. Thinking is therefore particularly vulnerable to the brain damage that in itself gives rise to dementia. The quality, quantity, clarity, and relevance of "ideas" and the ability to manipulate these are impaired.

Alzheimer's Disease (AD) (see Chapter 93, Clinical Aspects of Alzheimer's Disease)

A problem with new learning often is the first reported symptom in Alzheimer's Disease (AD). This affects the ability to add new information to episodic, semantic, and word memory stores. The greatest impact of this is felt on episodic memory, since remembering what has happened in day-to-day life is so fundamental to effective thinking and functioning. The person may forget an event of the previous

week or forget something he was told a few days earlier. Often this reflects more a registration deficit rather than a recall deficit – the person has not so much forgotten the new event as not recorded it in the first place. On the other hand, in the early stages of dementia, episodic memories from previous years are often retained, since they were laid down in long-term memory when the brain was still functioning effectively. This explains why memory for events of many years previously may be remembered when events of the previous week are not.

With reduced ability to form new memories, old memories tend to come to the forefront. The person may become repetitive and may talk frequently about the past. As the disease progresses, distant memories also are lost as the episodic memory store itself becomes degraded.

A deficit in working memory occurs in AD, with memory span and central executive function affected. There is impaired ability to "hold on" to information within working memory and the person may lose track of what they were saying. They may report getting stuck for words in conversation when it is actually the idea that has been forgotten. Problems with working memory also give rise to reduced ability to retrieve and manipulate information stored in other memory systems and a generalized "cognitive slowing" (Nebes and Madden, 1988; Nebes and Brady, 1992). This has a marked effect on thinking and thus on communication.

Semantic memory also is impaired. Ability to distinguish subtle differences between concepts diminishes. As the disease progresses, concepts themselves become degraded and merge. On a confrontation-naming test, the patient may call a "zebra" a "donkey" because knowledge of the fact that zebras have stripes and donkeys do not is inaccessible or has been lost. In its severest form, the patient has literally "forgotten" what the item is. As a result, there may appear to be problems with lexical memory, when in reality the problem here is semantic memory – it is not possible to produce an accurate name for an item when the underlying concept is unclear.

Degraded semantic memory results in "empty" speech, which is lacking in specificity and contains few content words – the patient tends to use many words that convey very little information.

Vascular Dementia (VD) (see Chapter 95, Vascular Dementia)

In Vascular Dementia (VD), thinking may be impaired in a way that is very similar to thinking in Alzheimer's disease. However, the picture can be more patchy with relative preservation or impairment of one function relative to another. This reflects the brain areas implicated in the individual vascular pathology. There may be significant insight into difficulties with consequential frustration.

Frontotemporal Dementias (FTD)

The frontal lobes are pivotal to thinking; they are the seat of adaptive behavior, abstract conceptual ability, set shifting, mental flexibility, problem solving, planning, personality, social awareness, social behavior, initiation, inhibition, drive, and motivation.

Thinking in the frontotemporal dementias (FTD) is dependent on the anatomic regions of the brain that are primarily affected. In the frontal dominant variant of FTD, "frontal" features emerge such as poor planning and reasoning, disinhibition, poor social awareness, tactlessness, and egocentricity. Pragmatic difficulties are common, whereby the person has difficulty judging the appropriateness of what they say in the situation.

In the early stage of primary progressive aphasia (PPA), thinking is unaffected. The person is able to carry out occupational tasks and activities of daily living (Tranel, 1992). However, whilst language impairment remains the prominent feature, other cognitive abilities eventually are compromised (Delecluse *et al.*, 1990; Graff-Radford *et al.*, 1990; Kempler *et al.*, 1990; Tyrell *et al.*, 1990).

In semantic dementia, there is breakdown in the conceptual database underlying thinking (Bayer and Reban, 2004). There is profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition. Speech is fluent and empty (Neary *et al.*, 1998).

Word Store, Word Sound Assembly and Sequencing and Grammar Application in Dementia

Alzheimer's Disease

Difficulties with word finding are commonly reported in the early stages of AD. The names of people and places can be a particular problem. The locus of this problem may be within thinking and/or the semantic system rather than within the word store itself. Selecting names of people and places requires fine, discriminatory conceptual judgments and strong semantic representations. This requires effortful processing skill; lower-frequency words can also be a particular problem. This may be because lower-frequency words are used less often. They are therefore less available than higher frequency words and, as such, are harder to retrieve. Lower-frequency words may also require more complex semantic judgments. Thus word-finding difficulties in AD may be, in large part, a reflection of task difficulty level rather than a problem with the word store itself.

Typically in AD, as the disease progresses from early to middle stages, difficulty with word finding is reported less often and becomes less problematic for the person. This may be because, as thinking becomes more impaired, the ideas the person wishes to express are less complex and require fewer low frequency words. Also, as the disease progresses and insight is lost, the person may become less aware of any difficulty with word finding and thus less frustrated.

The characteristic pattern in AD is for word sound assembly and sequencing and grammar application to remain relatively preserved until the more advanced stages of the illness. This is because these functions require more automatic and effortless processing and can run on "autopilot".

The most obvious linguistic deficit in typical AD is a failure to use language to convey information (Hier *et al.*, 1985). In summary, the AD patient may be said to "speak well" but "convey little".

Some AD patients have greater atrophy in brain regions responsible for language and therefore present with language difficulties disproportionate to their overall cognitive impairment. These patients may exhibit aphasic features, with struggle to find words and phonemic (sound substitution) errors. They are more likely to be helped by phonemic cueing, which helps them access the words for concepts they are trying to express. However, even where there is a language bias to the AD, the presentation may be qualitatively different from classic aphasia. The impairment sometimes seems to occur at the interface of thought and language. It is as if the person has difficulty thinking and speaking at the same time. If thought load is reduced (for example, when the person is talking about something they are clear about in their mind or when describing a picture in front of them), the language difficulties often lessen.

Vascular Dementia

The pattern of deficit in VD with cortical involvement is similar to that observed in AD. Infarction in brain areas responsible for language, can give rise to specific problems with word store or word store access.

Frontotemporal Dementias

The onset of PPA is, heralded by progressive deterioration of language function in the absence of generalized cognitive decline (Mesulam, 1982). Aphasia is nonfluent (Neary *et al.*, 1998). There may be problems with any one or more lexical components – with word store, word sound assembly and sequencing or grammar application.

Speech Muscle Programming in Dementia

Problems with speech muscle programming give rise to speech apraxia. This does not generally occur in AD in the mild and moderate stages. In VD, problems here are rare but could arise if a vascular event occurred in area of the brain responsible for speech muscle programming. It can be a feature of PPA. Here it may also present as a problem with coordinating respiration with speech (a 'respiration-to-speech apraxia'). This may present superficially as hyperventilation or panic.

Speech Muscle Activation in Dementia

Dysarthria typically occurs in the dementias associated with motor signs. These include Parkinson's disease (PD; *see* **Chapter 66, Parkinson's Disease and Parkinsonism in the Elderly**), dementia with lewy bodies (DLB; *see* **Chapter 96, Other Dementias**), progressive supranuclear palsy (PSP), cortico-basal degeneration (CBD) and Huntington's disease (HD). It may also be associated with VD.

Clinical Presentation of Communication in Alzheimer's Disease

Table 1 contains a transcription of the responses of four AD patients who were asked to retell a short story straight after it was presented by the examiner (Bayles and Tomoeda, 1992). The patients varied in severity of dementia, as measured on the global deterioration scale (GDS) (Reisberg *et al.*, 1982). The performances reflect the typical pattern of communication breakdown in AD.

None of the four patients show evidence of specific difficulty with word sound assembly and sequencing, grammar application, speech muscle programming, or speech muscle activation. Grammatical structure is disturbed in the GDS 4, 5, and 6 patients but this appears to be a consequence of hesitancy in thinking rather than impairment within grammar application *per se*. The GDS 6 patient shows that when output is driven by an appropriate thought, grammar can be intact (e.g. "I don't believe I can do that").

On thinking and word store, the GDS 3 patient performs well. There are relevant units of information within sentences that flow freely. The performance of the GDS 4 patient shows inaccuracies and hesitancy. The hesitancy is probably due to uncertainty with the facts rather than specific problems with the word store. Inaccuracy is even

Table 1 Typical performances of AD patients of varying severity on story retelling in the immediate condition. Patient is told the story below and is asked to retell it immediately

While a lady was shopping, her wallet fell out of her purse but she did not see it fall. When she got to the checkout counter, she had no way to pay for her groceries. So she put the groceries away and went home. Just as she opened the door to her house, the phone rang and a little girl told her that she had found her wallet. The lady was very relieved.
GDS 3 patient (mild cognitive decline)
A lady went shopping at the grocery store. Oh. When she got to the counter with her groceries, she reached for her wallet and it was gone. She'd lost it. So she put the groceries back and when she got home the phone rang. Little girl told her she'd found the wallet.
GDS 4 patient (moderate cognitive decline)
A lady went to a um sho.. food store and uh when she went to pay for her food the uh money fell on the floor and someone, a little girl came and picked it up and gave it to her.
GDS 5 patient (moderately severe cognitive decline)
The little girl picked up her wallet that had fal.. fallen out of her carriage and uh she took more than she had planned on taking, her moving it from the ground.
GDS 6 patient (severe cognitive decline)
I don't I don't believe I can do that, let's see (unintelligible). The only the only thing I know of it of it is to to get get back and then up and then up to to up to to turn to another thing that's the only way that's the only thing that I can I can can do it right right now now I'm I'm completely out in in that.

Table 2 Typical performances of AD patients of varying severity on story retelling in the delayed condition. Patient is asked to retell the story a short time later

GDS 3 patient (mild cognitive decline)
Can't do it. Completely gone. I've been concentrating on what we've been doing. It's out the window.
GDS 4 patient (moderate cognitive decline)
Today you told me a short story? Oh my memory is really going.
GDS 5 patient (moderately severe cognitive decline)
Heavens I don't know what story you mea.. asked me (prompt) No.
GDS 6 patient (severe cognitive decline)
That was it and and there and I saw one right out here that that they they came they came came out here and into into the street and . . .

greater in the description of the GDS 5 patient, who confabulates in an attempt to fill in the facts. There may, in addition, be problems with word store but this is difficult to disentangle from the problems with thinking that dominate. The GDS 6 patient is totally unable to recall the story reflecting marked impairment of thinking, including problems with attention and concentration. The patient is involved in his own thought. He demonstrates severe problems with thinking, and probably has problems with word store itself. However, again it is difficult to differentiate thinking problems from any specific problems with word store.

Table 2 contains a transcription of the same four patients' responses when asked to recall the same story a short time later. The GDS 3 patient, who repeated the story so well in the immediate condition, is now totally unable to recall the story. The GDS 4 and 5 patients appear to have forgotten the episode of having been told a story at all. The GDS 6 patient responds with totally inappropriate content, reflecting his egocentricity of thought and inability to attend to the task.

ASSESSMENT OF COMMUNICATION AND COMMUNICATION INTERVENTIONS IN DEMENTIA

Assessment of communication provides information that contributes to differential diagnosis of the dementias. Identification of relative strengths and weaknesses also helps in planning appropriate interventions and in guiding carers on management options and strategies that will optimize communication and quality of life. Formal assessment may, at times, seem threatening for the person with dementia. A basic principle therefore is to formally assess only to the extent required to guide diagnosis and management and within the patient's tolerance.

Assessing Communication Components and Processes

A primary focus of assessment is to determine to what extent the presenting problems are due to impairment within thought versus impairment within lexical components and processes. Assessment therefore aims to identify the locus of deficits, that is, where in the communication process the problems originate. The interdependency of thought and language can render this a challenge.

It is helpful again here to bear in mind the distinction between the conscious effortful processing required for thinking and word store access, and the normally unconscious automatic effortless processing needed for word sound assembly and sequencing, grammar application, speech muscle programming, and speech muscle activation.

General conversation allows preliminary evaluation of the more automatic components and processes. Speech muscle activation can be screened by noting any evidence of muscle weakness or dysarthria – slurred speech, indistinct speech, problems with volume control and problems with voice quality or pitch. Also note any problems with prosody resulting from poor motor control, that is, inability to employ or control intonation patterns. Problems with speech muscle programming (apraxia) may present with articulatory groping or awkwardness, struggle movements, or distorted speech.

Grammar application also may be evaluated in conversation. Sentence structure is best assessed when the person is talking about something with which they are familiar. This reduces load on thinking, thus filtering out as far as possible the knock-on effect of problems with thinking on sentence structure. Specific problems with grammar may present as "telegrammatic" speech output with paucity of function (noncontent) words plus/minus grammatical word part (morphological) errors (e.g. walk for "walked").

Any major problems with word sound assembly will show in conversation as phonemic paraphasias (sound substitution errors).

Reading aloud is a skill that can be carried out with automatic processing, bypassing the semantic system. This is demonstrated by our ability to read aloud while taking in nothing of what we have read. Asking the patient to read aloud can provide useful information on the more automatic components of speech and language.

It should, of course, be remembered that while word sound assembly and sequencing, grammar application, speech muscle programming, and speech muscle activation are normally unconscious automatic and effortless, pathology within specific brain areas can interrupt these normally effortless processes.

Word store and word sound assembly and sequencing should be assessed during conversation and on a confrontation picture-naming task comprising pictures with names of varying frequency levels. An analysis of naming errors on a naming task will help determine the locus of impairment. Table 3 lists features that might suggest specific problems with word store, word store access, or word sound assembly and sequencing. Typical naming errors suggestive of a semantic origin for word-finding difficulties would be naming a goat as a dog, for example. If only semantic or "visual" errors (e.g. naming a ruler as a "ladder") are present with none of the features listed in Table 3, the origin of the naming problem is more likely to be within thinking and/or the

Table 3 Features suggestive of specific problems with lexical components or processes

- Clear search or struggle (perhaps with frustration) to think of a word to express an apparently clear thought or idea.
- Clear acknowledgement, if a word is supplied, that this was the word they were trying to say.
- Giving a description that shows accurate concept knowledge, for example, "They come from Australia and they jump".
- Circumlocution around a word that demonstrates they know the concept behind the word they are trying to say, for example, "the soup was made of that thing that rabbits like".
- Self-cueing, for example, "I use it to open the door so it's . . . . . a key".
- Good response to phonemic cueing (being given the first sound of the word by someone else), for example, It's a k. . ."
- Use of gesture.
- Giving accurate information about the target word, for example, It begins with "b".
- Phonemic (sound substitution) errors, for example, "wartrode" for "wardrobe"; "flish" for "fish".

semantic system rather than within lexical processes and systems.

Routine psychometric assessments commonly use language to evaluate a range of cognitive skills – failure to identify those patients who have specific language or speech involvement out of proportion to overall generalized cognitive status can lead to false conclusions regarding the overall level of functioning and thus inappropriate decisions for management/placement.

A patient whose general conversation seems impaired by language difficulties but who does surprisingly well on confrontation tasks such as picture naming, may belong to that subset of dementia patients who have particular difficulty thinking and speaking at the same time (see earlier). If thought is assisted, for example, as in a picture-naming task where the concept they are expressing is visible, expressive language comes more easily.

An important element of the evaluation of the thinking component of the communication process is the evaluation of how the person manages with "nonlanguage" activities of daily living. Routine psychometric assessments can be used to obtain an overview of cognitive function in general, but allowances should be made for patients who have demonstrated specific difficulties with language.

Functional Assessment of Communication and Communication Interventions in Dementia

A commonly voiced objection to intervention in dementia is that the person will inevitably deteriorate and thus intervention constitutes an inefficient use of resources. However, the person with dementia has the right to receive interventions that will optimize strengths, compensate for weakness, reduce stress in both patient and carer and promote best possible quality of life. Failure to address the issues can have detrimental consequences for the mental health both of patients and carers. Communication in dementia is the responsibility of the whole multidisciplinary team, which should include a speech and language therapist whose role in empowering and educating others as well as providing direct specialist input is increasingly recognized (Position Paper, 2005).

Loss of meaningful interaction which results from communication breakdown in dementia is distressing for carers (Gilleard, 1984). In an evaluation of communication in 10 mild and moderate dementia patients (Ulatowska *et al.*, 1988), difficulty with staying on topic was reported in 25% of subjects. Sixty-three percent were reported to show memory deficits in conversation by repeating what they had just said, repeatedly asking for the same information or requiring instructions from others over and over again. Problems with communication have been reported by 68% of primary caregivers of dementia patients and were seen as problematic by 74% of these carers (Rabins *et al.*,1982). Bayles and Tomoeda (1991) found the most prevalent of 16 linguistic communication symptoms reported by carers of AD patients was difficulty finding the right word; the least prevalent was an increase in talkativeness.

In a study of the effects of dementia on functional communication (Powell *et al.*, 1995), the perceptions of the carers of 79 community-living dementia patients (59 probable AD; 20 vascular) were compared with the perceptions of family/close friends of a comparable group of 76 control subjects. Informants were asked to rate the prevalence of 32 symptoms of communication breakdown. Comparison of the magnitude of difference between the two groups for each question showed that each of the 32 symptoms was significantly more prevalent in the dementia group than in the control group. Table 4 shows the 32 symptoms, in order of frequency from most to least prevalent, that differentiated the two groups. These data demonstrate that the range of communication problems faced by carers of those with dementia is great.

The aims of communication interventions with people with dementia are many and varied (Powell, 2000a) (Table 5). The overriding aim should be quality of life for patient and carer.

The range of communication-based interventions promoted for people with dementia is wide (Powell, 2000a) Three commonly advocated approaches – reality orientation, validation, and reminiscence – have been the subject of recent systematic reviews (Spector *et al.*, 2005; Neal and Briggs, 2005; Woods *et al.*, 2005). Reality orientation involves the presentation of orientation information – time, place, and person related. It is thought to provide the person with greater understanding of their surroundings, possibly resulting in improved sense of control and self-esteem. Validation is an approach that involves verbalizing the feelings underlying confused behavior rather than reemphasizing facts. Reminiscence is the vocal or silent recall of the events of a person's life alone, with another person, or in a group. The reviews concluded that there is some evidence for the benefits of reality orientation on both cognition and behavior. No firm conclusions could be made about validation or reminiscence at present.

It is almost certain that there is merit in many of the approaches advocated – the challenge is to determine, on

Table 4 Symptoms of communication breakdown in dementia

1. Asks the same question a number of times
2. Struggles to think of the names of places
3. Trouble following television programs
4. Difficulty following a conversation when a group of people are talking
5. Struggles to think of people's names
6. Has trouble keeping a conversation going
7. Calls people by the wrong name
8. Starts to say something and then forgets what he or she was talking about
9. Tells you the same story or piece of information a number of times
10. Difficulty following a conversation with just you
11. Struggles to think of the names of objects
12. If asked to pass something that is nearer to him or her than to you, passes something else instead
13. Has trouble starting up a conversation
14. Drifts from the point during a conversation
15. When asked a question, gives an answer that has nothing to do with the question
16. Calls places by the wrong name
17. Trouble understanding the meaning of words when you talk to him or her
18. Calls objects by the wrong name
19. During conversation, changes the subject inappropriately
20. Deliberately avoids speaking to friends
21. Fails to say "Hello" to friends when meeting them
22. Talks to imaginary people or things
23. Stares at you too much during a conversation
24. Uses words like "thingey", "what's-a-name" or "thingumy-jig" instead of using a person's correct name
25. Uses words like "thingey", "what's-a-name" or "thingumy-jig" instead of using the correct name for an object
26. Uses words like "thingey", "what's-a-name" or "thingumy-jig" instead of using the correct name for a place
27. Talks too much at an inappropriate time
28. Uses a word in a conversation which sounds like the word you know he or she is trying to say but means something else
29. Uses "words" in conversation which are not real words
30. Talks out loud in an inappropriate place
31. Comes up too close to you when talking
32. Avoids looking at you during a conversation

Table 5 Some aims of communication interventions in dementia

- Improvement in functional memory skills, for example, the ability to remember to take medications
- Improvement in specific language skills, for example, comprehension and word finding
- Increased relevance of content of conversations
- Increased social interaction
- Delay in the progression of cognitive deficits
- Behavioral changes, for example, decreased agitation or anxiety
- Increased interest and responsiveness
- Improved well-being/comfort

an individual basis, who would benefit from which approach and when.

Planning effective programs of intervention requires that the clinician obtains a holistic profile of the patient, their carers, and environment. Alongside assessment of the communication components and processes (above), the following should be evaluated: hearing and vision; carer's perceptions of communication, carer–patient interaction, carer's management strategies and stress levels, daily lifestyle/activities/engagement opportunities, physical environment.

Hearing and Vision

Patients with dementia who, in addition, have problems with hearing and/or vision are highly vulnerable to the adverse effects of these sensory deprivations on communication. It is difficult for the person to capitalize on remaining cognitive abilities and they may become disproportionally handicapped relative to their underlying cognitive status. They are likely to have difficulty remembering that vision and hearing are a problem and may be unable to compensate, for example, by asking for a repeat when they have not heard. Remembering how to adjust and clean hearing aids and glasses and remembering when to use them becomes problematic. Carers often fail to recognize the person's deteriorating ability to cope with aids and are likely to require advice on aid maintenance. A nonfunctioning hearing aid or an aid blocked with wax simply acts as an ear plug, while glasses caked in debris may lead to misinterpretations and could increase risk of falls.

Carer's Perceptions of Communication, Carer–Patient Interaction, Carer's Management Strategies and Stress Levels

One of the most prevalent communication symptoms in dementia is a tendency to ask the same question a number of times. This behavior has been described as particularly stressful to caregivers (Quayhagen and Quayhagen, 1988). When carers are asked how they respond when faced with repetitiousness, replies vary: "I keep answering"; "I ignore it"; "I tell her she's already said that"; 'For the first five times I answer'; "I tend to walk away"; "I will get a piece of paper and write it down"; "I say that I'm not sure".

An interview with the carer will help identify communication difficulties that are most bothersome. Discussion of current management strategies may indicate alternative approaches that could be tried to enhance communication and limit distress (Tables 6–8). Some carers learn by trial and error what does and does not help in their situation, but timely discussion can help this process along. The relief carers feel from reassurance that their approaches to management are appropriate cannot be underestimated.

Daily Lifestyle, Activities, and Engagement Opportunities

Daily lifestyle can have positive or negative effects on communication. Impaired thinking often affects ability to take the initiative – this may make the person appear apathetic or deliberately negative. Thus, even in the early to middle stages of dementia, the person is likely to require direction and guidance in order to occupy time constructively and enjoyably and to maintain remaining abilities for as long as possible. Carers may need to be helped to understand this. It may be needed to be explained that, with appropriate

Table 6 General principles for managing communication problems in dementia

- React in a way that causes the least upset to patient and carer
- The most appropriate approach may differ among individuals
- An approach that works in one situation may not work for the same person in a different situation
- Use trial and error to find out what works best and when
- Avoid asking open-ended questions about recent events that set the person up for failure
- Supply missing words and names rather than let the person struggle
- Do not draw attention to mistakes
- Avoid confrontation – do not argue the point
- Try to think of practical ways around problem situations – for example, remove dirty clothing at night if this is a possible source of confrontation
- Try using a "validation"-type approach by responding to the patient's underlying emotion, for example, "You seem upset"
- Distract from repetition or perseveration
- Use a soothing, calm voice

Table 7 Practical strategies to help communication in dementia

- Memory aides, for example, diaries, notebooks, sticky notes
- Written instructions and written labeling of environment (e.g. contents of cupboard)
- Memory albums (Powell, 2000b; Bourgeois, 1992; Powell and Bayer, 1996)
- Timetables (see "daily lifestyle")
- Day-date-month clock for orientation
- Adapted radio with volume fixed and tuning set to favorite channel – only one large on/off switch visible and accessible
- Memory prompter with infrared motion detection that activates a prerecorded message. For example, placed near the door, motion activates "don't forget to take your keys"

Table 8 Helping communication where attention and comprehension are a problem

- Limit extraneous noise (TV/radio/trolleys in residential setting, etc.)
- When speaking, sit or stand close to the person with your face in clear view
- One to one is usually easier than a group
- Get eye contact (call name/touch arm)
- Use short simple sentences
- Speak slowly and clearly
- Give time for each short sentence to be understood
- Repeat and rephrase if necessary
- Point to objects or people as you mention them
- Be literal – do not use metaphors
- Break commands down into a series of individual steps (task segmentation)

prompts, the person may be able continue with many routine tasks or activities. For example, the person may no longer automatically select a CD to listen to, switch on and start the CD player. With the right prompts (e.g. "Shall we select a CD?") the occupation may be retained and enjoyed.

A routine and familiar structure to the day is helpful. In the early and middle stages, using a timetable or "weekly planner" may help provide structure and purpose to the day and promote confidence. A carer will need to help the patient fill in the timetable and use it. The timetable may record appointments (e.g. 11 o'clock hairdresser), essential tasks (e.g. sweep the path) and leisure activities (e.g. feed the birds). Checking the timetable regularly can help with orientation. Completed tasks could be marked off, giving a sense of achievement. Tasks and activities should capitalize on well-learned routines, especially those that are repetitive. This is because abilities based on more routine, automatic "procedural memory" are better preserved in dementia than abilities requiring more complex reasoning and planning skills.

Activities can help reestablish a sense of usefulness and pleasure and to reduce feelings of helplessness and futility (Mace, 1987). Carers should be guided by what the person may have enjoyed premorbidly, but should also consider new activities the person may now enjoy. It is a challenge to find activities that the person can enjoy with limited supervision.

The degree to which a relative carer should be asked to be involved in activities should be carefully assessed (Table 9). Carers are likely to be struggling to adjust emotionally to the illness and practically to the additional responsibilities of caring and may find organizing activities burdensome. Patient–carer support groups can allow the patient to explore new activities and friendships, while supporting the carer emotionally and practically. As the disease progresses, it often becomes appropriate to transfer some of the responsibility for activities/daily occupation to other agents, for example, volunteers, day centers, care workers committed to quality lifestyles.

In the middle and advanced stages of dementia, when the person may be in continuing care, it is just as important to find relevant activities and engagement opportunities. Failure to address the level of activity or engagement and to provide stimulation appropriate to the individual can have serious consequences. A lack of touch and attention, sensory impairments, and being deprived of conversation and mental stimulation may result in boredom, withdrawal, somatic complaints, visual distortions, hallucination and delusions, increased dependency, and a lower survival rate (Beisgen, 1989). On the other hand, too much stimulation can cause fear, anxiety, irritability, or panic. Many elderly people without dementia are happy to spend a large part of the day doing nothing or being passively rather than actively involved. Stimulation should therefore be appropriate to the individual and be designed to add pleasure and a sense of purpose in the moment, perhaps evoking pleasant memories, associations, and sensations. Care should be taken not to impose one's own needs or opinions on the person with dementia. It is important for professional caregivers to have available information concerning the individual's life history. It is helpful for extended care facility staff to remember that even though events, activities, and interactions may not be remembered explicitly, implicit memories of an interaction

Table 9 Points to consider when involving relatives in activity plan

- Carer's stress level
- Carer's cognitive status
- Realism of carer's expectations and ability to offer appropriate degree of encouragement
- Time, energy, and will of carer to be involved

Table 10 Ideas for adapting the environment to promote good communication

- Adequate lighting to limit misperceptions/"hallucinations"
- Good-sized window through which change of seasons and weather is visible
- Seasonal decorations for "absorbed" (not forced) orientation
- Photo and name on bedroom door
- Bright colors on door of bathroom and toilet for orientation
- Brightly colored tape on edges of steps
- Visually stimulating posters, pictures, mobiles, tropical fish
- Vibrant colors, for example, brightly colored plain furniture
- Multisensory environment that allows opportunity for appropriate tactile, auditory, olfactory, and visual stimulation
- Cover or remove mirrors if they cause distress
- Limit extraneous noises
- Rummage area or rummage box with miscellaneous items to search through may help with restlessness

or event can increase sense of well-being and raise level of alertness.

In an ideal setting, a range of communication approaches should be available and professionals should be trained formally to evaluate benefits and adverse reactions to interventions on an individual basis (Powell, 2000a). A tool such as the Cardiff lifestyle improvement profile for people in extended residential care (CLIPPER) can assist with this (Powell, 2000b). The profile aims to improve the lifestyle of people in continuing care who have difficulty communicating their needs and wishes. It encourages staff to develop greater awareness of verbal and nonverbal responses in order to identify pleasant and unpleasant activities and to plan effective interventions. Dementia care mapping is an observation tool designed to examine quality of care from the perspective of the person with dementia. It can be useful as part of a process of bringing about improvements within formal care settings (Kitwood and Bredin, 1992).

Physical Environment

People with dementia can have difficulty adapting to major changes within their physical environment. Carers should be advised to change the environment as little as possible. However, periodic removal of clutter can help patients discriminate the objects they need to carry out activities of daily life. The physical environment can be subtly adapted to promote optimum communication for moderately and severely impaired patients (Table 10).

KEY POINTS

- An information-processing model of communication provides a framework for understanding the relationship between thought and language.
- Understanding how impairments in thought and in language may present clinically can contribute to differential diagnosis of the dementias.
- Identification of relative strengths and weaknesses allows planning of appropriate interventions and guidance of carers on management options and strategies.
- The person with dementia has the right to receive interventions that will optimize strengths, compensate for weakness, reduce stress in both patient and carer and promote best possible quality of life.
- Failure to address communication issues can have detrimental consequences for the quality of life and mental health both of patients and carers.

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Delirium

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OVERVIEW

Delirium is a dangerous diagnosis. It is common; it is commonly missed; and it is associated with several adverse outcomes. Although most clinicians label patients with delirium as having an "acute change in mental status", the formal diagnostic criteria according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-Text Revision) paints a more complete and descriptive picture of these patients if put into sentence form: "A sudden onset of impaired attention, disorganized thinking, or incoherent speech. The patient usually has a clouded consciousness, perceptual disturbances, sleep-wake cycle problems, psychomotor agitation or lethargy, and is disoriented (American Psychiatric Association, 2000)."

PREVALENCE AND INCIDENCE FOR VARIOUS SITES AND SITUATIONS

In the hospital setting, using the available DSM criteria at the time, studies have found delirium in up to 22% of older patients on admission (prevalence), and up to 31% of older patients while hospitalized (incidence) (Francis *et al.*, 1990; Inouye *et al.*, 1993; Johnson *et al.*, 1990). Prevalence rates for confusion of any kind during admission have been found to be even higher (Levkoff *et al.*, 1992).

In general, surgical patients have been found to have higher rates of delirium than medical patients. In a review of primary data-collection studies, Dyer and colleagues found that rates are highest postoperatively among coronary artery bypass graft patients, ranging from 17 to 74% (>50% in five of the 14 studies reviewed). They also found that rates among orthopedic surgical patients ranged from 28–53% (>40% in five of the six studies). Of the two urologic studies reviewed, rates ranged from 4.5 to 6.8% (Dyer *et al.*, 1995). Past biases have blamed anesthesia agents for most cases, which wrongly have kept alive the belief, like that in the case of the intensive care unit (ICU), that delirium is unpreventable. Several studies have evaluated the association between routes of anesthesia (general, epidural, spinal, regional) and the risk of postoperative delirium. They found that the route of anesthesia was not associated with the development of delirium (Marcantonio *et al.*, 1998a; Williams-Russo *et al.*, 1996; Somprakit *et al.*, 2002).

One of the sites with the highest rates of delirium, but perhaps the most controversial because of so many complicating factors, is the ICU. Rates as low as 19% and as high as 80% have been found (Ely *et al.*, 2001a; Ely *et al.*, 2004a; Dubois *et al.*, 2001; McNicoll *et al.*, 2003). For years, however, people have ignored these facts, have called it inevitable and unpreventable, and have even labeled it "ICU-psychosis" so as to blame it on the ICU, which is something that cannot be changed. This may partly explain the high unrecognized rates of 66–84% (Ely *et al.*, 2004b).

Discharge or "transition" of patients out of the acute hospital setting has seen many changes over the past three decades (Makowski *et al.*, 2000). Data from postacute-care facilities (under such names as subacute-care facilities, skilled nursing facilities, rehabilitation centers, and long-term care facilities) reveal two major issues: patients are discharged from acute hospitals with persistent delirium and delirium at these sites persists for an extended period of time. Kelly and colleagues found that 72% of 214 nursing home patients who were hospitalized still had delirium at the time of discharge back to the nursing home. The delirium persisted for 55% of the patients at 1 month and 25% at 3 months after discharge (Kelly *et al.*, 2001). Marcantonio *et al.* (2000) found that 39% of 52 patients with hip fractures were discharged with delirium, which persisted for 32% of the patients at 1 month and 6% at 6 months after discharge.

In a large study of over 80 postacute-care facilities using the Minimum Data Set (MDS) to identify patients with any symptoms of delirium, Marcantonio *et al.* (2003) found a prevalence rate of 23% on admission. Using the Confusion

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Assessment Method (CAM) as a screening tool (Inouye *et al.*, 1990), Kiely *et al.* (2003) found that 16% of 2158 patients at seven postacute-care facilities met the full criteria for delirium, 13% met two or more of the criteria, and 40% had one of the criteria. In the Marcantonio study, of the 23% who had symptoms of delirium, 52% still had the symptoms at 1 week follow-up (Marcantonio *et al.*, 2003).

While one could argue that delirium in postacute-care facilities should be expected to some extent because of pressures on acute facilities to shorten length of stays, two studies that looked at point of prevalence within nursing facilities discovered a similarly high rate of delirium. Mentes *et al.* (1999) evaluated 324 long-term nursing home patients using the MDS and found that 14% of patients had delirium. Cacchione *et al.* (2003) prospectively evaluated 74 long-term nursing home patients and identified 24 (33%) patients with delirium. While neither study could determine whether the delirium was a persistent one after a hospital stay, or was an incident (new episode of) delirium, it is evident that incidence of delirium was common.

Home Care is an understudied site concerning delirium. However, two studies (detailed under the Section "Prevention and Management Interventions") showed lower rates of delirium among ill, older persons cared for at home compared to similarly ill, older persons cared for in the hospital. It is unclear whether something positive is being done in the home that prevents delirium or whether something negative is occurring in the hospital that contributes to the development of delirium (Caplan *et al.*, 1999; Leff *et al.*, 2004).

ASSOCIATED ADVERSE OUTCOMES

Delirium is one of the most serious illnesses patients can have or develop and one that clinicians should not miss at the reported rate of 32–66% (Inouye, 1998). Data about the adverse outcomes associated with delirium mainly come from studies of older patients in the hospital setting. Here, delirium has been found to be associated with hospital complications, loss of physical function, increased length of stay in the hospital, increased instances of discharge to a long-term care facility, and even higher rate of mortality (Francis *et al.*, 1990; Pompei *et al.*, 1994; Cole *et al.*, 2003; McCusker *et al.*, 2002a,b; McCusker *et al.*, 2003; Rockwood, 1999; Inouye *et al.*, 1998; O'Keeffe and Lavan, 1997; Thomas *et al.*, 1988). Mortality rates for hospitalized delirious patients have been reported to be 25–33%, as high as the mortality rates for acute myocardial infarction and sepsis (Inouye, 2003).

There has been some question in the past whether delirium was independently associated with these adverse outcomes, or whether it was merely a marker of severe illness and physical frailty since most studies identified older age, underlying cognitive impairment, severe, acute and chronic illness, and functional impairment as the predisposing factors. However, when adjusting for these factors, delirium has been found to be independently associated with poor outcomes in most studies (O'Keeffe and Lavan, 1997; McCusker *et al.*, 2002a; Rockwood, 1999; Inouye *et al.*, 1998).

Associated adverse outcomes among delirious ICU patients have shown prolonged ICU stay, prolonged hospital stay, and increased mortality compared to patients without delirium (Ely *et al.*, 2001a; Ely *et al.*, 2004a). Emerging data from postacute facilities have also shown associated adverse outcomes, related to loss of physical function and mortality (Marcantonio *et al.*, 2003; Cacchione *et al.*, 2003; Kelly *et al.*, 2001).

THE COMPREHENSIVE APPROACH TO DELIRIUM

In order to improve the adverse outcomes associated with delirium, it is not enough just to improve our skills in diagnosing delirium and treating the underlying medical causes. The following are the necessary components of a comprehensive approach for those involved in the care of older persons, and health-care systems that interface with older persons.

1. *Awareness*: Be aware of how commonly delirium occurs, where it occurs, and get others involved in the care of older persons to do the same.
2. *Diagnosis*: Know why it is important to differentiate and how to differentiate between delirium and dementia.
3. *Evaluation*: Identify and treat the underlying causes of delirium.
4. *Prevention*: Implement strategies or care systems that can prevent delirium.
5. *Management*: Manage patients who develop delirium.

Although there are no available studies to date that implement all five interventions, a multifaceted approach is warranted because of the nature of this multifactorial problem (Inouye, 2001).

Awareness

Delirium should become part of the medical jargon for all who care for older persons (Flaherty *et al.*, 2003). Furthermore, given the frequency with which delirium is seen and the seriousness of this diagnosis, the rates of incidence and outcomes associated with delirium should be monitored (that is, they should become quality-of-care measures) at all sites where delirium occurs (Inouye *et al.*, 1999b).

Diagnosis

Delirium is not dementia. The latest version of the DSM is the DSM-IV-TR (American Psychiatric Association, 2000). There is no difference in the core features of delirium in the DSM-IV-TR version compared to the previous version, DSM-IV, except that the DSM-IV-TR version recognizes that

delirium can arise during the course of dementia. Although this appears to be a minor detail, the message this gives to health-care professionals is a critically important one: "delirium is not dementia". Most types of dementia have a progressive downhill course. Delirium is reversible. A mislabeling, or lack of differentiation between these two diagnoses is thought to be the reason why delirium is missed by physicians at rates as high as 32–66% (Inouye, 1998) and by nurses up to 69% of the time (Inouye *et al.*, 2001). Misdiagnosis or late diagnosis may also partly explain why delirium is associated with adverse outcomes (Francis and Kapoor, 1992; Lyness, 1990). Table 1 details some of the differentiating characteristics between delirium and dementia, based on DSM criteria, keeping in mind that one of the criteria not in Table 1 is that delirium must occur in the context of a medical illness, metabolic derangement, drug toxicity, or withdrawal.

Altered level of consciousness (LOC) is an excellent clue in differentiating delirium and dementia because it is not always possible to know the patient's baseline mental status. Without ever having seen the patient before, one can determine whether the patient's LOC lies toward the agitated or vigilant side of the spectrum of LOC, or toward the lethargic, drowsy or stuporous side of the spectrum.

One can ask orientation questions, but since disorientation and problems with memory are present in both delirium and dementia, the key in determining delirium from dementia is *how* the patient answers. The delirious patient will often give disorganized answers, which can be described as rambling or even incoherent.

The classic identifiers of delirium are acute onset and fluctuating course, both of which are usually obtained by close caregivers (family or nurses). Although acute implies 24 hours, the term subacute is used to emphasize that subtle mental status changes can be overlooked by caregivers. Over a period of many days, the patient may appear to be slowly declining mentally due to the underlying dementia. If left unchecked, the initial delirium may impair other necessary functions, leading to further medical problems, such as dehydration and malnutrition, further complicating the delirium. This snow-ball effect explains in part why the etiology of delirium is typically multifactorial. Thus, if it is unclear how long the change has been occurring, patients should be put in the category of delirium and an evaluation should be done.

Attention is also one of the classic identifiers of delirium, which may often be helpful if the patient's baseline mental status is not known. It can be tested by having a conversation. Patients may have difficulty maintaining or following the conversation, perseverate on the previous question, or become easily distracted. Attention can also be tested with cognitive tasks such as days of the week backward, spelling backward, or digit span.

Psychomotor agitation or lethargy, hallucinations, sleep-wake cycle abnormalities and slow or incoherent speech can all be seen in patients with delirium, but these features are not necessary for the diagnosis.

Table 1 Differentiating delirium from dementia

	Delirium	Dementia
Consciousness	Decreased or hyper alert "Clouded"	Alert
Orientation	Disorganized	Disoriented
Course	Fluctuating	Steady slow decline
Onset	Acute or sub acute	Chronic
Attention	Impaired	Usually normal
Psychomotor	Agitated or lethargic	Usually normal
Hallucinations	Perceptual disturbances May have hallucinations	Usually not present
Sleep-wake cycle	Abnormal	Usually normal
Speech	Slow, incoherent	Aphasic, anomic difficulty finding words

Evaluation

General guidelines for the medical evaluation of patients are to consider all possible causes, proceed cautiously with appropriate testing, and keep in mind that delirium is usually caused by a combination of underlying causes.

After a physical check and ascertaining the history, which includes obtaining details from anyone considered a caregiver (e.g. family, nurse's aide) and a thorough medication list, the mnemonic D-E-L-I-R-I-U-M-S can be used as a checklist to cover most causes of delirium (Table 2).

Drugs are notorious for causing delirium. According to most authors in this area, "virtually any" (Carter *et al.*, 1996) and "practically every" (Lipowski, 1989) drug can be considered deliriogenic.

Several drugs have been found *in vitro* to have varying amounts of anticholinergic properties. However, since the pathophysiologic and neurotransmitter mechanisms of delirium go beyond anticholinergic mechanisms, a more practical approach is to remember certain categories of medications that have been reported to cause delirium, some more common than others. The mnemonic A-C-U-T-E C-H-A-N-G-E I-N M-S is long, as would be expected, but highlights why drugs are such a common cause of delirium (Table 3). In order to be as inclusive as possible, and because many older reports did not discuss strict delirium criteria, or such criteria were not commonly used, the following paragraphs describe not just delirium as a side effect, but psychiatric side effects that might indicate presence of delirium, such as hallucinosis, paranoia, delusions, psychosis, general confusion, aggressiveness, restlessness, and drowsiness.

Table 2 Causes of delirium

D	Drugs
E	Eyes, ears
L	Low O_2 state (MI, stroke, PE)
I	Infection
R	Retention (of urine or stool)
I	Ictal
U	Underhydration/undernutrition
M	Metabolic
(S)	Subdural

Table 3 Medications that can cause (have been reported to cause) an A-C-U-T-E C-H-A-N-G-E I-N mental status

A	Antiparkinson's
C	Corticosteroids
U	Urinary incontinence drugs
T	Theophylline
E	Emptying drugs (e.g. metoclopramide, compazine)
C	Cardiovascular drugs
H	H2 blockers
A	Antibiotics
N	NSAIDs
G	Geropsychiatry drugs
E	ENT drugs
I	Insomnia drugs
N	Narcotics
M	Muscle relaxants
S	Seizure drugs

Antiparkinsonian drugs probably cause delirium due to a tip in the tenuous balance of the neurotransmitters dopamine and acetylcholine, both implicated in the pathophysiology of delirium. Levodopa has been reported to cause mental status changes at a rate of 10–60% and include hallucinosis on a background of a clear sensorium, delusional disorders, and paranoia. Abnormal dreams and sleep disruption may precede the more frank delirium symptoms and may be an early clue to their onset. Selegiline has been reported to cause mental status changes described as psychosis, aggressiveness, even mania (Flaherty, 1998).

Corticosteroids have been reported to cause "psychiatric complications" in up to 18% of patients with doses above $80\,mg\,day^{-1}$. The mental status changes seen have been described as depressive/manic, an organic affective disorder with associated paranoid-hallucinating features, and general "confusion". Withdrawal of corticosteroids may also cause delirium (Flaherty, 1998).

Drugs for urinary incontinence (specifically antispasmodics) have the potential to cause delirium by two mechanisms: through the anticholinergic properties of the drug, or through causing urinary retention, known as the *cytocerebral syndrome* (discussed in the following text) (Blackburn and Dunn, 1990). Although older short-acting antispasmodics have more of a potential to cause delirium, newer sustained-release agents have been reported as well (Edwards and O'Connor, 2002).

Theophylline "madness" probably meets delirium criteria, as one of the first case reports described it: "the blood level, toxic on admission but decreasing over 48 hours, correlated well with the number of episodes of hyperactive periods marked by flailing of limbs, intense emotional lability, incessant crying and ripping out of intravenous lines and nasogastric tubes. Not always is there a direct correlation between the presence or severity of side effects and the toxic serum level of theophylline" (Flaherty, 1998).

Emptying drugs, or motility agents, are a class of drugs that are intended to stimulate the upper gastrointestinal tract through cholinergic mechanisms. However, these agents also have peripheral and central antidopaminergic properties. Reported mental status side effects include restlessness, drowsiness, depression, and confusion (Flaherty, 1998).

Cardiovascular drugs rarely cause mental status problems, but because they are so commonly prescribed for older persons, it is worthwhile to remember that some are more likely to cause problems, as well as a few that have been reported in case-reports. One of the first reports of confusion due to digoxin toxicity was over 100 years ago. Since then, reports of confusion even at therapeutic levels have been published (Flaherty, 1998).

Methyldopa and reserpine are centrally acting antihypertensives that have been reported to cause depression, nightmares, psychosis, and delirium. The centrally acting alpha agonist clonidine may cause depression, delirium, and hallucinations (Flaherty, 1998).

Several antiarrhythmics have been reported to cause mental status changes, thought to be either idiosyncratic or dose-related. Reported culprits include disopyramide, procainamide, quinidine, lidocaine, amiodarone, flecainide, mexiletine, propafenone, and tocainamide (Flaherty, 1998).

Antihypertensive agents that may cause mental status changes have primarily been reported in the literature through case reports. However, since they are so commonly used, it is worthwhile being suspicious about a few of them. These include beta-blockers (including in the form of eye drops), angiotensin-converting enzyme inhibitors, and calcium channel antagonists (Flaherty, 1998).

H2 blockers, because they are primarily renal excreted and may have some H1 activity (antihistamine receptor subtype-1), may cause delirium, especially if patients have underlying risk factors such as renal insufficiency and dementia (Flaherty, 1998).

Antimicrobials, like cardiovascular drugs, rarely cause mental status changes, but are so commonly used; some examples are worth being aware of: penicillin, erythromycin, clarithromycin, gentamycin, tobramycin, streptomycin, trimethoprim-sulfamethoxazole, ciprofloxacin, some cephalosporins, and the antiviral acyclovir, particularly at high doses. Most of these reports propose that the mechanisms by which antimicrobials cause mental status changes are related to impaired renal function, drug–drug interaction, and occasionally idiosyncratic behavior (Flaherty, 1998).

Several types of nonsteroidal anti-inflammatory drugs have been reported to cause delirium, even the newer selective cyclooxygenase-2 inhibitors (Macknight and Rojas-Fernandez, 2001), and aspirin and salicylate compounds (Flaherty, 1998).

"Geropsychiatric" medications is too large a category to go in-depth about, but a few comments are warranted to create some balance between reflexively blaming these drugs for the delirium just because "any drug that works in the brain, can cause a problem in the brain" and understanding that while no centrally acting psychiatric medication is completely safe, certain ones may be safer than others and psychiatric illnesses, especially depression, need to be treated (Flaherty, 1998).

Tricyclic antidepressants (TCAs) can cause delirium with an overall incidence ranging from 1.5 to 20%. The highest rates, of course, seem to be among older, previously cognitively impaired, and medically ill patients. Delirium can be caused by low or therapeutic doses and may not be associated with signs of peripheral muscarinic blockade such as dilated pupils or urinary retention. Some TCAs are not as anticholinergic as others (e.g. desipramine) so that the risk of delirium is not an absolute contraindication to their use (Flaherty, 1998).

Serotonin selective reuptake inhibitor (SSRIs) antidepressants have a much safer side effect profile compared to the TCAs as far as delirium is concerned. However, one of the main side effects of SSRIs, hyponatremia, can present as delirium in older persons. This has been reported with fluoxetine, fluvoxamine, paroxetine, and sertraline. Although frank delirium due to SSRIs is rare, most reported cases seem to point toward drug interactions as a plausible cause (Flaherty, 1998). However, to emphasize that no centrally acting drug is completely safe, in a study of 10 healthy volunteers, paroxetine increased ratings of confusion and fatigue (Brauer *et al.*, 1995). There are also case reports of confusion due to antidepressants such as mirtazapine (Bailer *et al.*, 2000) and venlafaxine (Howe and Ravasia, 2003).

The serotonin syndrome, although rare, since the use of L-tryptophan and monoamine oxidase inhibitors are less nowadays, is a constellation of symptoms that may include confusion, agitation and restlessness, myoclonus and hyper-reflexia, involuntary movements, shivering, diaphoresis, tremor, and fever. However, SSRIs alone and combinations such as sertraline and tramadol (a mu-receptor pain medication), trazodone and buspirone, and trazodone and methylphenidate have been reported to cause symptoms similar to those described in the serotonin syndrome (Flaherty, 1998).

Benzodiazepines (BDZs) were introduced in the 1960s and are one of the most widely used psychoactive drugs in most communities. Unfortunately, their use is highest among the elderly. In one study of over 400 hospitalized patients, aged 58–88 years, who had normal mini-mental status examination scores on admission, the use of BDZs was associated with a relative risk of developing cognitive impairment of 3.5 (95% CI; 1.4–8.8) (Foy *et al.*, 1995). Postoperative use of BDZs has also been found to increase the risk of delirium. Short-acting BDZs, even in small doses, have been recorded to cause problems, and the clinician should be aware that withdrawal from BDZs in the elderly may also present as delirium, perhaps more so when discontinuing short-acting BDZs compared to long-acting ones. However, there are models of successfully withdrawing patients from BDZs and this should be attempted whenever possible (Petrovic *et al.*, 1999).

Antipsychotics can cause delirium. In one study of patients who were transferred from the psychiatric ward to a medical ward because of delirium, 31% of the cases were due to low potency antipsychotic agents (Popli *et al.*, 1997). Whether the antipsychotic prescribed is considered a typical antipsychotic or an atypical antipsychotic, the clinician needs to keep in mind that none of these drugs have pure mono-neurotransmitter activity. Rather, they have varying degrees of activity, either agonist or antagonist to many of the neurotransmitters implicated in the pathophysiology of delirium, such as dopamine, acetylcholine, serotonin, and histamine (Tandon *et al.*, 1999). Thus, like other geriatric psychiatric medications, antipsychotic drugs can and should be considered as a potential cause of delirium.

Two additional points need to be made concerning antipsychotics. The neuroleptic malignant syndrome is classically described as a triad consisting of fever, elevated creatinine kinase enzymes, and confusion. However, some authors believe that a variant, or rather a clinical spectrum of the neuroleptic malignant syndrome can be seen, wherein patients may only have one or two of the triad features and may only have a small degree of these features. For example, patients may have subtle confusion and muscle rigidity, which is intermittent but only mild, or no elevation of creatinine kinase enzymes (Reilly *et al.*, 1991).

Patients with Lewy-body dementia have an increased sensitivity to neuroleptics. The clinical challenge here is that sometimes it is difficult to differentiate between Alzheimer's dementia and Lewy-body-type dementia (McKeith *et al.*, 1992).

The ENT drugs in the mnemonic are a reminder of the multiple drugs, in particular, over the counter (OTC) medications that are taken for respiratory or sinus illnesses. This category should encompass decongestants, antihistamines, expectorants, and antitussins. Older persons use a disproportionate share of OTC drugs, and the average number of OTC drugs used by ambulatory older persons has increased. The most worrisome of these ENT medications are the combination formulas, which contain two, sometimes three, or even four active ingredients. Antihistamines, particularly the drug diphenhydramine, can cause problems at high doses, at moderately high doses, after a first time oral dose in compromised elderly patients, and even with topical use. Common OTC decongestants include sympathomimetics such as pseudoephedrine and phenylpropanolamine, which are found in most cough and cold remedies, and phenylephrine, which is found in OTC nasal sprays. Mental status changes have been reported to occur at high doses, low doses, and even from overuse of nasal inhalation. Expectorants are probably safe to use alone in older patients although their actual clinical benefit has been questioned. Antitussins are also probably safe as long as they are only used by themselves (Flaherty, 1998).

One of the most commonly used, if not overused ENT medications is meclizine. Although used for dizziness because of its mechanism of action to decrease excitability of the middle ear labyrinth and block conduction in the middle ear vestibular-cerebellar pathways, it has the potential to cause mental status changes because of its central anticholinergic action at the chemoreceptor trigger zone. The anticholinergic properties were thought to be the cause of confusion and steady cognitive as well as functional decline in an older patient who had been on meclizine for 3 years. Within 1 month off the drug, the patient's function and

mentation improved. When rechallenged, the patient had cognitive and functional decline within 1 week (Molloy, 1987).

"I" is a reminder that medications used for insomnia because of their effect on sedation have potential to cause varying degrees of delirium. Nonpharmacological approaches should be used before medications for insomnia as well as a thorough evaluation of the causes of insomnia. Clinicians should be aware that most OTC sleeping aides come under a multitude of brand names without specifying the potentially dangerous deliriogenic medications, dyphenhydramine or scopolamine. Various herbal medicines, although thought to be safe, need to be evaluated to see whether they contain atropine or scopolamine (Flaherty, 1998).

Narcotics can be used safely in older persons with little risk of developing delirium, but a few important details need to be remembered. Meperidine is particularly risky in older persons, likely due to the anticholinergic activity of its active metabolite nor-meperidine. According to Lipowski's thorough review of drugs causing delirium, morphine and propoxyphene rarely appear to cause delirium, however, the latter drug can lead to dependence, abuse, and withdrawal symptoms. At the time of Lipowski's review, there were no reported cases of delirium due to codeine. The main problems associated with the use of narcotics are probably related to toxicity, overuse, or overdosage in patients with impaired hepatic or renal function (Lipowski, 1989).

Muscle relaxant is a misnomer because these medications act centrally in the brain, not locally at the muscles. Some of the commonly used muscle relaxants include cyclobenzaprine, methocarbamol, and carisoprodol, and have been reported to cause delirium (Flaherty, 1998).

Seizure medications have been reported to cause varying types of cognitive impairment including drowsiness, agitation, depression, psychosis, and delirium. The cognitive impairment is thought to be related to serum levels, but clinicians should keep in mind that most anticonvulsants are protein bound and if the patient's nutritional status is poor then there is potential that the amount of free drug will actually be higher than what is measured by the serum level (Flaherty, 1998).

In conclusion, although the list of medications that can cause delirium is long, the mnemonic, A-C-U-T-E C-H-A-N-G-E I-N M-S can help clinicians recognize some of the more common and some of the rare offenders. For patients who present with delirium or for patients who are at risk for delirium, the following general guidelines concerning medication management can be used.

1. Use nonpharmacological interventions whenever possible instead of a medication.
2. Do not treat vague symptoms with a medication (for example, do not routinely give H2 antagonists for vague gastrointestinal complaints).
3. Include an assessment of OTC medications as potential offenders.
4. Evaluate all drugs for drug–drug and drug–disease interactions.
5. If a drug is started, decide on how long that drug will be used. The old rule of "start low and go slow" needs to be expanded to "start low, go slow, and know when to stop".
6. The justification for prescribing medications should be based on therapeutic reasons and not on preventive reasons, and until the patient is no longer at risk for delirium or the delirium has resolved.
7. Do not treat adverse effects of drugs with another drug unless completely necessary (as may be the case with long-acting narcotics and laxatives).

The "E" in the D-E-L-I-R-I-U-M mnemonic stands for emotions and reminds the clinician that depression can have psychotic features and as such may present similar to patients with delirium. Although depression has classically been considered the masquerader of dementia, given some of the DSM-IV criteria for delirium such as disorganized thinking or psychomotor lethargy, depression should be considered a reversible cause of delirium.

Low O_2 (Oxygen) states in the mnemonic should highlight to the clinician that older patients with acute cardiovascular or pulmonary illnesses can present with delirium. It could be said that "delirium is as serious as a heart attack" because not only can the mortality rate of delirium be as high as that of myocardial infarction but also that the older delirious patients can have myocardial infarctions that are commonly missed or present atypically (Malone *et al.*, 1998). It is unclear whether patients, because of the delirium, cannot either describe or tell clinicians about chest pain, or whether there exists a cardiocerebral syndrome in which the stress of the myocardial infarction affects on the adrenergic system causing a stress on the balance in the central nervous system, that is, in cognition.

Not only are patients with stroke at risk of developing delirium as a complication of the stroke or the underlying comorbidities associated with the stroke but also delirium which may be the presenting feature of some stroke patients (Ferro *et al.*, 2002).

Infections are one of the most common underlying causes of delirium among older people. The most common types of infections that cause delirium are urinary tract infections and respiratory infections. However, subtle infections such as cholecystitis and diverticulitis should not be overlooked (Freeman and Kirdar, 1990). Although meningitis should be considered, it is not clear whether or not cerebrospinal fluid analysis is warranted in the initial work-up of delirious patients without other symptoms that point toward a central nervous system infection (Warshaw and Tanzer, 1993).

It is worth noting that because one of the risk factors identified for patients to develop delirium is hospitalization, procedures that seem to be standard and are carried out in hospitals should be questioned. One of these common procedures that occurs is the placement of an indwelling urinary catheter. It seems logical that the most common nosocomial infection for older patients is urinary tract infection because of the use of these indwelling urinary catheters. It has been reported that more than one-third of

the attending physicians and more than one-quarter of the resident physicians at four academic medical centers did not know which of their patients at any one time had one of these indwelling urinary catheters. These catheters can also be considered as a one point restraint that limit mobility, thus adding to the complications of hospitalization (Saint *et al.*, 2002). Given these risks without any clear benefit, indwelling urinary catheters are not indicated for urinary incontinence, urinary retention that can be managed with straight intermittent catheterization, and should not be used to monitor input and output unless this monitoring is critical in decision making and outcomes related to this parameter.

Retention of urine and feces can both cause delirium although typically the presentations differ. Urinary retention causing delirium has been well reported in the literature under the term cystocerebral syndrome (Blackburn and Dunn, 1990; Ble *et al.*, 2001; Liem and Carter, 1991). The original report was of three cases, all were older men who became acutely agitated and nearly mute. All three patients had large volumes of urine in their bladder and in all three patients, the agitated delirium resolved within a short time after emptying the bladder. Liem and Carter have suggested that the adrenergic tension related to the urinary retension might increase in the central nervous system and the consequent increase in catecholamines might produce delirium. Although this pathophysiological explanation has not been proven, clinicians should be very aware of this syndrome. One of the best ways to quickly evaluate for urinary retention is with a hand held bladder ultrasound. Although these have a fairly high initial cost, cost savings from the reduction in use of straight catheterizations may help balance this issue (Frederickson *et al.*, 2000).

Fecal retention as a cause of delirium has not been reported in the literature. However, since older patients for multiple reasons are at risk for fecal impactions, clinicians should be suspicious of this problem when the delirium is of the lethargic type.

Ictal states are a rare cause of delirium and are not difficult to diagnose clinically for patients with tonic clonic seizures. However, patients who experience absence seizures may go unnoticed by caregivers and may only seem to have fluctuating mental status changes. Although an electroencephalogram (EEG) is not indicated in the initial medical evaluation of delirium, it should be considered when pertinent history is obtained.

Underhydration is used in the mnemonic, not only to emphasize the fact that dehydration can be one of the underlying causes of delirium but also to highlight the fact that those at risk for dehydration are at risk for delirium. Although there is much debate and consternation about which, if any, physical signs are pathomnemonic for dehydration among older persons, one quick method is to calculate the blood urea nitrogen (BUN) and creatinine ratio. Although there are several circumstances when the BUN/Creatinine ratio may not be accurate, there are data to suggest that a ratio of greater than 17 : 1 puts patients at risk for delirium (Inouye *et al.*, 1993). Given this easy and commonly accessible parameter and given the data supporting the use of dehydration or difficulty with hydration as a target for interventions as will be seen below, dehydration should be considered on the top of the list as a contributing cause and not as only a risk factor for delirium, and should be treated as aggressively as possible keeping in mind the limitations of each patient related to their cardiovascular status.

Undernutrition, or malnutrition is rather complex and difficult to understand as a cause of delirium, most likely because unlike other causes of delirium it is less likely to be reversed quickly. It is evident, though, that malnutrition among the hospitalized patient is not only common but is also associated with longer hospital stays, postoperative complications, and even higher mortality. Clinicians as well as all health-care providers in the hospital should be aware that restricted diets are likely to exacerbate malnutrition. According to one study of over 1000 consecutive hospitalized patients, over 400 were malnourished according to the body mass index, and almost 50% of these malnourished patients had an order by a physician for a restricted diet (Thomas and Kamel, 2004). Malnutrition is most directly related to delirium probably through the issue of medications that are protein bound. Patients who are malnourished may have lower protein stores and thus protein bound drugs will have a higher free concentration that puts the patient at risk for delirium. Other proposed relationships between malnutrition and delirium, which have yet to be fully elucidated, include those mechanisms looking at cytokines (Banks *et al.*, 2003).

Metabolic abnormalities that cause delirium are not difficult to identify because of the availability of commonly used laboratory tests. A complete metabolic panel usually will identify hyponatremia or hypernatremia, hypocalcemia or hypercalcemia, and abnormalities of liver function or renal function. Thyroid function tests and B12 are typically put in this category.

Although delirium is not spelled with an "s" in the end, using the mnemonic DELIRIUMS emphasizes to the clinician that delirium usually has more than one cause. The "s" also reminds the clinician that a subdural hematoma can cause a mental status change. Although the mortality rate of subdural hematomas among younger people is quite high, the prognosis for older people is quite good as long as the diagnosis is not missed (Tagle *et al.*, 2003). The other difference between older and younger patients with subdural hematomas is that older patients may develop the subdural hematoma over a period of a few hours or days. Although there could be some debate as to whether or not all older patients presenting to a hospital with delirium should have some sort of brain imaging, most would agree that because this is a very reversible problem and which would cease to be reversible if the diagnosis is delayed, imaging should be considered if there has been a history of head trauma or falls or any suspicion that there was an unwitnessed fall.

One of the other causes of delirium not represented in the mnemonic is pain. Recognition of pain is improving, now identified as the *5th vital sign*, and should be considered as a readily treatable cause of delirium, especially associated with elective surgery (Lynch *et al.*, 1998).

Prevention and Management Interventions

Before identifying which interventions are effective and which are not, it is important to understand the goals of interventions concerning delirium. They are: (1) to prevent the development of delirium; (2) to reduce the adverse outcomes associated with delirium in those patients for whom delirium is not prevented; and (3) to provide health-care professionals with alternatives to physical restraints and pharmacological methods in the management of delirium.

It is also important to emphasize that delirium is a complex issue related to the challenge of identifying who is at risk of developing it, diagnosing it if it does develop, and getting other health-care professionals to do the same. Interventions that are successful will involve several components, many of which are not easily measured. These include education about the risk factors and diagnosis of delirium, a "culture" change about how *not* to use what seems logical and protective (for example, physical restraints or pharmacological sedation), and a realization that multicomponent interventions are not simple but can be done.

The most consistent message about successful interventions is to use an interdisciplinary team approach and follow geriatric principles.

One of the most rigorous studies to date because of the assessment methods used and the close follow-up of patients was a prospective study of a multicomponent intervention to prevent the development of delirium in hospitalized older patients (Inouye *et al.*, 1999a). The study identified patients at risk for delirium on the basis of a previously developed predictive model (Inouye *et al.*, 1993). The study used the following six out of seven risk factors for the development of delirium: baseline cognitive impairment, eye or visual problems, altered sleep/wake cycle, dehydration, restricted or decreased mobility, or hearing impairment (Table 4). The seventh risk factor, addition of >3 medications, was not used in the study, but is included in Table 4 for completeness (B-E-W-A-R-E). The standardized intervention protocols that were used in the study included the first six targeted interventions as described in Table 4 (P-R-E-V-E-N-T).

Delirium developed in 15% of 426 usual care patients compared to only 9.9% of 426 intervention group patients (OR, 0.60, 95% CI, 0.39–0.92). The total number of days of delirium and the total number of episodes of delirium were also significantly lower in the intervention group, but the severity of delirium and recurrence rates were not significantly different. The interdisciplinary team included a specialist geriatric nurse, two specially trained persons familiar with the standardized intervention protocols, a certified therapeutic recreation specialist, a physical therapy consultant, a geriatrician, and trained volunteers.

The importance of this study is twofold. This study probably underestimates the success of a multicomponent intervention such as this because of the likely contamination that occurred throughout the hospital through implementing some of the standardized protocols. Since the study was done within one hospital, it was unable to randomize patients to separate floors and thus, some intervention patients were on floors that also included patients from the usual care group. This was evident based on the 15% rate of delirium in the usual care group, which is lower than previous studies. Although a multicomponent intervention such as this seems labor-intensive and costly, cost-effective analysis have been favorable (Rizzo *et al.*, 2001).

Table 4 Risk factors for delirium (B-E A-W-A-R-E) and targeted interventions (P-R-E-V-E-N-T) based on intervention trial to prevent delirium

B	Baseline dementia?
E	Eye problems?
A	Altered sleep/wake cycle?
W	Water or dehydration problems?
A	Adding >3 medications, especially sedating and psychoactive ones?
R	Restricted mobility?
E	Ear problems?
P	Protocol for sleep (back massage, relaxation music, decreased noise, warm milk, or caffeine-free herbal tea)
R	Replenish fluids and recognize volume depletion
E	Ear aids (amplifier or patient's own hearing aid)
V	Visual aids (patient's own glasses, magnifying lens)
E	Exercise or ambulation as soon as possible
N	Name person, place and time frequently for reorientation
T	Taper or discontinue unnecessary medications. Use alternative and less harmful medications.

A study that targets a very high risk group for delirium, older patients with surgical repair of hip fractures, was performed using a geriatric consultation as the primary mode of intervention (Marcantonio *et al.*, 2001). In this study, 126 patients who were 65 years or older and admitted for surgical repair of hip fracture were randomized to geriatric consultation or usual care. The geriatric consultation was "proactive", which meant that the consultation began preoperatively (for 61% of the patients) or within 24 hours of surgery, and a geriatrician made daily visits for the duration of the hospitalization. Targeted recommendations were made on the basis of a structured protocol emphasizing geriatric principles as well as postoperative medical care. Recommendations covered areas such as treatment of severe pain, elimination of unnecessary medications, regulation of bowel/bladder function (including discontinuing bladder catheters by postoperative day 2), adequate nutritional intake, and early mobilization. The overall adherence rate by the orthopedics team to the recommendations was 77%.

Delirium developed in 32% of the 62 consultation group patients compared with 50% of the 64 usual care group patients (OR, 0.64, 95% CI, 0.37–0.98). There was a greater reduction of severe delirium, occurring in 12% of the consultation group and 29% of the usual care group (OR, 0.40, 95% CI, 0.18–0.89). Median length of stay did not differ in the two groups (5 days).

Two studies of "home–hospital care" have shown lower rates of delirium among medical patients cared for in the home compared to similar patients cared for in the hospital (Caplan *et al.*, 1999; Leff *et al.*, 2004). In the study by Caplan and colleagues, 100 patients with a mean age of 76 years (71% from home, 25% from nursing homes and 4% from hostels) with medical illnesses such as acute infections requiring intravenous antibiotics, deep venous thrombosis,

minor cerebrovascular accidents, or cardiac failure, were randomized within 24 hours of diagnosis to either home or hospital. Although the researchers used the term "confusion" instead of the formal diagnosis of delirium, they found a lower incidence of confusion (0 vs 20.4%; $P = 0.0005$), in the home group compared to the hospital group. Other geriatric complications were also found to be at a lower rate in the home group compared to the hospital group: urinary complications (incontinence or retention) (2.0% vs 16.3%; $P = 0.01$), and bowel complications (incontinence or constipation) (0 vs 22.5%; $P = 0.0003$) (Caplan *et al.*, 1999).

The study by Leff and colleagues identified older patients who required hospital level care for pneumonia, congestive heart failure, chronic obstructive pulmonary disease and cellulitis. Of those who went home for treatments associated with hospital care, compared to patients who completed their treatments in the hospital (average length of stay 2.9 days versus 4.9 days), the adjusted odds ratio for incident delirium was 0.25 (0.11, 0.58, adjusted 95% CI) (Leff *et al.*, 2004).

What about patients for whom delirium is not preventable or who already have delirium on admission to the hospital? The Delirium Room (DR) is a specialized four-bed room to provide 24-hour nursing care and observation by at least one nurse in the room and is completely free of physical restraints (Flaherty *et al.*, 2003). The hallmarks of the DR are the following. The four-bed DR is an integral part of an acute care for the elderly (ACE) unit. As such, the patients in the DR not only receive 24 hour close observation but also the benefits of the geriatric principles for which the ACE unit has been shown to be effective in preventing loss of functional decline (Landefeld *et al.*, 1995). Nursing inservices and protocols developed by nurses on how to identify and manage delirious patients are necessary. The DR is not isolated from the rest of the floor, rather it is the closest room to the main nurses' station. Having a location on the floor called the *Delirium Room* (see Figure 1) raises the awareness among health-care professionals that delirium is a serious diagnosis, with serious consequences. Putting delirious or potentially delirious patients together in a room does not increase agitation as previous literature might suggest.

Although the report of the Delirium Room was descriptive, it showed that over a 12-month consecutive time frame, out of the 69 patients with a diagnosis (according to the International Classification of Disease 9th edition) of delirium in the DR, negative associations found in other studies of delirious patients were minimized. No physical restraints were used and only 29% of the patients received new orders for medications considered to be pharmacological restraints (haloperidol, risperidone, or lorazepam), all at total

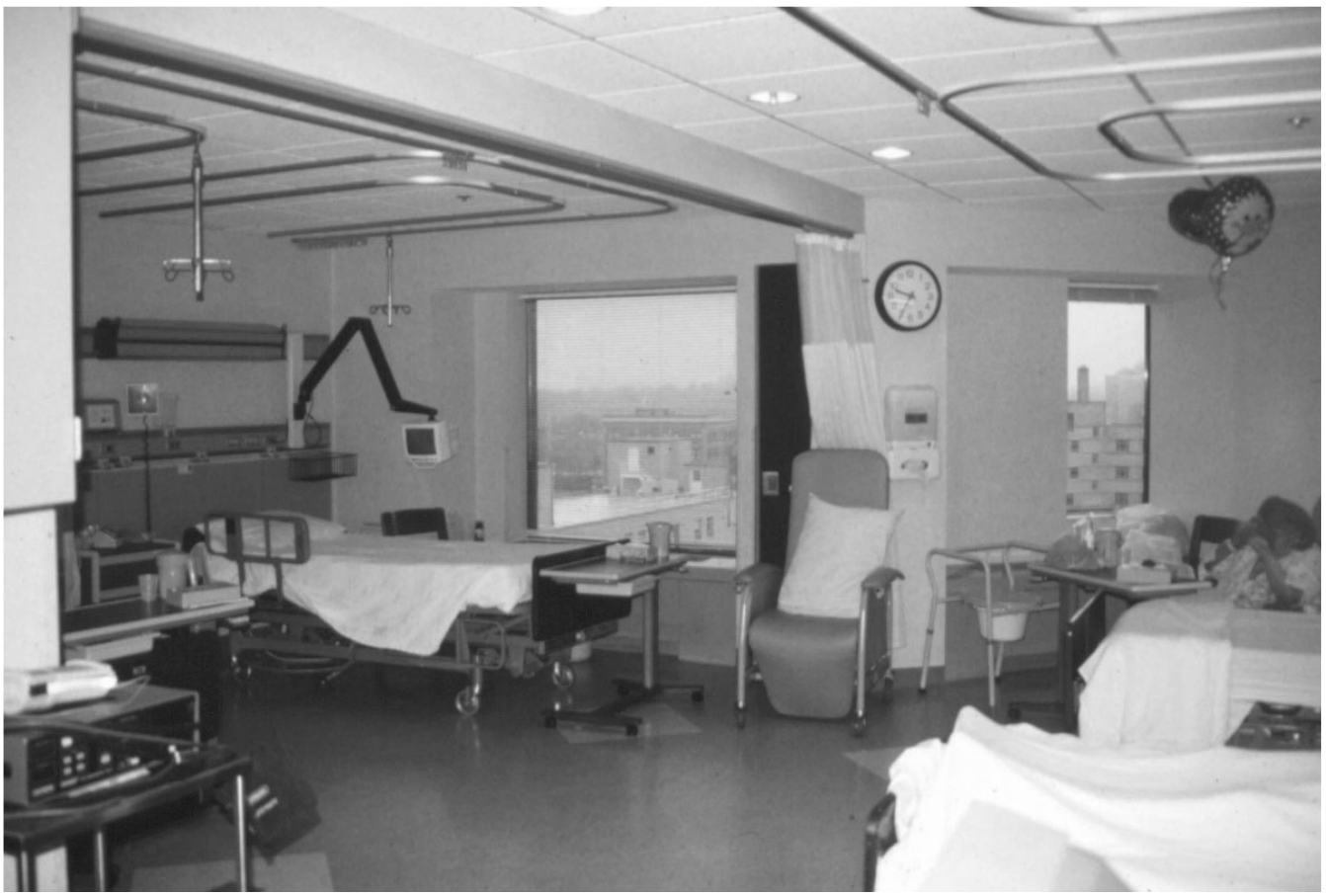

Figure 1 The Delirium Room, Saint Louis University Hospital, 1998

daily doses of less than 2.0 mg. Only 13% of the patients lost physical function and none of the 69 patients died during their stay in the hospital. Mean length of stay for these patients was not significantly different compared to the length of stay for all other patients over the age of 70 during the same time frame (Flaherty *et al.*, 2003).

The above studies have been highlighted because of their positive results. However, not all interventions have been successful. A thorough review of evidence concerning delirium management in the hospital setting by Boustani and colleagues looked at controlled clinical trials that used any intervention aimed at delirium among populations over the age of 55. They found 23 studies that met the inclusion criteria. Seven of the trials were among older hospitalized patients for medical conditions, eight trials among older hospitalized patients for surgical repair of hip fracture, six trials among older cardiac surgery patients, one trial for patients after bilateral knee replacement and one trial following gastrointestinal procedures. Most trials showed a lack of efficacy in reducing the severity or duration of delirium after its onset. However, overall, 86% of interdisciplinary team-based trials and 29% of nurse-based trials showed positive impact on delirium management (Boustani *et al.*, 2004).

The take-home message for delirium is that although this is a difficult problem to prevent, or manage when unpreventable, it can be done usually through a multicomponent intervention. No single simple intervention is likely to succeed, and it is not possible to tease out which of the multiple components are having an effect and which are the detractors. Nonetheless, multicomponent interventions still need to be considered as the standard of care because a "complex mutifactorial problem such as delirium is unlikely to respond consistently to a single approach (Inouye, 2001)".

PHYSICAL RESTRAINTS

Physical restraints should not be used for patients who are at risk of developing delirium or who have already developed delirium (*see* **Chapter 142, Restraints and Immobility**). In one study, physical restraints had the highest relative risk of five independent precipitating factors for delirium (Inouye and Charpentier, 1996), and another study found that physical restraints were significantly related to severity of delirium (McCusker *et al.*, 2001). Furthermore, the proposed reason for the use of physical restraints among delirious patients, to prevent injury primarily related to falls, is misconceived. Of three studies of restraint reduction programs in long-term care institutions, two showed no change in fall rate and one showed an increase in fall rate. However, all three studies showed a decrease in fall injury rates (Neufeld *et al.*, 1999; Capezuti *et al.*, 1998; Dunn, 2001). Of two studies in the hospital setting, restraint reduction was not associated with an increase in falls (Powell *et al.*, 1989; Mion *et al.*, 2001). The rate of restraint use in the study by Powell *et al.* (1989) went from 52 per 1000 patient-days to just 0.3 per 1000 patient-days. Although neither study reported injury rates before and after restraint reduction, the study by Mion and colleagues reported that injury rates after the restraint reduction program were low. Importantly, they were modestly successful ($\geq$20% reduction) in two of six intensive care units in restraint reduction and reported that no deaths occurred as a result of a fall or disruption in therapy, including in the case of intensive care unit patients on mechanical ventilators (Powell *et al.*, 1989; Mion *et al.*, 2001).

Furthermore, the fact that restraint-free environments can be achieved, as in some geriatric departments in European hospitals (De Vries *et al.*, 2004), ACE Units in United States hospitals (Flaherty *et al.*, 2003) and some nursing facilities (Gatz, 2000; Makowski *et al.*, 2000), adds to the evidence that restraint free care should be the standard of care.

PHARMACOLOGICAL RESTRAINTS

Currently, no antipsychotic or other pharmacological agent is approved by the US Food and Drug Administration (FDA) for the treatment of delirium. On the basis of the available data concerning medications used in the management of delirium and the commonly accepted reason to use them (for patients whose behavior interrupts the necessary medical care or puts themselves or others at risk of physical harm) (McNicoll and Inouye, 2004), antipsychotics should be considered a form of restraint until further evidence shows otherwise.

Delirium is not analogous to psychosis. In patients with schizophrenia, antipsychotics can improve behavior and function, with sedation being a common side effect. In patients with delirium, antipsychotics have not been shown to do this. It is argued that they control behavior, but it is unclear whether this is through the sedation effects of the drugs or their effect on the neurotransmitters thought to play a role in delirium. To further complicate matters for older persons, one of the main problems with antipsychotic drugs, whether atypical or typical, is that they are not pure in their mechanism of action. For example, although risperidone primarily affects serotonergic (5-HT_2A) receptors, it affects to some extent dopaminergic and alpha-1 receptors. Olanzapine, although it affects the 5-HT_2A receptors, similar to risperidone, its sedation properties are probably due to its effect on the histaminic receptors. Clozapine also affects histaminic as well as muscarinic receptors, and quetiapine has varying effects on histaminic and α-1 receptors and also has a small affect on dopaminergic and 5-HT receptors (Tandon *et al.*, 1999).

The available data for the use of antipsychotics in the management of delirium are poor because of the populations studied, types of studies done, or the presence of the common mistake of not including a placebo group in order to measure the natural course (duration) of delirium without pharmacological intervention. One randomized trial (Breitbart *et al.*, 1996) that is often referenced in review articles (Meagher, 2001; Burns *et al.*, 2004) condoning the use of antipsychotic medications compared haloperidol, chlorpromazine, and lorazepam in 30 delirious hospitalized patients with

AIDS, whose mean age was 39.2 years (range 23–56 years). Although the study by Nakamura *et al.* (1997) comparing haloperidol and mianserin included 60 patients with a mean age of 65 years, they did not have a control group either. Thus, when they reported improvement on a delirium rating scale at 1 week, one questions whether or not patients would have improved by this time anyway. Newer studies with atypical antipsychotics are also wrought with this error of not taking into account the duration of delirium without medication. One case report study using risperidone claims that the delirium cleared by day 14 (Sipahimalani and Masand, 1997). A prospective study of 64 patients with delirium who received risperidone reported improvement at day seven (Parellada *et al.*, 2004). Olanzapine was evaluated in a retrospective study of 11 delirious patients compared to 11 others who received haloperidol. It took 6.8 days and 7.2 days respectively for the peak clinical response (Sipahimalani and Masand, 1998). A case report of delirium due to olanzapine has been reported (Samuels and Fang, 2004).

The proper dosages of antipsychotics have also never been established. One recent text recommends that if severe agitation is present, haloperidol doses of 0.25–1.0 mg can be used as often as every 20–30 minutes with a maximum 24-hour dose of 3–5 mg. This dose is recommended because D2-dopaminergic receptors are saturated at low doses, and thus theoretically, doses above 5 mg over a 24-hour period are likely to only increase adverse events without providing additional clinical benefit. The goal should be an awake patient who is manageable, not a sedated patient, and the drug should be tapered and discontinued as soon as possible (McNicoll and Inouye, 2004). A recent study of mostly surgical delirious ICU patients, with an average age of 65 years, compared haloperidol and olanzapine. For patients over 60 years, haloperidol was initiated at 0.5–1.0 mg and olanzapine at 2.5 mg every eight hours. Younger patients were initiated at doses of 2.5–5.0 mg and 5 mg, respectively. The Delirium Index (measure of severity) decreased over time and clinical improvement was the same in both groups. The study did not detail what percentage of patients were mechanically ventilated (Skrobik *et al.*, 2004).

It is evident from the lack of evidence that randomized placebo controlled trials are needed. It should be noted that in a randomized controlled trial of a nonpharmacological intervention to prevent delirium, Inouye and colleagues found that even in the control group patients who developed delirium, the average total number of days of delirium was approximately 2.5 (Inouye *et al.*, 1999a). Although this study does not go into detail about the percent of delirious patients who received antipsychotics, or the dose, another study mentioned above (Flaherty *et al.*, 2003), found that only 29% of 69 delirious patients received any form of pharmacological restraint (antipsychotics, benzodiazepines, sedative/hypnotic), and this group had an average length of stay in hospital less than five days.

On the basis of the available current data the following conclusions can be made:

1. There is not enough evidence for the routine use of antipsychotic or other pharmacological approaches in the management of delirium.
2. On the basis of general geriatric principles, nonpharmacologic interventions that have no or less risk should be tried before any pharmacological approach is tried.
3. If pharmacological agents are used, the lowest possible dose should be tried first, keeping in mind the goal that is intended (manageable and awake, not over sedated).
4. On the basis of the very limited data, the category of drug of choice seems to be antipsychotics, not benzodiazepines or sedative-hypnotics.

KEY POINTS

- Delirium is common among older persons in the hospital, especially in surgical patients and patients in the intensive care unit (ICU), and in postacute-care settings, but not so common among patients with acute illnesses cared for at home.
- Delirium is a dangerous diagnosis and has been found to be associated with hospital complications, loss of physical function, increased length of stay in the hospital and ICU, increased incidence of discharge from the hospital to a long-term care facility, and even higher mortality.
- The comprehensive approach to delirium involves awareness, diagnosis, evaluation, prevention, and management. The causes of delirium can be remembered using the two mnemonics D-E-L-I-R-I-U-M-S and A-C-U-T-E C-H-A-N-G-E I-N M-S.
- Successful prevention and management interventions include a multicomponent intervention with protocols targeting risk factors to prevent the development of delirium, a geriatric consultation service for patients with hip fracture, and a specialized four-bed room to provide 24-hour nursing care, called *the Delirium Room*.
- Physical restraints should not be used in patients with delirium, and rarely should pharmacological restraints be used.

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Memory Clinics

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INTRODUCTION

Clinics specifically for the diagnosis and management of early dementia were first developed in the United States in the late 1970s. These were primarily research-based, linked to developing Alzheimer's disease (AD) and aging research centers and acted as a focus for expert assessment, investigation, treatment, and advice (Knopman *et al.*, 1985; Larrabee *et al.*, 1990). Initially described as "dementia clinics", the terminology soon changed to the more acceptable name of "memory clinic", or "memory disorders clinic". While the new title is less stigmatizing, it runs the risk of serving as a euphemism, avoiding an open and honest approach to the reality of dementia.

Predominantly service-oriented memory clinics were set up in the United Kingdom in the early 1980s (Bayer *et al.*, 1987; Van der Cammen *et al.*, 1987; Philpot and Levy, 1987), offering multidisciplinary, outpatient-based assessment and diagnosis for mainly older people with memory and other cognitive problems, in an acceptable and accessible environment. At first, many of these clinics were funded from outside the National Health Service and were based mainly in university departments of geriatric medicine or old age psychiatry. Existing services tended to consider memory clinics to be a luxury, allowing academics to indulge their narrow clinical interests away from the reality of budgetary considerations and the priorities of practical dementia care. However, this reflected the concentration of service provision on dealing with the behavioral and psychological symptoms of advanced dementia and on crisis intervention and institutional-based management. The first memory clinics played an important role in raising awareness of the value of elective intervention and interdisciplinary care for people with early dementia and acted as a focus for development of specialist knowledge and expertise in early diagnosis and management of people presenting with cognitive impairment.

Most of the early UK clinics were also very actively involved in research, especially recruiting into clinical trials of the emerging antidementia drugs. Largely thanks to the work of these centers, specific drug treatment for AD became available in the late 1990s and the focus of activity shifted toward provision of an effective clinical service for patients presenting with memory disturbances and best use of medication, together with psychosocial interventions and patient and carer support and education (Wilcock *et al.*, 1999). The evolution of hospital-based memory clinics into more community-based memory teams was the natural consequence, working alongside or as an independent part of traditional mental health teams for older people.

In 1993, a survey identified 20 active memory clinics in the British Isles (Wright and Lindesay, 1995), but considered them to be too academic and isolated from mainstream practice and also ill-equipped to provide for care after diagnosis. However, a follow-up survey just a few years later (Lindesay *et al.*, 2002) identified at least 58 active clinics and noted that the newer clinics were tending to be smaller, less academic and less involved in research than the more established clinics. In 2001, the UK government published two important documents. The National Institute of Clinical Excellence (NICE) guidance on use of drugs for treatment of AD (NICE, 2001) advocated the need for further development of memory clinics to support best use of the drugs and the National Service Framework (NSF) for Older People (Department of Health, 2001) recommended memory clinics as an essential component of hospital-based services.

While most clinics focus on diagnosis of mild cognitive impairment (MCI) and early dementia, others encompass all acquired cognitive disorders, including head injury and epilepsy (Kopelman and Crawford, 1996). A few specifically target people with purely subjective memory loss, or younger people with early-onset dementia, or people with learning disabilities (Hassiotis *et al.*, 2003). Many concentrate on diagnosis and assessment with a view to best use of available medication and those in academic centers continue to conduct a lot of research, including clinical trials of newer drug treatments. The emphasis on assessment for drug treatment and the powerful influence of the pharmaceutical industry

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has tended to detract from the importance of additional or alternative perspectives and the provision of a holistic, multiprofessional and multiagency approach to dementia care should be central to the activity of all clinics.

Referral may be open access (those willing to see all-comers), or restricted to secondary or tertiary referrals, or to selected individuals who meet predetermined criteria. In general, patients referred by their general practitioners (GPs) seem more likely to have dementia than self-referrals, though the reassurance given to those without organic disease (the "worried well") should not be underestimated. Some so-called memory clinics are merely rebranded old age psychiatry outpatient clinics, or community-based services solely monitoring antidementia drugs. Others are innovative service developments, for example, clinics providing memory-screening tests in shopping malls or mobile clinics and telemedicine to aid evaluation and treatment in patients' homes.

DEVELOPMENTS AROUND THE WORLD

Memory clinics are now a feature of health services for older people in centers around the world, but they exist in various forms and are variously based in neurology, psychiatry, or geriatric secondary care services; most involve multiprofessional assessment, often with everyone coming together to share results in a diagnostic consensus meeting. Despite the differing needs and varied settings, the fundamental similarity between memory clinics across the world is striking.

In Switzerland, there is a collaborative group of 11 memory clinics enabling an active program of education and training for health professionals and clinical research. The GP plays an important role in initial assessment before comprehensive diagnosis and treatment recommendations are made in the memory clinic, including memory training and caregiver support activities. There is also close involvement with the National Alzheimer's Association (Monsch *et al.*, 1998).

In France, memory clinics are well established as expert centers for early diagnosis and management of dementia and have an important educational and research role (Mahieux, 2000). The multidisciplinary day hospital has been proposed as the ideal setting for a memory clinic, though some experts have questioned whether a single specialist in charge of adjusting examinations and management to particular situations would be preferable to a routine multispecialty approach (Derouesne, 1997).

In Italy, the "Progetto Memoria" provided what was effectively a mobile memory clinic, bringing memory testing to communities in a bus (Zappala *et al.*, 1995). A national project has also seen the development of regional centers for the diagnosis and care of people with AD. In other Northern European countries, memory clinics have become the centers of a broader model of care, with preliminary home visits by a nurse and/or psychologist before clinic attendance, and further home visits afterwards to discuss assessment results and plan future management.

In the southern hemisphere, memory clinics providing multidisciplinary assessment and management for community-living people with dementia are developing in every continent, from Brazil and Mexico, to Hong Kong and Singapore, to South Africa and Australia. The memory clinics in Australia are amongst the longest established (Ames *et al.*, 1992) and have developed into a coordinated network of clinics across the state of Victoria (Cognitive, Dementia and Memory Services (CDAMS) Clinics). These have highlighted the importance of clinics being sensitive to the needs of people from a range of cultural and linguistic backgrounds (LoGiudice *et al.*, 2001), a challenge also being addressed in many North American clinics.

WHY THE NEED?

The worldwide growth in memory clinics has largely developed because of increasing demand and expectations of patients and families, frustrated by the difficulties of obtaining informed diagnosis and advice from existing services. They are not a replacement or alternative to these, but rather a more focused service providing a consistent approach to assessment, more specific diagnosis and a single resource for expert information and support (Table 1). Demographic changes are rapidly leading to greater numbers of patients with age-related cognitive disorders and there is appropriate reluctance to attribute forgetfulness merely to age. The growing awareness that memory failure is not inevitable and that effective intervention is available has lead to a desire for

Table 1 Potential benefits of memory clinics

Benefits for patients and families
- Nonstigmatizing, specialist resource
- Expert multidisciplinary assessment and diagnosis of cognitive disorders
- Ensures treatable conditions are not overlooked
- Early identification of dementia and intervention
- Antidementia drugs are effectively targeted, monitored, and stopped as appropriate
- Education and practical support for patients and carers
- Empowers people with dementia while they are still able to maintain control over their lives
- Provides advice on memory aids and memory training
- Opportunities for counseling and psychosocial management
- Continuing care in the community may reduce need for institutionalization
- Access to research studies

Benefits for service provision
- Addresses growing demand for specialist diagnosis and treatment
- Encourages earlier referral and multidisciplinary management
- Develops awareness of dementia in primary care
- Provides standardized assessment and diagnosis
- Gateway to services
- Efficient targeting and monitoring of scarce resources (including medication and psychosocial interventions)
- Expertise in legal and ethical issues
- Facilitates audit, planning, and evaluation of services
- Elective decisions may help to avoid crises in care
- Postponement of institutionalization may reduce costs
- Focus for professional education and research activity

comprehensive assessment, diagnosis, advice, and treatment to be provided by professionals with specific expertise.

In many areas, existing services for diagnosis and management of memory disorders have been inadequate, with no clear professional responsibility and a widespread lack of specialist expertise and experience. There is a growing appreciation of the complexity of the needs of these patients and that optimal assessment and management requires a multidisciplinary rather than a monodisciplinary approach (Verhey *et al.*, 1993; Bayer *et al.*, 1990).

Even in expert hands, assessment and management of mild cognitive disturbance is not always straightforward, with a difficult differential diagnosis ranging from the trivial to the very serious and from the easily reversible to the irreversible. Not all forgetful old people have dementia and not all demented old people have AD. Comprehensive assessment reduces the chances of inappropriate labeling. There is a multiplicity of available assessment tools and investigations and some informed selection need to be made, without access to the definitive diagnostic test of histopathology. Once a working diagnosis has been reached, there is also a wide spectrum of available medical, psychological, and social interventions that need to be tailored according to the requirements of the individual.

The availability of specific drug treatment for AD and some other dementias and the need to identify suitable patients and to monitor drug efficacy is the most obvious justification for early diagnosis. However, the emphasis on a medical model of care and the perceived influence of the pharmaceutical industry in driving forward the expansion of memory clinics has attracted criticism. Wider benefits of early recognition and intervention are now better appreciated (Moniz-Cook and Woods, 1997).

While reversible dementia is uncommon, nearly all patients will have problems that can be helped and appropriate intervention can be instigated at a stage when it is likely to be most effective. A positive diagnosis reduces the risk of inappropriate management and avoids wrong assumptions being made. It empowers people with dementia to become involved in decision-making while they are still able to do so. The opportunities for forward planning may improve the psychosocial health of carers and also help to lessen the risk of crises in care at a later stage. Certainly, a proactive approach is likely to be more efficient as well as more humane than one that is crisis-driven.

ARE THEY EFFECTIVE?

The rapid growth in memory clinics has occurred despite lack of specific evidence from randomized controlled trials about their effectiveness. However, there is much indirect evidence from numerous clinical trials of anticholinesterase drugs for AD supporting early diagnosis and treatment for dementia (Bullock, 2002) and evidence that psychosocial support and caregiver education can also improve outcomes (Moniz-Cook and Woods, 1997).

One randomized controlled trial by LoGiudice *et al.* (1999) has looked at the quality of life for carers of 50 community-dwelling patients with mild to moderate dementia, randomized to attend a memory clinic or act as a control group. Those carers attending the memory clinic were found to have significant improvement in psychosocial health-related quality of life, particularly in the domains of alertness behavior and social interaction, which was maintained at 12 months. However, there was no significant improvement in carer burden or knowledge of dementia.

Luce *et al.* (2001) compared consecutive referrals to the memory clinic in Newcastle upon Tyne with referrals to the traditional and well established old age psychiatry service in the same city. Memory clinic patients were younger, had lower levels of cognitive impairment and a wider range of diagnoses, with those diagnosed as having dementia being at least 2 years earlier in the course of the disease than those seen in the standard service. The authors concluded that memory clinics target a distinct patient group compared to traditional old age psychiatry services, identifying cases of dementia much earlier and having the potential to make valuable contributions to patient care in terms of access to treatments, services, and support networks, and in terms of obtaining information and preparing for the future.

Another British study in the more rural area of Dorset (Simpson *et al.*, 2004) compared consecutive new referrals to a memory clinic with consecutive new domiciliary requests within the same old age psychiatry service over the same period of time. The clinic patients had fewer behavioral and psychological symptoms of dementia, but were otherwise similar in demographic and clinical characteristics. Subsequently, they were less likely to have a psychotropic drug prescribed, but were more likely to have documented risk management, care planning and follow-up, with a trend toward fewer moves into residential care and psychiatric ward admissions.

Surveys of memory clinic users' opinions of their experiences are generally very positive. van Hout *et al.* (2001) used questionnaires with patients, relatives, and general practitioners to measure their perception of the quality of care of an outpatient memory clinic. Positive opinions were recorded on the way the results were communicated, the usefulness of the assessment and attitude of the clinicians. In contrast to GPs and relatives, patients were less positive about the clarity of the diagnostic information received, and both relatives and GPs were negative on information and advice given to relatives. A subsequent study by the same researchers highlighted the importance of providing information not only on issues considered relevant by clinicians, but also tailored to the individual needs of patients and carers (Verooij-Dassen *et al.*, 2003). An Australian study of GPs' satisfaction with services provided by memory clinics also found them to be positive about the completeness and utility of the assessment and diagnostic information provided, but relatively less satisfied with advice regarding the family's coping and community support services for the patient (Gardner *et al.*, 2004). It was considered that the service enhanced the capacity of

GPs to provide ongoing care to people with dementia, but that the establishment of firmer communication and collaborative protocols between the clinics and GPs would improve their usefulness.

THE MEMORY CLINIC TEAM

In order to provide a comprehensive service, memory clinics are characteristically multidisciplinary in nature, with a number of different professionals, each offering a particular expertise. Involvement is often based less on possession of any specific subspecialist qualification than on interest and knowledge. In some centers, the medical input may be from a geriatrician, in others from a neurologist, and in others from a psychiatrist. Ideally, there should be all three specialties involved. The other constant member of the memory clinic team tends to be a psychologist, not just to carry out neuropsychological assessment to aid diagnosis and management, but also to advise on and to undertake psychosocial interventions with both patient and family. Another invaluable team member is a specialist nurse, who can help with both the medical and psychological assessment and management. This can be carried out beyond the physical confines of the clinic, facilitating and reinforcing the process in the patient's own environment. Finally, dedicated administrative help is essential, not only to ensure the efficient running of the clinic, but also to cope with the forgetful patients who phone repeatedly to check the time of their appointments.

Beyond these core team members, there needs to be easy access to other professionals, such as speech and language therapists, occupational therapists and social workers. Increasingly, there is also a need for someone competent to provide genetic counseling and advice to worried relatives. Developments in drug therapy suggest an important potential role for the pharmacist and newer diagnostic techniques may require greater involvement of radiologists and neurophysiologists. Volunteers and support workers from the local Alzheimer's Society are becoming closely associated with some clinics, providing additional practical support and counseling to newly diagnosed patients and their families.

The optimum size of the team is likely to be between four and seven, united by a common feeling of direction and purpose. While each member should be able to identify the specific and general contribution they can make, a flexible working style which crosses conventional professional boundaries will provide greatest job satisfaction and most effective care for patients.

As in other aspects of geriatric practice, getting the multidisciplinary team to work effectively is essential for the smooth running of the clinic. Good teamwork takes time to develop and whoever is the team leader (usually the senior physician or psychiatrist) needs to strike a balance between overstructuring clinic activities and allowing individuals to function totally independently. The team will not work effectively when one particular professional (or profession) considers the guarding of their perceived area of expertise as a priority, setting up artificial borders which others fear to cross. A belief in the importance of professional hierarchies, concerns over territory and differences in terminology will act as barriers to effective care delivery and can lead to wasteful duplication of effort and apparently contradictory management advice. Individual members should be encouraged to view the value of their contribution as depending on the functioning of the whole team.

WHAT HAPPENS IN A MEMORY CLINIC?

There would seem to be general agreement that a memory clinic can provide in one setting all the essential components of comprehensive assessment leading to diagnosis for older people presenting with memory problems. The assessment will include full history and medical examination, detailed neuropsychological and neurobehavioral assessment, and appropriate laboratory tests and neuroimaging (Knopman *et al.*, 2001). Some clinics have a totally standardized approach, where everyone gets everything, while others will tailor the assessments to what is specifically indicated and what has not been done before. While some clinics will restrict themselves to a one-off evaluation, confirming a diagnosis and perhaps recommending an appropriate intervention, others will aim to provide ongoing support and more comprehensive management. Certainly, diagnosis divorced from effective intervention is likely to be unsatisfactory for all.

Clinics should be held close to the community they serve. Holding them away from the stigmatizing settings of geriatric or psychiatric hospitals will help to encourage referral and attendance. Remembering to keep appointments is an obvious problem for this client group and sending reminders a few days before and asking people to confirm that they will be coming will help to reduce nonattendance. Forewarning people about how long the assessment will take is advisable. While in some clinics assessments take all day, moving from one professional to another, many patients find this tiring and cannot cooperate fully. Some psychometric tests need to be repeated at a set interval, so initial assessment will require more than one visit. Certainly, given the gravity of the potential diagnoses, a case can be made for all patients to be tested on at least two occasions a few weeks apart. We have found that a maximum of 60–90 minutes a visit (of which 30 minutes may be taken up with cognitive testing) is optimum.

Patients should be asked to come with someone who knows them well and can provide corroborative background. The presence of a close relative or carer will also help to ensure that advice and information provided in the clinic is acted upon. Ideally, there need to be two clinic rooms, allowing opportunity for patient and informant to talk separately to different team members.

History and Medical Examination

The essential first step in clinic assessment must be to obtain a detailed and accurate history. Cognitive impairment in elderly patients is often unrecognized. A patient who superficially appears alert, pleasant and cooperative, and denies any significant symptoms is too often assumed to have no problems and mild dementia is easily overlooked. Establishing the reason for referral is a good place to start.

The onset and duration of symptoms is crucial and claims that difficulties date from some seemingly relevant event such as an accident, bereavement, or hospital admission must not be accepted unquestioningly. Often, a sudden change in circumstances merely draws attention for the first time to preexisting problems. Changes in role are often of significance and questions should be asked about loss of competence in everyday skills and activities (e.g. driving, traveling away from home, handling correspondence and finances, taking medication regularly). The nature and progress of any changes should be established.

It is essential to take a history from both the patient and from a carer or friend (a neighbor may be of more value than an uninvolved relative) and specific examples of practical difficulties should be elicited. Associated mood disturbances, personality change, and behavioral difficulties must be sought. Specific questions should be asked about delusions and hallucinations. Present and past consumption of alcohol, use of prescribed and nonprescribed drugs, and the patient's general medical condition need to be established. A family history may give pointers to the diagnosis and sometimes explains a patient's excessive concern or apprehension. Much useful information is often available in previous medical records.

The Cambridge Mental Disorder of the Elderly Examination (CAMDEX) (Roth *et al.*, 1986) attempts to standardize the clinical information gathered in the course of a diagnostic interview with history being obtained from both the patient and a relative. Some details are therefore duplicated, but it serves as a useful starting place for those less confident in eliciting all the relevant issues. Questionnaires, such as an informant questionnaire on cognitive decline in the elderly (IQCODE) (Jorm and Jacomb, 1989), can be completed by relatives before clinic attendance as an aid to establishing their report of changes in everyday cognitive function compared with 10 years before. Numerous other assessment scales, for example, of neuropsychiatric symptoms, depression, activities of daily living, quality of life, and carer burden, are available (Burns *et al.*, 1999) and can be incorporated into clinic practice. They are valuable as an objective basis for documenting change and as a source of data for audit and research.

A medical examination, with particular attention to the cardiovascular system, central nervous system and special senses (eyes and ears) is also required. This may help to elucidate the cause of the memory problems, may identify physical consequences of the condition (poor nutrition, neglected personal hygiene, signs of physical abuse), or may identify coexisting morbidities. Focal neurological signs will suggest vascular disease or a space-occupying lesion, and extrapyramidal signs will raise the possibility of Parkinson's disease or dementia with Lewy bodies (DLB). Primitive reflexes (e.g. palmo-mental, grasp, pout, rooting) are common in most forms of dementia, though not always easy to elicit. Myoclonus may be seen in prion disease, Huntington's disease, and early-onset AD, and muscle fasciculation may suggest motor neurone disease associated with frontotemporal dementia (FTD).

Cognitive Assessment

Following the history, an objective assessment of cognitive functioning is required. This will aim at establishing strengths and weaknesses of a variety of functions relative to a standardized, norm-referenced scoring system. In this way the nature and extent of cognitive deficits can be determined, informing diagnosis and management, and acting as a comparator for past and future assessments. Ideally an experienced psychologist should undertake testing, though much useful information can still be obtained by any suitably trained professional, using screening tests such as the mini-mental state examination (MMSE) and clock face drawing. This combination was shown to be an easily administered, nonthreatening, and highly sensitive screening test for dementia in a memory clinic population (Schramm *et al.*, 2002). As most of these tests are designed for detecting cortical rather than subcortical deficits, they should be supplemented by a simple measure of executive function, such as verbal fluency or proverb interpretation. When possible, assessment should be made of premorbid intellectual status, to assist in the satisfactory interpretation of other test scores. Tests must also be appropriately selected to take account of limitations imposed by deficits such as language impairment and dyspraxia. For example, recognition memory tests may reduce the demand on expressive language, normally required in recall-memory tests. A standardized measure of mood is also desirable.

There is a very wide choice of psychometric tests suitable for use with memory clinic patients and choice will be governed by the main purpose of the examination and the time available, as well as personal preference and experience. Computer-based assessment of cognitive function is becoming more available and has the advantage of being sensitive to small changes in performance and allowing detailed assessment of attention and motor responses. At present, its use is still mainly confined to research settings. An outline of the assessments used routinely in the Cardiff memory clinics is shown in Table 2.

Whatever tests are chosen, they must be acceptable to the person being tested, and with no content that belittles their adult status. Consent to the assessment procedure needs to be obtained and the tester should spend some time in explanation of the purpose of specific tests, and be competent to answer queries regarding their usefulness and acceptability. Sensory and physical limitations should be accommodated as

Table 2 Cognitive tests used routinely in the memory clinics in Cardiff

- National Adult Reading Test (NART)
- Mini-mental State Examination (MMSE)
- Middlesex Elderly Assessment of Mental State (MEAMS)
- Story Recall (immediate and delayed)
- Irving Names Learning Test (NLT)
- Kendrick Object Learning Test (KOLT)
- Kendrick Digit Copying Test (DCT)
- Frontal Assessment Battery (FAB)
- Verbal Fluency (Animals and FAS)
- Trailmaking Task
- Graded Naming Test
- Clock drawing

much as possible, by the provision of adequate lighting, additional specialist earphone amplifiers, suitable seating, and minimum distractions. During testing, realistic reassurance should be provided, with feedback phrased positively to highlight strengths as much as weaknesses. At the end of testing, patients should be given an opportunity to make their own observations on their performance.

Observations of the person's concentration, cooperation, anxiety, and motivation during assessment should be carefully weighed against performance. The approach of the patient to each test and his or her satisfaction with the outcome is often as revealing as the particular score obtained. Results should be considered in the context of the patient's previous education and experience, their age and presence of sensory impairments and comorbidity, and diagnostic cutoffs for each score treated as guides rather than absolutes. In particular, a "normal" score does not exclude the possibility of significant problems, including dementia. In such cases, more detailed testing will often reveal minor detriments in a range of tests, which are inconsistent with the patient's expected level of functioning. It is nearly always desirable, and sometimes essential, for assessment to be repeated at a future date in order to detect any progressive deterioration. Longitudinal follow-up increases the accuracy of diagnosis, particularly in mild dementia.

Laboratory Tests

A routine screening battery of laboratory tests will be indicated in most patients when first seen (van Crevel *et al.*, 1999). These should include a full blood count, urea and electrolytes, liver function tests, calcium and phosphate, random blood glucose, thyroid function, and vitamin B12 and folate. A more extensive range of tests may be indicated in younger people with dementia and in those with atypical presentations or signs and evidence of systemic illness. These might include plasma viscosity or C-reactive protein and autoantibodies for inflammatory disease and tumor markers for malignancy and paraneoplastic syndromes. Syphilis serology is now less commonly carried out as a routine, but still needs to be considered. Genetic testing, for example, for apolipoprotein genotype, is not yet diagnostically useful, but may be rarely indicated when familial dementia is suspected. It should only be undertaken after appropriate counseling, preferably in collaboration with a specialist genetics service.

An electrocardiogram is desirable in any patient with possible vascular disease and in patients with a bradycardia or history of dysrhythmia who are being considered for AChE drug treatment. An electroencephalogram may be useful in suspected encephalitis, metabolic encephalopathy, seizures, or prion disease and in confirming the presence or absence of delirium, in which it is almost always abnormal. Lumbar puncture for examination of cerebrospinal fluid is not widely used, though it is useful in patients with suspected infectious, inflammatory, autoimmune or demyelinating disease. In normal pressure hydrocephalus (NPH), it may help in predicting the suitability for surgery. Rarely, nerve conduction studies may help to diagnose FTD associated with motor neurone disease, muscle biopsy may be useful in mitochondrial disorders and even cerebral biopsy may be justified in suspected primary cerebral vasculitis.

Neuroimaging

The role of neuroimaging in the routine management of memory clinic patients is still debated. Certainly neuroimaging no longer merely fulfils the negative role of excluding "treatable" conditions that mimic or cause dementia, but can positively contribute to differential diagnosis and provide useful prognostic information. Depending on availability, computed tomography (CT), magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT) may all contribute to clinical care. Various other techniques are available in research centers.

Recent diagnostic guidelines suggest that at least one structural CT or MRI examination should be made over the course of a dementing illness to rule out space-occupying or vascular lesions, and that SPECT (or PET) should be used in cases of significant diagnostic uncertainty. In practice, it may not be possible to perform neuroimaging in every memory clinic patient with suspected dementia. Indications for scanning have therefore been proposed, including presence of focal neurological signs, recent onset of epileptic fits or recent head injury, any suspicion of intracranial tumor, including raised intracranial pressure, or evidence of a source for metastases outside the brain, any suspicion of NPH and any suspicion of stroke disease. However, the clinical utility of such clinical predictors to select memory clinic patients most likely to benefit from neuroimaging has not been demonstrated (Condefer *et al.*, 2003).

Imaging with CT is probably the radiological investigation most used in memory clinic patients, owing to its wide availability. It can show good detail of the brain structure and is especially useful in identifying dementia due to space-occupying lesions, hydrocephalus or large cerebral infarcts. Smaller lacunar infarcts are less easily seen and absence of infarcts does not exclude the possibility of vascular disease. Generalized and localized cortical atrophy is a common

finding in older patients, not necessarily associated with clinically abnormal brain function. Some patients with AD will have a normal scan. Nevertheless, the presence of atrophy is useful supportive evidence of degenerative brain disease. Overall, CT may be expected to impact on diagnosis and treatment in about 1 in 8 of dementia cases.

The use of magnetic resonance imaging is less widely available, less tolerated by patients, and more expensive than CT. However, contrast sensitivity and spatial resolution is better, even without use of contrast agents and it does not suffer from bone artefacts. Evidence of generalized atrophy is no more diagnostically useful than with CT, but measurement of the size of the hippocampus and entorhinal cortex plays an important role not only in diagnosis of AD, but also in identifying patients with mild cognitive impairment who are at risk of progressing to dementia. Smaller infarcts can be seen more clearly than with CT, and MRI has the potential to detect focal signal abnormalities that may assist the clinical differentiation between AD and vascular dementia (VaD). Severe temporal lobe atrophy and hyperintensities involving the hippocampal or insular cortex are more frequently noted in AD. Basal ganglionic/thalamic hyperintense foci, thromboembolic infarctions, confluent white matter, and irregular periventricular hyperintensities (leukoencephalopathy) are more common in VaD. Leukoencephalopathy involving at least 25% of the total white matter must be present to diagnose small vessel cerebrovascular disease.

Functional imaging using SPECT allows regional cerebral blood flow to be visualized and quantified. In established AD there is a reduction of flow in mainly temporoparietal regions, though this finding is inconsistent in the early stage of the disease when diagnosis is most problematic. In FTD, SPECT shows diminished perfusion anteriorly. In VaD, multiple focal deficits may be seen.

WHAT INTERVENTIONS CAN BE OFFERED?

At the very least, patients assessed in memory clinics should receive an informed discussion of their diagnosis and prognosis, with arrangements made for ongoing review, support, and management. In a few patients, there will be a reversible cause for their symptoms (e.g. medication side effects, hypothyroidism, vitamin B12 deficiency, cerebral vasculitis, Wernicke–Korsakoff's syndrome) which will respond to specific treatment. The proportion of patients with reversible dementia is probably less than 4%, but concurrent medical conditions causing mild cognitive disturbances are much more common and are potentially treatable (Hejl *et al.*, 2002). Depression, whether primary or secondary, is especially deserving of energetic treatment, generally using a selective serotonin reuptake inhibitor (SSRI) that is free of cognitive side effects. Even in patients with established dementia, appropriate medical intervention may help cognition and slow progression of the disease. Control of vascular risk factors may favorably influence the clinical course of degenerative as well as vascular cognitive impairment. Timely use of specific drug treatments for AD and probably VaD and DLB will give significant benefit to a majority of patients taking them.

Certainly, all patients with cognitive difficulties and their carers will benefit from informed discussion about their problems. Advice can be given on the appropriate use of memory aids, memory training, and specific psychological interventions for patients and families. Financial and legal advice will usually be appropriate and practical suggestions to help with problems of daily living and safety concerns, particularly the advisability of continued driving. Issues surrounding advanced directives are attracting growing attention. Meeting the needs of carers is also important, by providing information, individual counseling, access to support groups, and respite care through contact with local Alzheimer's organizations and relevant community services.

Diagnostic Disclosure and Meeting Information Needs

Most advocates for people with dementia and their carers now believe that, in most cases, patients should be told what is wrong with them, what the implications are, what can be done for them and what treatment is likely to involve. Breaking the news in a timely and tactful manner is an important role for memory clinic staff. Reactions of AD patients to being told their diagnosis include relief (as the diagnosis provides an explanation for their difficulties), disbelief (as they may lack insight and do not feel ill), loss (grieving for failing intellectual abilities and limitations in the future) and fear of becoming a burden. All these can be satisfactorily addressed.

Practice of diagnosis disclosure amongst specialists is changing (Gilliard and Gwilliam, 1996). In the 1990s, less than one-third of old age psychiatrists and geriatricians "usually told" people with mild dementia their diagnosis, whereas recent studies report that a majority of specialists now regularly disclose diagnosis. However, a recent survey of carers of people with AD or other dementia in 11 European countries found that in 46% of cases, diagnosis had been disclosed to the family only and not to the patient, 46% of carers found information provided to them was insufficient and 29% subsequently had no regular contact with any health professional (OPDAL, 2003).

Memory clinic patients should be given the opportunity to learn as much or as little as they want to know about their condition, with information provided in a sensitive and measured way (Table 3). Patients and carers both have individual needs and each should be addressed separately. As well as clearly describing diagnosis, specific attention should be given to comprehensible and practical information about coping strategies, care services, likely course of the disease and treatment, specific drug treatment and follow-up. Wald *et al.* (2003) has proposed the "rule of threes" for information provision to carers of people with dementia. At diagnosis, they want information about what dementia is, medications available, and behavioral and psychiatric

Table 3 Recommendations for telling a diagnosis of dementia to patients and family (OPDAL, 2003)

- Communication of the diagnosis should ordinarily occur in a joint meeting with patient and family
- Use simple language. Avoid technical jargon that may conceal the truth
- Use a graded approach which is patient led and allows the information given to be matched to what the patient wants to know
- Allow sufficient time to explain and to answer questions from the patient and family
- Assess the patient's and the family's understanding and arrange follow-up (to reinforce information provided, clarify misunderstandings, and answer questions that are outstanding)
- Use the term "Alzheimer's disease" (or other appropriate medical diagnosis) rather than just dementia and ensure that they understand the sense of both terms
- Mellow the bad news with the possibility of therapeutic approaches (not just drugs). Avoid conveying the feeling that "nothing more can be done"
- Make it clear that a reorganized family network can alleviate burden and maintain quality of life
- Inform the patient about the possibility to take decisions about his/her future

symptoms of dementia. In an early follow-up appointment they want information about services, the course of the illness and what to do in a crisis. In a later follow-up appointment they want information about support groups, benefits and financial and legal issues. At a later stage, they want information about psychological therapies, the effects of the illness on carers and complementary therapies.

Information giving is not only a medical responsibility. All members of the multidisciplinary team should consider every therapeutic encounter to be an opportunity for education and information provision. Dedicated time should be put aside during every memory clinic consultation for information provision – it should never be merely an after-thought at the end of the assessment. Verbal information should be backed up by written information, with recommendations for further reading. Increasingly, people are turning to the Internet for more detailed information and trustworthy websites should be recommended to those interested. Mention should be made of local support group and meetings and contact details of local Alzheimer support organizations. A telephone contact number for information and advice is always appreciated and unlikely to be abused.

Memory Aids

The most simple and effective methods of helping patients with cognitive difficulties are the establishment of regular routines, the careful organization of daily activities, and the use of environmental cues and external memory aids. None of these require the patient to learn new strategies of thinking or remembering and may thus be potentially useful in those with even moderately severe dementia. Written aids such as diaries, checklists and carefully positioned notes as reminders are often of benefit and reusable sticky note pads are ideal for sticking in conspicuous places. Labeling or color coding of switches and doors may sometimes be helpful. A timer, or digital alarm watch, may act as a reminder to take medication, to attend to cooking or other household tasks, or to refer to an appointments diary for guidance as to planned activities. In the kitchen, use of a microwave cooker may avoid food being incinerated in a conventional oven, red warning lights on electrical appliances may help to remind when they are on, and use of kettles that whistle may ensure that a planned cup of tea is made and prevent open pans boiling dry. More sophisticated electronic devices and programmable organizers are generally too unfamiliar to the present generation of older people to prove useful, but assistive technology that does not require the person to operate it is attracting much interest.

Memory Training

The idea of cognitive training as a method of improving, retaining, or regaining skills is attractive to those worried about memory loss and to relatives who hope that developing problems might be minimized. Recent evidence suggesting that education and continued intellectual activity may reduce the risk of developing AD has further increased interest in this area.

Experience of formal training programs designed to improve the cognitive skills of healthy elderly subjects and those with cognitive deficits is limited (Clare *et al.*, 2003; De Vreese *et al.*, 2001). Those most likely to gain appear to be well-motivated, healthy individuals wishing to conserve their mental faculties as a prophylactic measure. There is little evidence of sustained benefit or generalizability in those with established dementia and regular tests and "exercises" for the memory can easily become counterproductive. Positive benefits to patients may even be at the cost of increased distress to carers.

Specific approaches have included relaxation techniques, organization of material (e.g. with the use of categorization, associative cues, and mnemonics), regular and repeated practice sessions, using spaced retrieval to rehearse information, techniques for improving visual imagery (e.g. pegword methods, face-name association etc.), and verbal strategies (rhymes, first letter cueing, alphabet searching etc.). Computer-aided cognitive training is also being developed. Reactivating therapy, including manual and creative activities, self-management skills and orientation tasks, has been claimed to improve cognitive performance and psychosocial functioning of people with mild dementia. Training in groups with other people with memory impairment or with family members and carers may provide opportunities to harness a wider range of training resources and facilitate expression of mutual support. Another approach is to involve family members in providing the cognitive training at home.

Drug Treatments

Nearly all clinics would now see themselves as central to the effective prescribing of specific antidementia drug treatments. Careful initial assessment and diagnosis is essential

before any pharmacological intervention is considered and the impact of treatment and the indication for its continuing use must be kept under regular review. The size of any drug effect that can be considered worthwhile is open to debate. Statistically significant improvement on psychometric tests does not necessarily equate with meaningful change in quality of life and a noticeable improvement or stabilization is more important than change in test score. Patients and carers tend to be more positive than professionals when assessing apparently small benefits of treatment, with three quarters believing that halting progression of symptoms of early dementia for about six months justifies intervention. Such modest effect would seem comparable to that achieved by the drugs now available (Bullock, 2002).

The acetylcholinesterase inhibitor (AChEI) drugs have become the mainstay of treatment for AD, and may also have benefits in VaD and DLB. They act by inhibiting the breakdown of acetylcholine within the synapse, increasing its availability to muscarinic and nicotinic receptors. In mild to moderate AD, the available AChEI (donepezil, rivastigmine, and galantamine) have all been shown to be statistically better than treatment with placebo, with improvements in cognition, ADL and overall clinical global impression and with positive effect on aspects of behavior such as apathy, anxiety, hallucinations, and agitation. There is also evidence of efficacy in more severe AD and suggestion of potential savings in health-care costs, carer time and burden, and delay in need for permanent institutional care. All AChEIs have qualitatively similar cholinergic adverse effects, including nausea, vomiting, diarrhea, fatigue, and dizziness. These are generally mild and short-lived, resolving despite continued therapy. Caution with use of AChEIs should be observed in the presence of bradycardia and atrial or ventricular conduction disorders. Muscle cramps, insomnia, and nightmares are more common with donepezil and can sometimes be reduced by administering the drug in the morning rather than at night. About 40–60% of AD patients respond to AChEIs. So far similarities appear to be greater than the differences between the available AChEIs, but it may be reasonable to consider switching drugs if patients do not tolerate or respond to the first drug used.

Memantine is a noncompetitive NMDA (glutamate) receptor antagonist that blocks pathologically elevated glutamate. Glutaminergic overstimulation and consequent calcium overload has been implicated in neurodegeneration and memantine offers neuroprotection, while still allowing physiological receptor activation. The drug has recently become available for treatment of moderately severe to severe AD and there is also preliminary evidence of efficacy in milder AD and VaD. In clinical trials in patients with severe AD, patients taking memantine showed significantly less deterioration in functional, cognitive, and global measures and need for institutionalization, and demands on caregiver time were significantly reduced. The addition of memantine to donepezil treatment appears to show benefit over donepezil alone.

Antioxidants are thought to reduce free radical production and the excessive lipid peroxidation that can lead to neuronal damage. This is thought to be the likely mechanism supporting the use of vitamin E, selegiline, and Ginkgo biloba in people with mild cognitive impairment and dementia, though proof of efficacy is very limited.

THE MEMORY CLINIC AS PART OF LOCAL DEMENTIA SERVICES

The WHO consensus statement on the organization of care for elderly people with mental health problems (World Health Organisation, 1998) highlighted specific principles that should underpin service development. Good-quality dementia care should be comprehensive, taking into account not just the medical aspects of the problem but also the psychological and social consequences. It should be accessible and user-friendly, minimizing obstacles to effective assessment and intervention. It should be responsive, listening to and understanding the problems brought to its attention, and able to act promptly and appropriately. Finally, assessment and care should be individualized, tailored to the needs of the patient and their family.

The consensus document emphasizes that a team approach is essential, not just multidisciplinary but transdisciplinary, going beyond traditional professional boundaries, and providing responsive, coordinated and community-orientated intervention. An effective memory clinic team can be the foundation of a comprehensive dementia service, encouraging early recognition and specialist referral, providing thorough initial assessment and careful diagnosis and ensuring appropriate high quality support and care which can be flexibly integrated with other local service providers.

KEY POINTS

- Recent years have seen a rapid growth in memory clinics offering specialist assessment, diagnosis, treatment and advice for people with memory disorders and their families. They also act as a center for professional education and research.
- Most clinics focus on diagnosis and management of dementia, emphasizing benefits of early presentation, psychometric assessment, differential diagnosis, appropriate use of drug treatments, and psychosocial interventions.
- They have a multidisciplinary approach, with medical, psychology and nursing input and close working relationships with other professionals and dementia services.
- Potential benefits include improved quality of life of patients, reduced carer burden and delayed institutionalization.

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Cellular Changes in Alzheimer's Disease

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INTRODUCTION

A considerable interest in Alzheimer's disease has developed in the last two decades among clinicians and basic researchers. This interest parallels the growing awareness in the medical community that this devastating disease is quite common in the aged population and that most cases of severe mental deterioration in aged people can be attributed to Alzheimer's disease and do not simply result from "normal" aging of the brain.

Although the neuropathological lesions of Alzheimer's disease were described around the beginning of the twentieth century, a controversy about the nosology of the disease was generated by psychiatrists and neurologists at the same time. Initially, Alzheimer's disease was often used to designate a relatively rare cause of presenile dementia, restricted to patients less than 65 years of age, as opposed to "senile dementia" affecting older patients. The realization that Alzheimer's disease and senile dementia constitute the same pathological entity can in some ways be traced back to detailed anatomic clinical studies (see, for example, reference (Tomlinson *et al.*, 1970)). Careful neuropathological examinations of large series of the brains of patients affected with dementing conditions showed that the cerebral lesions of Alzheimer's disease were present in about 50% of these patients. These studies also stressed two important findings: first, the neuropathological lesions of Alzheimer's disease are commonly found in patients affected with senile dementia (i.e. over 65 years) and, from the neuropathological point of view, there is no reason to distinguish between the two conditions; second, dementia resulting from vascular lesions, although not infrequent, is not the preponderant cause of dementia in the aged. Vascular dementia accounted for about 15% of all dementia cases, and in another 10%, vascular lesions were admixed with the cerebral lesions of Alzheimer's disease.

This chapter deals essentially with major facts related to our present knowledge of the neurobiology of Alzheimer's disease.

NEUROPATHOLOGY AND THE DIAGNOSIS OF ALZHEIMER'S DISEASE

The clinical diagnosis of Alzheimer's disease relies on the demonstration of a dementing syndrome and the exclusion of other possible causes of dementia (*see* **Chapter 93, Clinical Aspects of Alzheimer's Disease**). Diagnostic criteria based on clinical data have been introduced, such as the NINCDS–ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association), and the DSM-III-R criteria (*Diagnostic and Statistical Manual of Mental Disorders*, revised third edition). These diagnostic criteria include assessments of the cognitive functions of the patient and results of laboratory examinations and neuroimaging techniques. It is noteworthy that a definitive diagnosis of the disease cannot be made without neuropathological confirmation. Numerous clinicopathological correlation studies have been performed in Alzheimer's disease; using the NINCDS–ADRDA criteria, the clinical diagnosis of Alzheimer's disease has often been confirmed by postmortem neuropathological examination in more than 80% of cases (Tierney *et al.*, 1988).

NEUROPATHOLOGICAL LESIONS IN ALZHEIMER'S DISEASE

Brain atrophy, characterized by a decrease in brain weight, ventricular dilatation, and sulci widening, is often observed at the macroscopic level. This atrophy can, however, be moderate and can overlap significantly with brain atrophy observed in normal aged people.

The neuropathological diagnosis of Alzheimer's disease is based on the demonstration of two characteristic lesions, neurofibrillary tangles (NFT) and senile plaques, in sufficient numbers and in several selected areas. Neuropathological criteria have been proposed in several studies (Khachaturian, 1985; Braak and Braak, 1991; Mirra *et al.*, 1991) and

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interrater reliability of neuropathological diagnosis assessed in collaborative studies (Duyckaerts *et al.*, 1990). NFT and senile plaques per se are not pathognomonic of Alzheimer's disease: both lesions increase in number during "normal" aging and NFT are found in a variety of other neurological diseases; however, NFT are never abundant in the brain of cognitively normal people.

NFT are fibrillary inclusions accumulating in neurones. In pyramidal neurones, NFT often adopt a "flame-shaped" form, filling the perikarya and the base of the apical dendrites (Figure 1a,b). Some NFT remain in the neuropil after neuronal death and are called *extracellular NFT*. NFT are composed of bundles of abnormal filaments, called *paired helical filaments* (PHF, due to their ultrastructural aspects, although their fine structure might be more complex); these 25-nm-wide filaments show regular constrictions, to 10 nm wide every 80 nm (Figure 2a and 2b). PHF are found in neuronal cell bodies, in dendrites, and even in axons and synapses.

NFT have been reported to appear first in the transentorhinal cortex, a transitional cortex located around the rhinal sulcus at the ventral part of the temporal lobe; in the next stage, they are found in the entorhinal cortex, the hippocampus, and other limbic areas; in the final stage of the disease, they spread to the associative cortex of temporal, frontal, parietal, and occipital lobes (Braak and Braak, 1991). NFT are also commonly found in some subcortical nuclei (nucleus of Meynert, thalamus) and in some brainstem nuclei, for example, in the locus ceruleus and in the raphe nuclei. In the entorhinal cortex, NFT predominate in layers II and IV; neurones in these layers provide major afferents (layer II) to the hippocampus and relay major hippocampal efferents (layer IV). It has been proposed that the dysfunction of these neurones destroys the main connections of the hippocampal formation, leading to the memory disorders frequently observed in the disease. In the cerebral cortex, NFT predominate in neurones in layers III and V (these neurones are involved in corticocortical connections). Some areas are relatively spared from the formation of NFT, for example, the primary motor and sensory cortex, the cerebellum, and the spinal cord. This relatively stereotyped and hierarchical

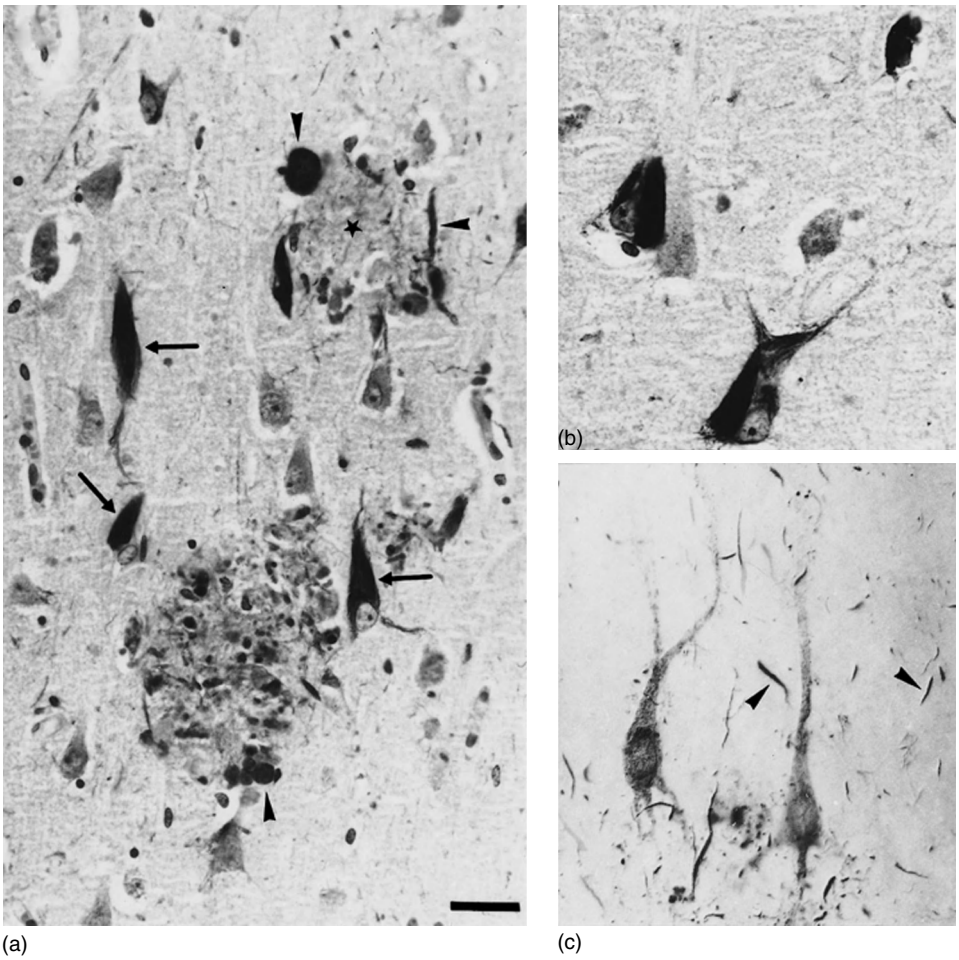

Figure 1 Tissue sections of the hippocampus in a case of Alzheimer's disease, immunolabeled with an anti-tau antibody. (a) Neurofibrillary tangles (arrows) and dystrophic neurites (arrowheads) in two senile plaques are labeled by the anti-tau antibody. The amyloid deposits (stars) in the core of the senile plaques are unlabeled. (b) Higher magnification showing two pyramidal neurones containing neurofibrillary tangles. (c) Two neurones show a diffuse and granular tau immunoreactivity, probably corresponding to an early stage of neurofibrillary tangle formation. Arrowheads point to neuropil threads, also immunolabeled by the anti-tau antibody. Sections in (a) and (b) were counterstained with haematoxylin-eosin. Scale bar: (a) 25 μm; (b), (c) 30 μm

spreading of NFT pathology has been confirmed by biochemical analysis (Delacourte *et al.*, 1999). Neuropil "threads" are small linear or curved neurites, which also contain abnormal filaments and are, as are NFT, immunolabeled by anti-tau antibodies (Figure 1c) (see the following). These neuropil threads are generally abundant in areas rich in NFT.

Neurones containing NFT seem to have a reduced level of protein synthesis and a lower metabolism, as they have been observed, among other things, to have a reduction in the size of their rough endoplasmic reticulum and a decrease in their content of RNA.

Apart from the human species, NFT are not or are rarely present in other species. The molecular basis of the selective susceptibility of neurones to develop NFT in different brain regions, and even in different architectonic areas inside these regions, is still poorly understood.

The other characteristic neuropathological lesion, the senile plaque, exists in several morphological types, which might constitute different developmental stages of this lesion. The "classical" senile plaque consists of a meshwork of dystrophic neurites (Figure 1a) surrounding an extracellular deposit of amyloid substance (Figures 3a and 4a); this amyloid substance can be stained by classical dyes for amyloid, such as thioflavine and Congo red, and is composed of 10-nm-wide amyloid fibers (Figure 4b). These dystrophic neurites in senile plaques contain accumulations of degraded membranous organelles and often-abnormal paired helical filaments. "Primitive" plaques are composed only of dystrophic neurites, and "burned-out" plaques only of a dense amyloid core. With the advent of sensitive immunocytochemical markers, "preamyloid" or "diffuse" plaques have been described: these plaques are made only of an extracellular deposit of Aβ peptide (the main component of plaque amyloid, see the following) not yet organized in the form of amyloid fibers (Figure 3a). These diffuse plaques are abundant at early stages of the disease and can also be found in normal people. It is believed that at least some diffuse plaques evolve to the stage of "classical" senile plaques during the progression of the disease. Fibrillary astrocytes and microglial cells are also found in classical senile plaques; microglial cells might be involved in the processing of the Aβ peptide (Dickson, 1997).

The distribution of senile plaques during the progression of the disease seems to vary from individual to individual. These lesions are initially found in the ventral part of the frontal and temporal lobes (including the hippocampus) and then they spread quickly to associative cortical areas; in advanced stages they can be found in high numbers in most regions of the cortex (predominantly in layers II and III), including primary areas. Senile plaques are also abundant in subcortical nuclei (thalamus, striatum) and in the brainstem, and amyloid deposits can be found in the cerebellum. In the cortex, Aß deposits precede NFT (Metsaars *et al.*, 2003). Unlike NFT, senile plaques have been evidenced in a variety of aged mammals.

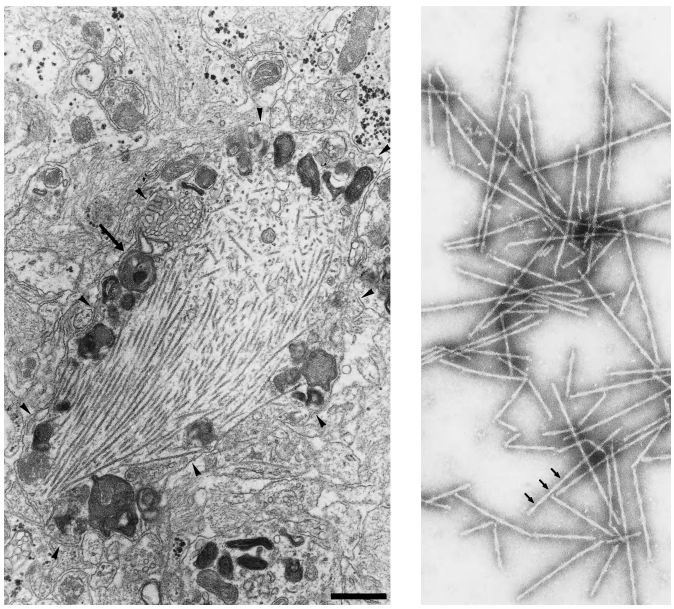

Figure 2 (a) Ultrathin section of cortical tissue (biopsy material) in a case of Alzheimer's disease, examined by transmission electron microscopy. An abnormal neurite (its limits are marked by arrowheads) contains numerous paired helical filaments (small arrow) and degraded membranous organelles (large arrow). The accumulation of these membranous organelles can result from disturbances of their axoplasmic transport. (b) Isolated paired helical filaments are shown by negative staining. These abnormal filaments exhibit regular constrictions (arrows). Scale bar: (a) 500 nm; (b) 200 nm

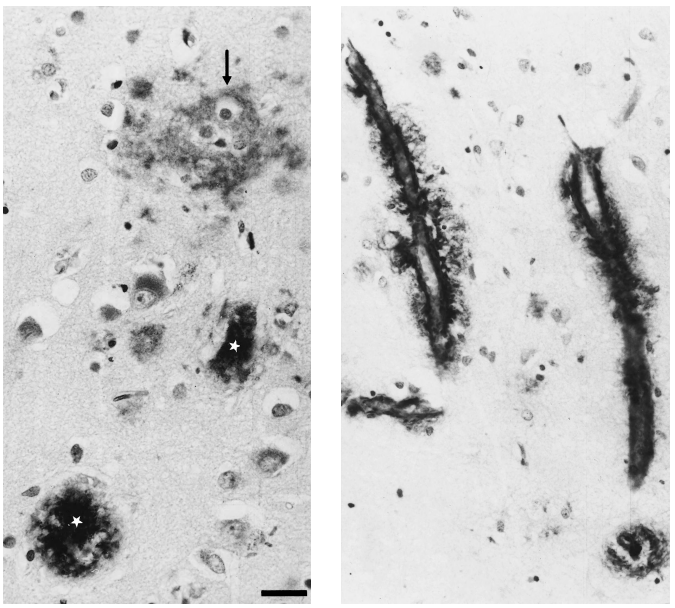

Figure 3 Tissue section of the cortex in a case of Alzheimer's disease, immunolabeled with an anti-A4/β-amyloid antibody and counterstained with haematoxylin-eosin. (a) A4/β-amyloid deposits in classical senile plaques (stars) are strongly labeled, whereas the A4/β-amyloid immunoreactivity in a diffuse plaque (arrow) is less intense. (b) These blood vessels show a strong A4/β-amyloid immunoreactivity in their walls. Some immunoreactivity is also visible in the adjacent neuropil. Scale bar: (a), (b) 30 μm

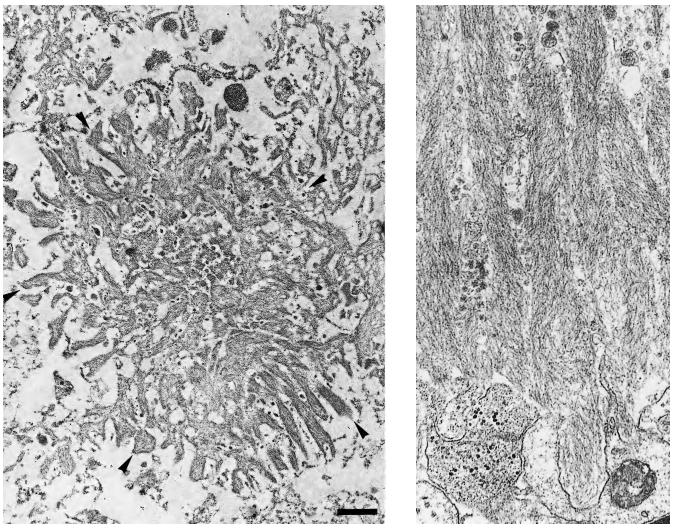

Figure 4 Ultrathin sections of cortical tissue in a case of Alzheimer's disease. (a) Low magnification of the amyloid core of a senile plaque (the general limits of the amyloid core are marked by arrowheads). (b) Higher magnification showing the bundles of amyloid fibers in the amyloid core of senile plaque. Scale bar: (a) 1 μm; (b) 80 mn

Many clinicopathological studies have established that the number of NFT in cortical areas is strongly correlated with the severity of dementia; this correlation is less strong with the number of senile plaques (Duyckaerts *et al.*, 1990; Arriagada *et al.*, 1992).

Other types of tissue lesions have been described. A loss of neurones has been reported in several studies. This cell loss is, however, variable among regions and is methodologically difficult to assess (Mann, 1991) but is more marked in AD than in normal aging (Morrison and Hof, 1997). This cell loss correlates with the number of NFT and might even outnumber them. A loss of synapses and synaptic markers (correlated with the number of NFT) has been well documented (Masliah *et al.*, 2001). Other lesions include a shrinking of the dendritic arborization, granulovacuolar degeneration, Hirano bodies, and gliosis. In many cases, although to a variable degree, amyloid deposits are found in the walls of small arterioles (amyloid angiopathy) (Figure 3b) and it has been suggested that they disturb the blood–brain barrier function (Jellinger, 2002). Biopsies of the olfactory epithelium (which contain dividing neuroblasts whose axons project to the olfactory bulbs) demonstrate dystrophic neurites in patients with Alzheimer's disease, but these changes have also been observed in normal adults (Trojanowski *et al.*, 1991). Cortical Lewy bodies are found in association with NFT in a population of demented patients, but this is probably more characteristic of a separate nosological entity (the so-called *diffuse Lewy body disease*). Many neurones also show various indices of metabolic dysfunction, even in the absence of NFT: reduction in nucleoli volume, disruption and loss of the Golgi apparatus (Stieber *et al.*, 1996), reduction in translational activity and global levels of messenger RNA, decrease in the activity of mitochondrial cytochrome oxidase (Hatanpää *et al.*, 1996) and so on.

A severe decrease in the level of acetylcholine and acetylcholinesterase in the cortex, but not of postsynaptic muscarinic receptors, has been repeatedly observed in the disease, reflecting the loss of cholinergic neurones in the nucleus of Meynert, whose axons project to cortical areas (Whitehouse *et al.*, 1982). This cholinergic deficit has generated many therapeutic attempts to correct it by the use of cholinergic agents and anticholinesterase drugs. Cortical neurones producing the neuropeptides somatostatin and corticotrophin-releasing factor are also frequently affected. Projection neurones producing noradrenalin and serotonin, and cortical neurones producing glutamate, gamma-aminobutyric acid (GABA) and various neuromodulators, have also been observed to be affected, although variable results have been published (Bowen, 1990). Dystrophic neurites in senile plaques and neurones containing NFT can be labeled by antibodies to different neuropeptides and different enzymes involved in the synthesis of neurotransmitters, suggesting that these lesions are not specific for a single type of neurotransmitter.

GENETIC ASPECTS

Although most cases of Alzheimer's disease appear to be "sporadic", it has become increasingly evident in recent years that genetic factors influence the development of the disease in a significant proportion of cases (Rocchi *et al.*, 2003).

Familial cases with a pattern of autosomal dominant transmission account for up to 10–15% of all cases. Genetic linkage studies have indicated that Alzheimer's disease is genetically heterogeneous; familial cases of Alzheimer's disease can have an early or a late onset, the age of onset being relatively constant within a family. Several mutations in the gene for the amyloid peptide precursor (APP), localized on chromosome 21 (16 mutations found to date), have been described and are responsible for 2–3% of familial Alzheimer's cases. Most interestingly, patients affected with trisomy 21 systematically develop the neuropathological lesions of Alzheimer's disease (NFT and senile plaques) and dementia when they age, suggesting that a gene dosage effect can lead to an "Alzheimer-like" phenotype.

Mutations in the *presenilin 1* gene localized on chromosome 14 (140 mutations found to date) have been demonstrated to be responsible for most cases of early onset familial cases, accounting for up to 80% of the cases of familial Alzheimer's disease. *Presenilin 1* is necessary for the γ-secretase activity generating the Aß peptide (see the following text). Mutations in the closely related *presenilin 2* gene present on chromosome 1 (10 mutations found to date) have been identified as being responsible for many of the remaining familial Alzheimer's cases. The presenilins are serpentine transmembrane proteins (Thinakaran, 1999) that have been localized in the endoplasmic reticulum and in the Golgi apparatus.

Apart from these genetic mutations, it has been discovered that the apolipoprotein E genotype affects the risk of developing Alzheimer's disease and its mean age of onset, acting as a susceptibility gene (Roses, 1996). Three main alleles of the apolipoprotein E gene exist (APOE2, E3, E4) and the gene is present on chromosome 19. Each inherited APOE4 allele increases the risk and lowers the mean age of onset, whereas the inheritance of an APOE2 decreases the risk and increases the mean age of onset of the disease. Homozygotes for APOE4 have a risk of developing the disease, which is eight times greater, and a mean age of onset of the disease (<70 years), which is 20 years shorter, than APOE2/3 individuals (>90 years). The mechanisms by which different apolipoprotein E isoforms can modulate the susceptibility to the disease are not yet clearly understood (Lahiri *et al.*, 2004), although it has been suggested that a differential binding of apolipoprotein E isoforms to Aβ and/or tau proteins might be one such mechanism (Roses, 1996).

Aß PEPTIDE AND THE AMYLOID PEPTIDE PRECURSOR

Many investigators have chosen to study senile plaques and NFT as a route to elucidating the pathogenesis of the disease, and important progress has been made in the molecular analysis of these lesions.

The amyloid deposits in senile plaques and in the cerebrovascular angiopathy have been found to be composed of a peptide of 39–43 amino acids (now called *Aβ peptide*) (Glenner and Wong, 1984; Masters *et al.*, 1985). This peptide is derived from a precursor, APP, expressed in neurones and in a variety of nonneuronal cells (including outside the central nervous system) (Octave, 1995; Ling *et al.*, 2003). APP is a transmembrane protein, which might play a role in contacts with the extracellular matrix and has been found to be concentrated at the level of synaptic contacts and in lipid rafts of the plasma membrane. Several isoforms of APP have been identified, which show differential tissue expression.

In one metabolic pathway, APP is cleaved by an enzyme ("α-secretase") and its N-terminal portion is secreted outside the cell. This cleavage occurs inside the sequence of the Aβ peptide and thus cannot generate the latter (hence this pathway is also called *non-amyloidogenic*). In another metabolic pathway the Aβ peptide is generated from APP by cleavage with two other enzymes: the ß-secretase generating its N-terminus and γ-secretase generating its C-terminus (Haass, 2004; Wilquet and De Strooper, 2004). The γ-secretase activity results from the assembly of a multiprotein complex containing *presenilin 1* (Takasugi *et al.*, 2003). This pathway is called *amyloidogenic*, and thus, all factors favoring it could potentially precipitate the disease. For instance, cells expressing APP with mutations at sites described in familial Alzheimer's disease produce more Aβ peptide or more of the longer Aβ peptide (which form amyloid fibers more readily). Transgenic mice overexpressing a mutated APP protein develop amyloid deposits (but not NFT) and coexpression of mutated APP and PS1 proteins greatly accelerates the formation of these Aß deposits (for a review, see (Gotz *et al.*, 2004)). Before forming extracellular deposits, the Aß peptide seems to accumulate intracellularly in neurones, an event that might be critical in the pathophysiology of the disease, for example, some transgenic mice overexpressing mutated APP develop neuronal deficits before developing extracellular amyloid deposits (Casas *et al.*, 2004). In Alzheimer's disease, however, there is no major overexpression of APP (contrary to what is observed in Down's syndrome).

In addition to the Aβ peptide, other components have been identified in the amyloid deposits: these include α_1-antichymotrypsin, apolipoprotein E, components of the complement pathway, various molecules of the extracellular matrix (proteoglycans, heparin sulfate), and so on. Molecules such as aluminum and zinc have also been identified in some studies. The physiopathological role of these additional components is still difficult to delineate, although some of them (e.g. α_1-antichymotrypsin, apolipoprotein E) have been observed to promote amyloid-like fibril formation *in vitro* and could thus act *in vivo* as "pathological chaperones", favoring amyloid fibrillogenesis. Transgenic mice overexpressing a mutated APP protein do not develop amyloid deposits if their APOE gene is invalidated. Quite interestingly, Aß vaccination has been successful in removing Aß deposits in transgenic mice (Morgan *et al.*, 2000). Initial attempts on AD patients have, however, resulted in mitigated results, due to serious side effects in a proportion of patients (Broytman and Malter, 2004).

NEUROFIBRILLARY TANGLES AND TAU PROTEINS

Neurofibrillary tangles have been found by immunochemical and biochemical methods to be composed of a microtubule-associated protein called *tau* (Brion *et al.*, 1985; Buée *et al.*, 2000; Lee *et al.*, 2001). This protein is expressed in neurones, where it probably plays a role in the maintenance of the stability of microtubules, particularly in the axons, by its ability to bind to tubulin. Microtubules are one of the three main fiber systems that form the cellular cytoskeleton. Microtubules are essential for the maintenance of the shape of the neurone and its extensions, and play a fundamental role in targeted intracellular transport of various molecules and organelles. One particular aspect of transport in neurones is the axoplasmic transport along axons, which provides energy-generating machinery and neurotransmitters at the synaptic level. Inactivation of the tau gene leads to developmental malformations in the central nervous system characterized by defects in the formation of long axonal tracts (Takei *et al.*, 2000). In the human central nervous system, six isoforms of tau proteins are generated by alternative splicing from a single gene localized on chromosome 17. Pathogenic mutations in the tau gene have been identified in familial forms of frontotemporal dementia (Rademakers *et al.*, 2004) and are often associated with the formation of tau-positive

neurofibrillary lesions. Such mutations have, however, not been identified in Alzheimer's disease. Nevertheless, transgenic animals expressing mutant forms of tau develop NFT and constitute a powerful *in vivo* experimental model (for a review, see (Gotz *et al.*, 2004)). The existence of a tau pathology in several neurodegenerative diseases, including Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, and so on, has led to their grouping under the term of *tauopathies* (Buée *et al.*, 2000; Lee *et al.*, 2001).

Tau proteins in PHF present several types of posttranslational modifications, resulting in several populations of modified tau proteins. Well-documented modifications are a high state of phosphorylation (Brion *et al.*, 1991; Delacourte, 1994), partial proteolysis (Wischik *et al.*, 1988), ubiquitination (Morishima-Kawashima *et al.*, 1993), and glycation (Yan *et al.*, 1995). These modified tau proteins have been called *PHF-tau* proteins (for a review, see (Buée *et al.*, 2000)). The accumulation of NFT in brain tissue is correlated with a decrease in the levels of normal, soluble tau and an increase in the PHF-tau proteins (Mukaetova-Ladinska *et al.*, 1993). A diffuse or granular accumulation of tau in neurones can represent an early stage, preceding the formation of bundles of PHF (Figure 1c) (Bancher *et al.*, 1989; Braak *et al.*, 1994).

The ability of tau proteins to interact with microtubules is decreased when the protein is phosphorylated at selected sites. Although tau is already significantly phosphorylated in the fetal (Brion *et al.*, 1993) and the adult (Matsuo *et al.*, 1994) normal brain, much of the tau protein present in neurofibrillary tangles is highly phosphorylated, and the presence of highly phosphorylated tau species in the brain of patients has led to the suggestion that these phosphorylated proteins would be unable to maintain a stable network of microtubules in affected neurones, leading to disturbances of cellular functions such as axoplasmic transport (Dustin and Flament-Durand, 1982; Brion, 1992; Roy *et al.*, 2005). Actually, decrease in the number of microtubules (Flament-Durand and Couck, 1979) in tubulin expression (Hempen and Brion, 1996) and in the ability of tubulin to polymerize in microtubules (Iqbal and Grundke-Iqbal, 1995) have been observed in the disease. Several protein kinases, for example, the glycogen synthase kinase-3ß (Leroy *et al.*, 2002), the cyclin dependant kinase 5 (Cruz and Tsai, 2004) and protein phosphatases have been identified as *potential candidate enzymes* involved in the regulation of tau phosphorylation (Anderton *et al.*, 2001; Planel *et al.*, 2002; Geschwind, 2003) and it has been suggested that a relative imbalance in their activities might play a role in the generation of the highly phosphorylated tau proteins found in the disease. Such an imbalance might also result from aberrant activation or inhibition of signal transduction pathways in Alzheimer's disease. Aberrant cell cycle activation in neurones is one of the evoked mechanisms (Arendt, 2003). An increased concentration of hyperphosphorylated tau proteins detached from microtubules would favor their aggregation in PHF and additional neuronal dysfunction. Experimental modulation of tau phosphorylation in culture systems and in transgenic animals is currently an active area of research, with the hope of interfering with the mechanisms of formation of abnormally phosphorylated PHF-tau species.

NFT have been reported to be immunoreactive *in situ* with antibodies to other molecules (ubiquitin, microtubule-associated protein 5 (MAP5), neurofilaments, APP, etc.), suggesting an *in situ* interaction between these molecules and the PHF components. Most consistent is the identification of the stress polypeptide ubiquitin (also identified by protein sequencing). Ubiquitin (also present in neuronal inclusions found in other neurodegenerative diseases, such as the Lewy bodies) is covalently conjugated to molecules destined to be proteolyzed by the proteasomal system.

RELATIONSHIP BETWEEN NEUROFIBRILLARY TANGLES AND SENILE PLAQUES AND PHYSIOPATHOLOGICAL CONCEPTS OF THE DISEASE

One leading physiopathological hypothesis (the "amyloid hypothesis") of Alzheimer's disease is that an abnormal processing of APP leads to an excessive generation of the Aβ peptide that is directly responsible for the development of the disease (Hardy, 2003; Selkoe and Schenk, 2003). According to this hypothesis, Aβ deposits would become toxic for surrounding neurones and their processes when they form amyloid fibers, and would induce the formation of abnormal tau proteins and NFT. The main support for this hypothesis comes from the observation that people affected by APP mutations develop full-blown Alzheimer's disease, including the classical neuropathological lesions (senile plaques and NFT tangles). Down's syndrome patients also offer strong support for this hypothesis, as the earliest lesions found in these patients are diffuse Aβ deposits, with NFT and senile plaques appearing later (*see* **Chapter 101, The Older Patient with Down's Syndrome**). In addition, the Aβ peptide has been observed to be neurotoxic in culture when it is aggregated in the form of amyloid fibers (Busciglio *et al.*, 1995). It has been postulated that the toxicity of the Aβ peptide is mediated by a variety of mechanisms: the Aβ peptide has been reported to induce oxidative damage, mediated by the generation of free radicals, to trigger apoptosis in neurones, to sensitize neurones to excitotoxic amino acids, to increase intracellular calcium, and so on (Atwood *et al.*, 2003).

On the other hand, in most studies it has been difficult to correlate dementia with the loading of Aβ peptide in the brain of patients, whereas many reports have pointed to the correlation between the number of NFT and synaptic loss and the degree of dementia. Some investigators have thus favored the hypothesis that early changes in the neuronal cytoskeleton and/or synaptic degeneration are key events in the development of neuronal dysfunction in the disease (Terry, 2000).

The relationship between the formation of senile plaques, and NFT remains a central issue for the understanding of the physiopathology of the disease. A link between abnormal processing of APP and the formation of NFT is quite probable (e.g. people affected by APP mutations also develop NFT). APP, Aβ and tau might directly interact (Giaccone *et al.*, 1996). APP is transported along axons by fast axoplasmic transport and any interference with this transport, as suggested in neurones developing NFT, might be expected to affect its metabolism (Hirokawa and Takemura, 2004). An abnormal metabolism of APP might also be secondary to alterations in its intracellular trafficking. It also seems possible that the formation of NFT and of amyloid deposits occur independently, as there is no complete chronological and topographical overlap in their evolution. For instance, NFT develop in transgenic animals expressing mutants' tau proteins, in the absence of amyloid deposits, but they do not develop in transgenic animals expressing mutants' APP proteins and developing Aß deposits, in the presence of a wild-type human tau (Boutajangout *et al.*, 2004). However, coexpression of mutants' tau and APP proteins enhances the formation of NFT (Lewis *et al.*, 2001). A current hypothesis is thus that Aß peptide could accelerate the formation of NFT that appear at low levels during normal aging.

Other physiopathological concepts of the disease are also currently being investigated. A lack of trophic factors would lead to the degeneration of selected neuronal populations, for example, a lack of nerve growth factor has been suggested to play a role in the degeneration of cholinergic neurones in the nucleus basalis (severely affected in Alzheimer's disease) (Lang *et al.*, 2004). Evidence of oxidative damage has been found in brain tissue of AD patients and could also play a pathogenic role (Perry *et al.*, 2002). An inflammatory reaction (suggested by the presence of microglial cells and inflammatory molecules in senile plaques) might also lead to neuronal insult (Eikelenboom and Van Gool, 2004). The roles played by apoptosis and excitotoxicity are two research avenues (among others) being actively investigated. Although aging is a major "risk factor" for the disease, it seems improbable that Alzheimer's disease is simply an exacerbation of normal aging mechanisms (Morrison and Hof, 1997).

Although these various hypotheses are not necessarily exclusive, it is, however, still difficult to discriminate between mechanisms that play an important role in the development of neuronal dysfunction and secondary processes that are rather a consequence of primary mechanisms but might nevertheless contribute to the evolution of tissue lesions.

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KEY POINTS

- The definitive diagnosis of the disease relies on the neuropathological examination, showing the presence of neurofibrillary tangles and senile plaques.
- Neurofibrillary tangles are composed of hyperphosphorylated forms of the microtubule-associated protein tau and the Aß amyloid peptide is the main molecular component of senile plaques.
- According to the amyloid cascade hypothesis, the Aß peptide is neurotoxic and could accelerate the formation of neurofibrillary tangles. The latter lesions are, however, more strongly correlated to the severity of dementia.
- Neuronal and synaptic loss in selected brain areas occurs in the disease. This loss is more important in AD than during normal aging.
- A few cases of Alzheimer's disease have a familial transmission and are mostly due to pathogenic mutations in the presenilins and the amyloid peptide precursor genes.

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Clinical Aspects of Alzheimer's Disease

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INTRODUCTION

With the aging of the population, Alzheimer's disease has become a major public health problem. General awareness of the problems posed by this disease is increasing, but its overall cost for society, already very high, will no doubt continue to rise as its prevalence also increases exponentially with age. The advances in pathophysiology and clinical knowledge made in recent years, along with improvements in treatment, are considerable. One of the clinician's prime concerns at the present time is to diagnose the disease as early as possible, which implies that it is distinguished from other important causes of dementia, and institute rapid and appropriate management (including appropriate investigations). This will inevitably comprise a detailed account of the domestic and social situation, caregiver information, accompaniment, and support of the patient and his or her family throughout the duration of the illness.

THE DIAGNOSIS OF ALZHEIMER'S DISEASE

Alzheimer's disease is responsible for 75% of all dementias. It affects 5% of the population aged over 65 years and 30% of persons aged over 85. Dementia disorders are responsible for about 50% of cases of dependency in the elderly (Aguero-Torres *et al.*, 1998). Among the known risk factors are the following:

- age: increasing age is associated with exponential increase of the incidence of Alzheimer's disease;
- family history of the disease;
- presence of the e4 allele of the *apolipoprotein E* gene on chromosome 19: this increases the risk of development of dementia of Alzheimer type. This risk is greater and the onset of the disease is earlier in subjects who are homozygous for the e4 allele;
- gender: prevalence and incidence seem to be higher in women in the majority of studies;
- head injury;
- trisomy 21, but the family link between dementia of Alzheimer type and Down's syndrome is debated.

Hormone replacement therapy for the menopause, nonsteroidal anti-inflammatory drugs and certain nutritional factors such as the consumption of antioxidant agents may be protective factors against Alzheimer's disease.

Alzheimer's disease is characterized clinically by cognitive impairment, dominated by memory complaints, which may or may not be associated with a syndrome of aphasia, apraxia, and agnosia. All these lead to disorders of instrumental function, executive function, and judgment. The clinical presentation and the course of the disease may be extremely varied. The clinical disorders observed often differ widely from one subject to another, depending on factors such as age at onset, rapidity of progression and the diversity of cognitive and behavioral disturbances. For these reasons, clinical diagnosis may be a problem for the practitioner, who should refer to predetermined clinical criteria such as those of the DSM-IV and NINCDS-ADRDA (appendix 1) (American Psychiatric Association, 1995; McKhann *et al.*, 1984).

In Alzheimer's disease, memory impairment is constant and is a requisite for diagnosis; it is also very often the first sign. The onset of the disorder is generally insidious and difficult to detect, and the course slow and progressive. The early stage is usually marked by memory disturbance which may go unnoticed for some time by the family and friends, be attributed to normal aging or concealed by the patient. The majority of clinical evidence indicates that a considerable time may elapse – an average of −3 years – between the appearance of the first symptoms and establishing the diagnosis (Freels *et al.*, 1992; Knopman *et al.*, 2000).

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Memory disorders primarily relate to recall of recent events or short-term memory, while older memories are better preserved. Later, the disease progresses and gradually affects other cognitive domains (language, attention, calculation, orientation in time and place) as well as more complex functions such as executive function that allows planning and performance of successive, organized tasks. The course of the disease is also marked by major disturbances of judgement and reasoning, which may result in behavioral problems. These problems have a progressive impact on the activities of daily living (ADL) function and on independence which may become apparent initially in domestic activities, and then in essential ADL, with the patient becoming progressively dependent. Problems of sphincter control, alteration of nutritional status, and disturbances of balance and gait accelerate the process of dependence.

Mood is often disturbed, with symptoms of depression or anxiety or excessive lability resulting in frequent swings from apathy to agitation. Although progress has been made in the diagnosis of the disease, many patients are still seen at a late stage when the neuropsychiatric symptoms have become unmistakable. Forms with slower progression have been described, characterized essentially by memory problems that evolve very slowly over 15 to 20 years, without physical complications; inversely, very rapid and serious forms exist, which lead to the death of the patient within a few years.

The principal factors of aggravation of cognitive disturbances are iatrogenic (psychotropic drugs) and intercurrent physical conditions. Nutritional and vitamin deficiencies, sensory deficits, hypothyroidism, vascular risk factors or stress linked with family relationships (a possible source of conflict) or the domestic environment (risk of falls) also intervene.

Psychological and behavioral signs and symptoms are frequent, but generally develop in the advanced stages of Alzheimer's disease (unlike frontotemporal dementia where they occur earlier). Their onset often requires emergency management. They affect cognitive performance and decrease the tolerance of family and friends toward the patient's problems. They may prompt the family to seek medical advice for the first time and allow a diagnosis to be made.

The advantages of early diagnosis include the avoidance of certain behavioral problems arising directly from the disease and which could have unfortunate consequences such as errors, which could financially embarrass the patient or his or her family, or patients continuing to drive when they have lost the ability to act safely.

Briefly, the diagnosis of Alzheimer's disease may be made in four main clinical situations:

1. An elderly patient who is seen because of memory difficulties: this may be a case of anxiety or depression, or it may be true early Alzheimer's disease, or mild cognitive impairment (MCI) (Petersen *et al.*, 1999). MCI corresponds to a memory complaint evidenced by psychometric tests (in particular, a short-term memory deficit that is not improved by cueing, together with globally normal cognitive function). Every year, a proportion of these patients progress to Alzheimer's disease.
2. A patient who is brought to the clinic by the family because they have noticed memory or behavior disturbances: in such cases cognitive function is often severely impaired.
3. An emergency call from an agitated or confused patient: here, among other causes we must exclude distended bladder, fecal impaction, or electrolyte or metabolic imbalances. Careful history-taking and interviews with the family are also important.
4. A patient whose performance has slowed, with fatigue or lack of energy: the differential diagnosis must include other neurological disorders: hypothyroidism, normal-pressure hydrocephalus, Parkinson's disease, vascular disorders, depression.

In each of these diagnostic situations, after a comprehensive examination, the following investigations should be made:

– neuropsychological investigation, whose nature depends on the complexity of the clinical picture;
– laboratory tests (hemoglobin, erythrocyte sedimentation rate (ESR), thyroid function, lipid profile, blood glucose, serum creatinine, electrolytes, etc.);
– brain CT scan (usually without contrast agent).

In the more difficult forms of the disease and in specialized facilities, more specific investigations can be carried out such as MRI, brain scintigraphy, or ApoE4 typing (these are not recommended as routine tests).

At the present time, the diagnosis of Alzheimer's disease is a positive diagnosis and not one of exclusion. The case history, the results of clinical, neuropsychological and psychiatric examination, supported by imaging findings make it possible to establish the diagnosis with a high degree of probability in most cases. It is still very important to make a precise diagnosis of Alzheimer's disease so that it is not confused with another type of degenerative dementia (e.g. frontotemporal dementia, Lewy body dementia, focal atrophy), or vascular dementia, which is sometimes associated with Alzheimer's dementia, but should not be missed.

BOX 1

The diagnosis of dementia is defined by the ICD-10 of the WHO and makes it possible to exclude:

– depressive syndromes,
– confusional syndrome,

– drug-related cognitive decline (mainly secondary to long-term abuse of neuroleptics),
– mental deficiency and social deprivation.

The following are the most frequent dementias other than dementia of Alzheimer type:

Nondegenerative dementias:

– vascular dementia: this is the second commonest cause of dementia syndromes after Alzheimer's disease; vascular lesions are the exclusive etiology in 15 to 20% of dementias and are associated with other etiologies (mixed dementias) in 15 to 20% of cases, so that nearly one-third of syndromes can be considered as having a vascular origin;
– hydrocephalus with normal pressure;
– metabolic disorders: thyroid disorders, vitamin B12 deficiency, hypercalcemia, hepatic encephalopathy;
– secondary to a brain tumor.

Non-Alzheimer degenerative dementias:

– Lewy body dementia: characterized by associated recurrent hallucinations (visual in particular), an unstable cognitive state and motor symptoms of Parkinson's disease;
– Frontotemporal dementia: where cognitive disturbances have a secondary role. Behavioral problems signal the onset of the disease and not memory complaints, unlike Alzheimer's disease;
– Focal atrophy: which causes cognitive dysfunction but which may remain isolated for a long period;
– Alcoholic dementia: characterized by slowed psychomotor performance, disturbances of language, and visual spatial coordination;
– Creutzfeldt-Jacob's disease: which is associated with psychiatric, cognitive, and neurological signs/symptoms.

Mixed dementias:

Cerebral vascular lesions are associated with degenerative dementia of Alzheimer type.

Alzheimer's disease is diagnosed increasingly early. The growing number of *memory clinics* plays an increasing role here; general practitioners who have become increasingly aware of the problems and issues in dementia and patient's families (who previously tended to consider a failing memory as the normal consequence of aging) are more prone to refer patients to these specialized centers. The complaints of the patients and of the family must be assessed, placing them in their social, cultural, and psychological context, and attention should be given to changes in relation to previous capacities.

In order to acquire a diagnosis of established Alzheimer's disease, in addition to the case history and clinical examination, global evaluation scales such as Folstein's Mini-Mental State Examination (MMSE) can be administered in a few minutes at the patient's bedside by the physician. Thus, for all cases of Alzheimer's disease that meet the DSM-IV criteria, the global scales are sufficient for diagnosis. The initial evaluation and then the follow-up of disease progression can be based on various parameters: decline of cognitive function, assessment of dependence, or decline related to changes in living arrangements. However, all these factors remain subordinate to others such as marital status, or quality of management at home, itself dependent on the level of resources and services available, which vary according to the country.

For evaluation of cognitive function, the MMSE remains the instrument generally used. It is a simple scale with 30 questions and can be administered in about 10 to 15 minutes. It objectively evaluates temporospatial orientation, a mental arithmetic task requiring working memory, recall of three words, reproduction of a complex design which detects constructive apraxia, and a simple language assessment (Folstein *et al.*, 1975). Among the global evaluation scales, the Clinical Dementia Rating (CDR) assesses six different domains: memory, orientation, judgement, community affairs, home and hobbies, and personal care. Each domain is scored from 0 to 3 (0: no impairment; 0.5: very mild, 1: mild; 2: moderate, and 3: severe (Hughes *et al.*, 1982; Morris, 1993). The dependence scales evaluate the ability to perform the various activities of daily living. Among them, the ADL scale explores, in six items (personal hygiene, dressing, toileting, mobility, continence, and eating) the basic activities of daily living. It is used to evaluate dependence of elderly persons in hospital, living in retirement homes, or being cared for in their own home (Katz *et al.*, 1970). The instrumental activities of daily living (IADL) scale evaluates more complex activities of daily life (such as using the telephone, doing housework, or managing money) (Lawton and Brody, 1969).

The MMSE and the IADL should systematically be used when an elderly person complains of memory problems. These scales allow the general practitioner either to reassure the patient or to refer him or her to a specialized center, bearing in mind that it is often only through repeated visits that cognitive disturbance or decreased independence can be detected at the start of the disease.

EVOLUTION OF ALZHEIMER'S DISEASE AND PATIENT FOLLOW-UP

Alzheimer's is a chronic disease. Various complications can cause the subject to lose his or her independence and eventually become permanently bedridden. Such a state is always

accompanied by its own complications: pressure sores, infections, undernutrition, and therefore by high morbidity, loss of quality of life, and suffering, all of which result in high medical costs.

One of the essential aims of medical follow-up of Alzheimer's patients is to preserve satisfactory physical independence and a better quality of life. It is possible to maintain a patients' independence for activities of daily living even at very advanced stages of the disease. There appears to be no correlation between the histopathological lesions and the quality of life or independence of the patients.

We will now look in turn at
- our present knowledge of the natural history of Alzheimer's disease;
- the principal complications of the disease;
- the type of medical follow-up that we are able to propose at the present time.

The Evolution of Alzheimer's Disease

The natural history of Alzheimer's disease is now much better understood because of recently published long-term and retrospective studies. The study of Grossberg and colleagues retraces the history of 100 subjects with Alzheimer's disease confirmed by autopsy. The authors observed that the mean time elapsing between the onset of symptoms and the clinical diagnosis of the disease was 32.1 months (±37.9) and time elapsing between clinical diagnosis and institutionalization was 23.9 months (±33.6). Institutionalization therefore occurred at a mean of 56.5 months after the onset of the first symptoms. The mean duration of the disease after the onset of the first symptoms to the death of the patient was 101.3 months, or nearly 8.5 years. The longest duration of the disease was 252.1 months, or nearly 21 years, for one of these patients. The authors of this study reported that in typical Alzheimer's disease, the diagnosis was made at the age of 75 or 32 months after the onset of the first signs. Admission to a retirement home took place on average 24 months after diagnosis, or 57 months (4.5 years) after the onset of the first signs of the disease. The subject then spent about 44 months in the retirement home before dying (Jost and Grossberg, 1995).

Alzheimer's disease is one of the most frequent causes of death, even if this has long been unrecognized. Study of the causes of death in 1995 in the United States reveals that 7.1% of all deaths can be attributed to this disease, which is the third leading cause of death (Ewbank, 1999). A prospective study recently carried out in the state of Washington found concordant results, and revealed that certain factors decreased the duration of the patients' life and in particular, rapid decline of cognitive function, loss of independence, and falls were poor prognostic factors. Identification and follow-up of these factors may help the patient and his or her family to better plan their future (Larson *et al.*, 2004). Median survival also appears to depend on age at the time of diagnosis (Brookmeyer *et al.*, 2002).

Principal Complications

Three signs should attract the attention of the physician caring for a patient with Alzheimer's disease:

- weight loss;
- alteration in balance and gait/posture with an increased risk of falls;
- behavioral disturbances.

These are the basic essentials of noncognitive follow-up of these patients. Nevertheless, regular evaluation of the patient's neurocognitive function should not be neglected.

Weight Loss and Alzheimer's Disease

When he first described the disease in 1906, Alois Alzheimer emphasized the occurrence of weight loss in his patient. However, this weight loss has long been mistakenly considered as occurring at the late stages of the disease. We now know than it can occur as soon as the first symptoms of the disease appear.

The sooner a management strategy is set up, the more effective it will be. Otherwise, we may rapidly find ourselves confronted with undernourished, anorexic subjects, where there is very little room for maneuver between doing nothing (often seen as abandonment of treatment) or setting up enteral nutrition (which is then seen as artificial prolongation of life), whereas early on, especially in subjects who live alone at home, a visit from a home help will often be sufficient to assist these patients in doing their shopping and preparing their meals. It therefore appears to be essential to assess the nutritional status of each Alzheimer's patient, particularly if he or she lives alone or has little family support.

The pathophysiological mechanisms of weight loss are complex and have only partially been elucidated. Alteration of nutritional status may be secondary to the development of inability to perform the activities of everyday living or to disturbances of eating behavior. However, numerous studies have shown that weight loss is observed in the course of the disease even when the subjects still have a satisfactory energy intake. Certain authors suggest that atrophy of the internal temporal cortex or the effect of the e4 allele may play a role in weight regulation (Grundman *et al.*, 1996; Vanhanen *et al.*, 2001). Clinical practice shows that weight loss is accompanied by a variety of complications (decreased immunity, muscle atrophy, falls, and fractures) that affect the state of health and increase the risk of institutionalization and mortality.

Mobility Problems, Falls, and Risk of Accidents

In patients with Alzheimer's disease, posture rapidly becomes incorrect as a consequence of aging (arthritis, impaired vision, muscle wasting, etc.) but this may also be directly related to Alzheimer's disease (Kluger *et al.*, 1997; Franssen *et al.*, 1999) or to medication. Disturbances

of equilibrium can lead to numerous falls and fractures, or to abusive use of restraint. Accidents generally occur in patients in whom Alzheimer's disease has not been diagnosed: drug-related accidents or accidents in the street or in the home. Balance and mobility problems have major psychological consequences leading to anxiety and a feeling of insecurity. They can result in decreased physical activity and loss of social contacts.

Psychological and Behavioral Signs and Symptoms

These problems are observed in the majority of patients with dementia, and in particular, in Alzheimer's disease. The Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994) has helped clarify the definition of these disturbances. The NPI makes it possible to define the type of disturbance (it covers the field of the 10 most common neuropsychiatric symptoms) and also its frequency, severity, and emotional impact on the family and relatives. Of these symptoms, apathy is probably the most frequent. In the medical literature, apathy, considered as a deficiency syndrome, is reflected in lack of initiative and interest, social withdrawal, and flattening of affect.

The majority of studies show that "depressive symptoms" are an integral part of the classic picture of Alzheimer's disease. These symptoms are found in more than 80% of patients (Lyketsos *et al.*, 2001). Depression is also a frequent disorder in this population (Weiner *et al.*, 2002). The prevalence of anxiety symptoms varies depending on the authors. Anxiety may, in fact, be difficult to diagnose because of other symptoms masking the anxious patient. It can be the cause of agitated or inhibited behavior. Psychotic manifestations (delirium and hallucinations) can result in aggressive behavior and consequently affect the emotional state of the family and relatives, who often find it difficult to tolerate the persistence of such behavior and strongly press for symptomatic treatment to be given. It is therefore not surprising that numerous authors report a greater risk of institutionalization in these subjects.

Sleep disorders are a major problem in the medical follow-up of patients with Alzheimer's disease. Specific changes in sleep architecture have been described in the great majority of patients. Sleep becomes less and less restorative, which explains the high frequency of daytime sleep. These symptoms can rapidly make life intolerable for the family or the residents of a retirement home.

There are various types of sleep disorder. Typically, agitation and anxiety appear in the late afternoon. If the patient is not rapidly calmed, this state worsens; he or she refuses to go to bed and remains anxious and agitated for the best part of the night. It may be necessary to relieve this anxiety at the end of the afternoon by giving an anxiolytic, followed by appropriate use of a hypnotic with a short half-life to allow the patient to sleep. Hypnotics are even more effective if given to a patient who is already calm and not anxious. A second typical case is that of patients who have been given neuroleptics because they presented with behavioral disorders. They are then often somnolent during the day and may even be restrained in bed or in an armchair, so it is only to be expected that they should be agitated at night. Neuroleptics must be stopped during the day, and these patients must be mobilized and a normal sleep–wake rhythm restored. Walking or any kind of physical exercise, in particular in the late afternoon, is a good means to help prevent anxiety at this time of day as well as nocturnal agitation. Aberrant motor behavior and wandering, the irrepressible need to walk about, is a dysfunction that is peculiar to dementia states.

Agitation in the patient with Alzheimer's disease may also be related to associated pathologies that have not been diagnosed (e.g. infections). Poor interpretation of sensory stimuli may also be the cause of a number of episodes of agitation in these patients. Sometimes, no cause is found. Problems such weight loss, difficulty in walking, falls, and nocturnal agitation will develop in almost all Alzheimer's subjects at one time or another in the course of the disease. They sometimes occur simultaneously. Undernutrition increases the likelihood of muscle wasting and falls. Falls often lead staff to use restraint during the day, resulting in agitation at night. All these factors rapidly end in the patient becoming permanently bedridden.

Other Symptoms

Alzheimer's disease is one of the causes of epilepsy in the elderly subject. Numerous patients develop extrapyramidal symptoms. Resting tremor is rarer than in idiopathic Parkinson's disease or in drug-induced striatal syndromes. On the other hand, rigidity and bradykinesia or a "parkinsonian" gait are more frequent (Mitchell, 1999). An underlying brain disorder, in this instance Alzheimer's disease, is a risk factor for confusion in the elderly. Sphincter problems generally develop in advanced forms.

At a late stage of Alzheimer's disease, muscle and joint contractures may develop, leading to a permanently bedridden state and to death because of the complications of decubitus ulcers. The value of walking and passive mobilization of the joints to prevent such contractures must be stressed.

Medical Follow-up

Once the diagnosis has been established, patients can be followed by standardized gerontological evaluation (Rubenstein *et al.*, 1984). One of the principal aims of management is to postpone the period of loss of independence that precedes death. It is very important to provide therapeutic management for these patients and their families. This need is felt by the family, and if it is not met, they will often turn to alternative medicine. Standardized evaluation allows rapid and objective exploration of several facets of the elderly patient: dependence (ADL, IADL), memory deficit and the syndrome of aphasia/apraxia/agnosia (MMS), the risk of pressure sores (Norton's scale), nutritional status with the MNA (Mini Nutritional Assessment), study of walking and

balance (Tinetti's test). Two other tools may also be useful: the NPI, which explores the psychiatric complications of the disease (as described earlier), and the Zarit scale (Zarit *et al.*, 1980) which assesses caregiver burden. These two questionnaires are administered to the family. The NPI quantifies the psychiatric aspects of the disease (which cause considerable distress to the family, distress they have difficulty in expressing). The Zarit scale, by exploring caregiver burden, makes it possible to adapt the services proposed or helps to pose the indication of admission to a retirement home when this seems necessary.

It is wise to have discussions about the possibility of the subject moving to a retirement home at an early stage and when the subject is relatively well, rather than wait until the last minute and then have to resort to emergency admission under poor conditions for all those concerned: the patient, the family, and those close to them.

Here we must stress that therapeutic management must be well organized. Apart from purely pharmacological treatment (specific treatments for Alzheimer's disease and treatment of the various symptoms), we propose the following management strategy:

Comprehensive clinical examination of the patient must be carried out initially and then every 3 months. This examination must be repeated if a new incident occurs (e.g. agitation, fever). In particular, bladder distension should be sought (in women and in men), as well as polyuria and altered general health. It should include examination of vision and hearing, and of the teeth and mouth to seek for poor dental condition or fungal infections. Signs of depression or anxiety and mobility problems should be sought. It is also important to look for fecal impaction, constipation, and gastric or abdominal pain especially in those patients who cannot adequately express their complaints. The same is true of rheumatological pain, which may be the cause of unexplained refusal to walk.

The interview should yield information on the living arrangements of the patient, the quality of support from his or her family and relatives and the impact of the disease on the couple, and there should be no hesitation in asking questions about any difficulties the subject may have in managing personal affairs.

Among the radiological examinations and biological tests a chest X ray is advisable (this is particularly useful for patients who attend a day center or who live in an institution, if a resident with whom the patient may have been in contact develops tuberculosis or a lung infection). It will serve as a reference.

Study of the cardiac silhouette can show associated heart failure. Plain abdominal X ray can exclude high faecal loading that could not be found by digital rectal examination. Lastly, a basic ECG is useful, as well as a battery of laboratory tests which should include a complete blood count/ESR, urea and electrolyte, glucose, thyroid-stimulating hormone (TSH), liver function tests, and urine culture.

The standardized gerontological evaluation should be carried out in all patients at the time of diagnosis and then every 6 months or when a change in circumstances occurs, whether social (death of a family member or relative, change of living arrangements, institutionalization, hospitalization), or the onset of an intercurrent disease. Social evaluation should look at the living arrangements of the patient (alone, with family, in institution), and the characteristics of family and relatives (availability, state of health, age). The family must also be fully informed about the services available and the possibilities of legal protection when this is necessary, bearing in mind that it is better to anticipate and prevent problems than have to suffer them.

Specific Pharmacological Treatments for Alzheimer's Disease

Treatment has a double aim: to stabilize or at least to delay the progression of the disease and to reduce the psychological and behavioral problems that often accompany it. These replacement therapies act on the consequences of the lesions, but not on their cause. They are prescribed to reduce neurotransmitter deficiency and so to improve the clinical signs or to delay the progression of the deficiencies observed. The improvement gained ceases after treatment is discontinued.

Anticholinesterase inhibitors are the first drugs to show proven efficacy in Alzheimer's disease. They increase the level of acetylcholine (ACh) in the synapse, by blocking acetylcholine esterase (AChE) which breaks down ACh in the synaptic cleft.

The undesirable side effects are cholinomimetic, that is, nausea, vomiting, diarrhea, agitation, and confusion. Because of these cholinergic properties, prudence is necessary, particularly in poorly controlled asthma, disorders of cardiac rhythm and repolarization, poorly controlled epilepsy, and duodenal ulcer.

Three drugs are now commercially available: donepezil, rivastigmine, and galantamine. Tacrine (Cognex*) is no longer used because of its liver toxicity. Donepezil chlorhydrate (Aricept*) is the second anticholinesterase inhibitor to have been marketed (in 1996 in the United States). It should be started initially at the effective dose of 5 mg (once daily); the optimal dose of 10 mg (once daily) is reached after 6 weeks of treatment. This progressive dose increase makes it possible to limit the side effects. Rivastigmine (Exelon*) is given twice daily. The treatment is begun with a gradually increasing dose: 1.5 mg morning and evening for 2 weeks, then 3 mg morning and evening (6 mg a day is the lowest effective dose), then 4.5 mg morning and evening and finally 6 mg morning and evening (12 mg daily is the maximum dose). The dose of galantamine (Reminyl*) must also be increased gradually. Treatment is started at a dose of 4 mg twice daily for about 1 month, then increased to 8 mg twice daily (and sometimes up to 24 mg a day).

In practice, treatment must be initiated by a physician experienced in the diagnosis of Alzheimer's disease. If there is no absolute contraindication (known hypersensitivity to the molecule, severe liver failure) or relative contraindication (cardiac rhythm disorders, atrioventricular block, sinoatrial block, active gastric or duodenal ulcer, severe asthma,

severe decompensated obstructive airways disease), anticholinesterase treatment is indicated in the mild to moderate stages of the disease. Briefly, these stages correspond to MMS scores of 10 or more, associated with relatively good independence. However, these molecules also seem to have beneficial effects at the advanced stages of the disease, above all on behavior. It is necessary for a relative or friend to monitor compliance. Treatment is started gradually, with a clinical check-up 3 to 6 months later. Such intense biological surveillance appears not to be required for the new anticholinesterase inhibitors (rivastigmine, donepezil, galantamine).

Specific treatment for Alzheimer's disease can only be contemplated as part of a care plan which includes treatment of behavioral problems, nutritional problems and mood, appropriate social management (services delivered to relieve the informal caregiver), and psychological support. Treatment may be discontinued if there is major gastrointestinal intolerance, respiratory decompensation, worsening of cardiac rhythm disorders. If there is any doubt, treatment may be temporarily suspended. Adverse events often occur when doses are changed and regress in a few days. If they do not, it is advisable first of all to add a symptomatic treatment (for gastrointestinal problems, for example), then if this fails, to go back to a lower dose and attempt a more gradual increase.

Poor compliance is also a possible cause of discontinuation of treatment, as is the death or departure of the family member or person who was responsible for the patient's medication.

Lastly, treatment may be stopped if there is no improvement and/or stabilization after 6 months. But in this case, most authors emphasize that a similar drug of the same class should be tried for a sufficiently long period. It should be noted that entry to an institution is all too often the cause for unjustified discontinuation of treatment.

In practice, every patient with mild to moderate Alzheimer's disease should be able to benefit from specific treatment if there is no contraindication. In 2003, a new therapeutic class became available, the antiglutaminergic agents (*N*-methyl-D-aspartate (NMDA) antagonists). Among them, Ebixa* (memantine) is reserved for the time being for the moderately severe and severe forms of the disease.

MANAGEMENT STRUCTURES

The concern of the clinician at the present time must be to identify patients as early as possible in order to rapidly set up a medical and nonmedical intervention strategy, with the aim of maintaining as long as possible satisfactory independence for the patient and his or her family and friends.

Management at Home with Increased Support

Pharmacological and nonpharmacological management of the patient and support and assistance to family and relatives remain the decisive factors in postponing admission to an institution. The majority of patients with dementia live at home, and they are often cared for by the family alone, without any help from professionals.

However, intermediate solutions between care at home by the family and institutionalization have been developed in recent years: care at home with increased support, respite families, day care centers, or temporary care centers are possibilities that offer specific and appropriate management to persons with Alzheimer's disease. But families are still too often insufficiently informed, the facilities available differ widely depending on location, and the financial cost of the services proposed or of the accommodation are still an obstacle to appropriate management of the elderly person with dementia.

Management at home with increased support calls upon external professional help, working as a team with a common objective, and usually coordinated by the general practitioner. Various professionals and services intervene, which are adapted and modulated according to the needs of the patient and his or her family. The following assistance can be provided:

- *nursing care* for toileting, prevention of decubitus ulcers and distribution of medication. This is provided by a nurse in private practice or by a care association;
- *physiotherapy*;
- *the help of an occupational therapist* with, if necessary, *conversion of the accommodation* to reduce the risk of accidents in the home (increased security, prevention of the risk of falls, locking of doors and potentially dangerous places);
- *the services of a home nurse or a helper*, the latter trained in the physical and psychological management of dependent persons;
- *a home help* for the daily activities the person can no longer carry out (shopping, housework, meal preparation). Visits may be daily except for weekends and public holidays. These services are organized by the local health/social councils and the hourly cost depends on the beneficiary's financial resources; similar assistance may be provided by an independent home help;
- a *meal delivery service*, which some local councils provide and which is subject to the same conditions as domestic help;
- *provision of a tele-alarm*, a device that is indicated in mild to moderate dementia without marked temporospatial disorientation and above all without major behavioral disturbance.

Relatives and family also require support if maintenance at home is to be prolonged. Numerous studies have shown that the decisive factor in institutionalization of patients was less dependent on the severity of the disease than on the stamina of the caregiver, usually the spouse. The family need information and assistance if they are to react and adjust well to the disease. This information and support can be provided by the family doctor and the staff of specialized centers (day

care center, day hospital, memory clinic) aided by the various associations.

Hospitalization at Home and Hospitalization in Medium- or Long-stay Units

The physician plays an essential role in detecting intercurrent disorders or complications of the disease. He may make it possible to avoid hospitalization by preventing or treating factors of aggravation such as urinary, bronchial or skin infections, foot care problems, constipation, dehydration, sensory deficits, and so on.

Hospital at home, usually planned for a limited period, is often a more beneficial alternative than hospitalization in a medium-stay unit or admission to a convalescent home. It comprises the intervention in the home of a genuine health-professional team with a doctor, nurse, and nursing auxiliary.

But admission to hospital may become necessary to manage an acute psychiatric or medical problem or to give the family some respite. The following structures all have as their primary aim the rehabilitation of the subject and discharge to his or her own home:

Departments of medicine (geriatrics, neurology, internal medicine, or psychiatry) offer specialized management of the problem that motivated the admission to hospital. But sometimes these facilities are not adapted to aged, demented patients (for example, in internal medicine departments the premises are not suited to management of a behavioral problem, while in psychiatry departments it may be difficult to give a physical complication the specialized medical management required).

The acute-care unit can take in Alzheimer patients whatever the stage of the disease and whatever the intercurrent or associated diseases for a stay lasting a few days. There are very few of these facilities.

Community Residences, Respite Families, and Short-stay Centers

Between the home and long-stay facilities (private retirement home or long-stay unit in a hospital), *community residences* offer patients some independence, with the possibility of access to catering services (restaurant, room service).

Retirement Homes and Long-stay Units

Admission to a long-stay unit may become indispensable when management at home becomes too heavy a burden for the family. Many innovative experiments are being carried out in the hospital setting. They all try to improve the quality of life and management of these patients. Specialized units are being developed; these may be day care units, sheltered units, or true units for diagnosis and rehabilitation. Unfortunately, such initiatives are still very rare and there are many difficulties in the way of their creation, due to lack of funding.

The general practitioner accompanies Alzheimer patients for perhaps 10 years, and copes, with the help of a specialized center, with all the complications that develop throughout the course of the disease. Some can be managed at home; others will require hospitalization. Hospitalization is known to be in itself a factor aggravating the problems of the elderly person in general (frequent episodes of confusion), and these are all the more likely when the care facility is not adapted to behavioral disturbances. This raises the problem of how these hospital facilities can be converted to meet the specific needs of this very particular population.

CONCLUSIONS

Alzheimer's disease has long been considered as an exaggerated manifestation of normal aging, an irremediable end-of-life phenomenon, about which nothing could be done. Over the last 10 years, through advances in our understanding, this view has been replaced by its recognition as a specific neurodegenerative disease state, partly amenable to treatment.

KEY POINTS

- Alzheimer's disease is the commonest cause of dementia.
- The prevalence of Alzheimer's disease is greater than 20% in subjects over the age of 90.
- In the early stages, the disease is characterized by memory and learning difficulties and then language, constructional deficits, apraxia, and dysphasia may intervene.
- Diagnosis is dependent on a thorough clinical evaluation supported by various objective tests for meeting the DSM-IV criteria or the ICD-10 definition.
- There are a range of anticholinesterase treatments available, but these must be viewed as part of an overall management strategy.

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APPENDIX 1

DSM IV : Dementia of the Alzheimer's Type

1. The development of multiple cognitive deficits manifested by both (1) memory impairment (impaired ability to learn new information or to recall previously learned information) (2) one (or more) of the following cognitive disturbances:
   (a) aphasia (language disturbance)
   (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
   (c) agnosia (failure to recognize or identify objects despite intact sensory function)
   (d) disturbance in executive functioning (i.e. planning, organizing, sequencing, abstracting).
2. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
3. The course is characterized by gradual onset and continuing cognitive decline.
4. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
   (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g. cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
   (2) systemic conditions that are known to cause dementia (e.g. hypothyroidism, vitamin B or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   (3) substance-induced conditions.
5. The deficits do not occur exclusively during the course of a delirium.
6. The disturbance is not better accounted for by another Axis I disorder (e.g. Major Depressive Episode, Schizophrenia).

With Early Onset: if onset is at age 65 years or below
With Delirium: if delirium is superimposed on the dementia
With Delusions: if delusions are the predominant feature
With Depressed Mood: if depressed mood (including presentations that meet full symptom criteria for a Major Depressive Episode) is the predominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.
Uncomplicated: if none of the above predominates in the current clinical presentation

With Late Onset: if onset is after 65 years
With Delirium: if delirium is superimposed on the dementia
With Delusions: if delusions are the predominant feature
290. meet full symptom criteria for a Major Depressive Episode) is the predominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.
290.0 Uncomplicated: if none of the above predominates in the current clinical presentation.

Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease: Neurology, 1984; 34 : 939.

1. The criteria for the clinical diagnosis of probable Alzheimer's disease include
   Dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests
   Deficits in two or more areas of cognition
   Progressive worsening of memory and other cognitive functions
   No disturbance of consciousness
   Onset between ages 40 and 90, most often after age 65
   Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.
2. The diagnosis of probable Alzheimer's disease is supported by
   Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia)
   Impaired activities of daily living and altered patterns of behavior

Family history of similar disorders, particularly if confirmed neuropathologically
Laboratory results of
Normal lumbar puncture as evaluated by standard techniques
Normal pattern or nonspecific changes in EEG, such as increased slow-wave activity
Evidence of cerebral atrophy on CT with progression documented by serial observation.

3. Other clinical features consistent with the diagnosis of probable Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include
Plateaus in the course of progression of the illness
Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss
Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increase muscle tone, myoclonus, or gait disorder
Seizures in advanced disease
CT normal for age.

4. Features that make the diagnosis of probable Alzheimer's disease uncertain or unlikely include
Sudden, apoplectic onset
Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and seizures or gait disturbances at onset or very early in course of the illness.

5. Clinical diagnosis of possible Alzheimer's disease
May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course
May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia
Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

6. Criteria for diagnosis of definite Alzheimer's disease are
The clinical criteria for probable Alzheimer's disease
Histopathologic evidence obtained from a biopsy or autopsy.

7. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as
Familial occurrence
Onset before age of 65
Presence of trisomy 21
Coexistence of other relevant conditions such as Parkinson's disease.

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Mild Cognitive Impairment

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INTRODUCTION

The concept Mild Cognitive Impairment (MCI) has been introduced to describe cognitive impairment in nondemented subjects. The prevalence of MCI varies between 2 and 30% in the general population and between 6 and 85% in a clinical setting (average 40%) (Visser, 2000). Subjects with MCI are of major clinical importance because they have an increased risk of developing Alzheimer-type dementia. However, there is much confusion about the concept of MCI: there is no uniform definition, there is no single underlying cause, and the long-term outcome appears to be heterogeneous. In this chapter, definitions of MCI and terminology used, causes of MCI, outcome of MCI, and predictors of dementia will be discussed.

DEFINITIONS AND TERMINOLOGY OF MCI

MCI refers to the presence of cognitive impairment that is not severe enough to meet the criteria of dementia. It has been operationalized in many ways. In a review of the literature performed in 2004, we identified more than 40 definitions of MCI. On the basis of these different MCI definitions, six major concepts can be identified: MCI definitions based on cognitive complaints only, on the presence of mild functional impairment only, on the presence of impairment on cognitive tests only, on a combination of cognitive complaints and test impairment, on a combination of mild functional impairment and test impairment, and on mild functional impairment or test impairment (Table 1). Definitions that fall within the same concept can be further classified according to the cognitive domain that is impaired: impairment in at least the memory domain, in only the memory domain, in any domain, or in a combination of domains. Also, the definition of impairment on cognitive tests is variable and ranges from a score 1 standard deviation below the mean in healthy young subjects to a score 2 standard deviations below the mean in age-matched control subjects. As can be seen in Table 1, the terminology is variable because different terms refer to similar MCI concepts and the same terms are used for different MCI concepts. The MCI definition that is most widely used is that of amnestic MCI (Petersen *et al.*, 1999). It requires a memory complaint, impairment on a memory test after correction for age and education, preserved general cognitive functioning, intact activities of daily living, and absence of dementia. However, due to a lack of detailed criteria, this definition has been operationalized in many different ways. Another common MCI definition is that of Age-Associated Memory Impairment (AAMI) (Crook *et al.*, 1986). It requires a complaint of memory impairment, a score on a memory test one standard deviation below the mean performance of healthy young adults, adequate intellectual functioning, absence of dementia, and absence of diseases that may cause memory impairment. This definition was common in the period 1986–1995, but it is presently less often used.

The lack of standardization is confusing and limits the interpretation of MCI studies. In the remaining part of the chapter, the term MCI will be used for cognitive impairment that do not meet criteria for dementia. It does not refer to any specific definition.

CAUSES OF MCI

One of the most important causes of MCI is Alzheimer's disease. However, all somatic, other neurological, or psychiatric disorders that influence brain functioning can also cause MCI. From a diagnostic perspective, these conditions can be classified in three groups (Visser, 2003). The first group of conditions are obvious causes for MCI. This means that they are a sufficient cause for the impairments and can be identified by clinical examination and/or ancillary tests like laboratory tests or neuroimaging (see Table 2 part A for examples). The second group of conditions are sufficient causes for the MCI that can presently not be diagnosed by

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Table 1 Main MCI concepts

1.	Cognitive complaints Examples: MCI (Tei *et al.*, 1997), minor cognitive impairment (Visser *et al.*, 2002a), questionable dementia (Thompson *et al.*, 2002), memory impairment (Tierney *et al.*, 1996).
2.	Mild functional impairment Examples: MCI or questionable dementia (a score of 0.5 on the Clinical Dementia Rating scale) (Morris *et al.*, 2001), MCI (a score of 3 on the Global Deterioration Scale) (Reisberg *et al.*, 1982), Minimal dementia (Roth *et al.*, 1986).
3.	Impairment on cognitive tests Examples: MCI (Bennett *et al.*, 2002), CIND (Conquer *et al.*, 2000).
4.	Cognitive complaints and test impairment Examples: Aging-associated cognitive decline (Levy, 1994), age-associated memory impairment (Crook *et al.*, 1986), age-related cognitive decline (Celsis *et al.*, 1997), amnestic MCI (Petersen *et al.*, 2001).
5.	Mild functional impairment and test impairment Examples: MCI (Larrieu *et al.*, 2002), CIND (Wu *et al.*, 2002).
6.	Mild functional impairment or test impairment Examples: CIND (Ebly *et al.*, 1995), MCI (Albert *et al.*, 1999), Questionable dementia (Devanand *et al.*, 1997).

MCI, mild cognitive impairment; CIND, cognitive impairment no dementia.

Table 2 Causes of mild cognitive impairment

A.	Disorders that have a strong relationship with mild cognitive impairment and that can often be easily recognized by clinical examination and/or ancillary tests Parkinson's disease, Huntington's disease, severe brain trauma, brain infections, large intracerebral tumors, cerebral bleeding, large cerebral infarcts, extensive white matter pathology, severe depression, psychotic disorders, longstanding and severe alcohol intoxication, drug intoxication (i.e. prolonged use of high doses of benzodiazepines), severe thiamine or vitamin B12 deficiency, unregulated diabetes mellitus or thyroid disorders.
B.	Disorders that have a strong relationship with mild cognitive impairment, but that are difficult to recognize by clinical assessment and/or ancillary tests Predementia or prodromal stage of Alzheimer's disease, Lewy body disease, frontotemporal dementia, vascular dementia, Parkinson's disease, multiple system atrophy, or Huntington's disease.
C.	Disorders that have a weak relationship with mild cognitive impairment Mild brain trauma, transient ischemic attack, epilepsy, disorders that chronically or temporarily impair brain perfusion (hyper/hypotension, stenosis of the carotid artery, generalized atherosclerosis, cardiac surgery), mild depression, bipolar disorders, anxiety disorders, regulated diabetes mellitus or thyroid disorders, mild thiamine or vitamin deficiency, heart failure, obstructive sleep apnea syndrome, chronic obstructional pulmonary diseases, anemia, severe liver or kidney disorders, hearing loss, "normal aging", fear of dementia, psychosocial problems in relation to work, relationships, life phase change, or somatic disorders.

clinical examination or ancillary tests (see Table 2 part B for examples). The third group of conditions have a weak relation with MCI, that is, subjects with such conditions may have MCI on a group level, but it is not clear whether the disorder is the cause for MCI in individual patients (see Table 2 part C for examples). In most studies on MCI, which will be discussed below, subjects with MCI due to obvious causes have been excluded.

OUTCOME OF MCI

MCI is not a stable condition. Depending on the cause, subjects may progress to dementia, may continue to have MCI, or may improve. A meta-analysis of studies with a short to intermediate follow-up period (average 3.1 years, range 1.1–5 years) indicated that on average 10% (range 2–31%) of the subjects with MCI developed dementia at each year of follow-up (Bruscoli and Lovestone, 2004). The conversion rate to dementia appeared to be higher in a clinical setting than in a population-based setting. Similar data were obtained from another meta-analysis (Visser, 2000). This meta-analysis also showed that about 90% of the subjects who converted to dementia had Alzheimer-type dementia. Studies with a follow-up longer than 5 years indicated that subjects continued to convert to dementia at longer follow-up intervals. After 8–10 years, 50 to 80% of the subjects had become demented (Morris *et al.*, 2001; Petersen *et al.*, 2001). Figure 1 shows the long-term outcome of subjects older than 60 years with cognitive complaints and amnesic MCI from the Maastricht Memory Clinic. This figure shows that the conversion rate is dependent on the way MCI is defined. It is noteworthy that the annual conversion rates decline with longer follow-up intervals and that even after 10 years of follow-up a substantial number of subjects have not become demented.

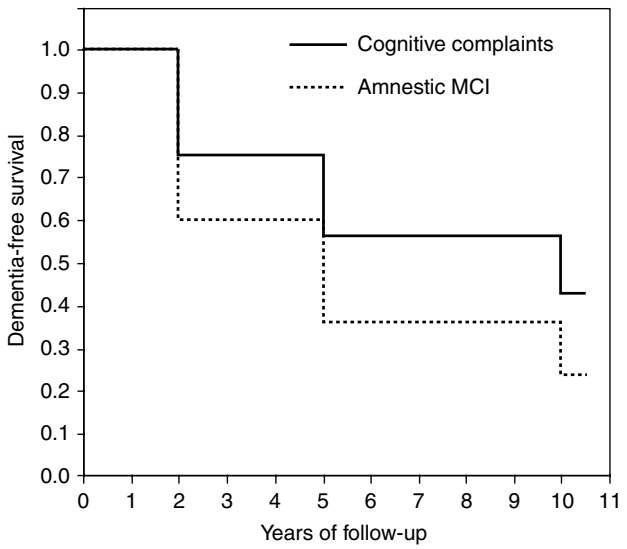

Figure 1 Long-term outcome of subjects older than 60 years with cognitive complaints ($N = 56$, straight line) and amnestic MCI ($N = 33$, dotted line) from the Maastricht Memory Clinic. Follow-up evaluations were performed after 2, 5, and 10 years. The average age at baseline was 69 years (range 60–84 years). 96% of the subjects with dementia had probable AD

PREDICTORS OF DEMENTIA IN SUBJECTS WITH MCI

It is of major importance to identify subjects with MCI who become demented, in order to give them a prognosis and to allow for starting treatment in an earlier phase than is possible now. Many variables have been tested as predictors of dementia in subjects with MCI (DeCarli, 2003). Since the majority of the subjects with dementia have Alzheimer's Disease-type (AD-type) dementia, these predictor variables can be regarded as predictors of AD-type dementia, rather than of dementia in general. Most of the studies discussed below had a follow-up period of 5 years or less (3 years on average). We will first discuss studies that tested predictive accuracy of single variables and then studies that tested predictive accuracy of a combination of variables.

Predictive Accuracy of Single Variables

Predictors Tested in More than Four Studies with a Similar Design

Age, mini-mental state examination (MMSE) score, functional impairment, memory impairment, medial temporal lobe atrophy, and the apolipoprotein E (APOE) genotype have been tested as predictor in more than four studies with a similar design. We have pooled data from these studies (Table 3). Age, the MMSE score, medial temporal lobe atrophy, and the APOE genotype were weak predictors with the odds ratios between 2 and 5 (the odds ratio is a global measure of diagnostic accuracy – an odds ratio of 25 of more indicates a good diagnostic accuracy). Functional impairment and memory impairment were moderately strong predictors with odds ratios between 5 and 8. None of the variables combined a high sensitivity (i.e. the percentage of subjects with dementia at follow-up in whom the predictor was present) with a high positive predictive value (PPV) (i.e. the percentage of subjects in whom the predictor was present and who had dementia at follow-up).

Other predictor Variables

Cognitive predictors. Impairments on neuropsychological tests in domains other than memory such as language function (as measured for example by the Boston Naming Test or verbal fluency), executive functions (as measured for example by the Stroop Color Word test card 3 or the Trail Making Test B), or attention (as measured for example by the Symbol Digit Substitution Test) were also predictors for dementia, but the predictive accuracy was generally less compared to that of tests of memory (Visser, 2003).

Neuroimaging predictors. One study found that the presence of white matter lesions was predictive of dementia (Wolf *et al.*, 2000), but this finding was not replicated in other studies (Korf *et al.*, 2004; Maruyama *et al.*, 2004). Several studies have shown that Single-Photon Emission Computed Tomography (SPECT) hypoperfusion in the parietal–temporal region or posterior cingulate gyrus may be predictive for dementia, but findings have been conflicting (Celsis *et al.*, 1997; McKelvey *et al.*, 1999; Huang *et al.*, 2002; Okamura *et al.*, 2002; Encinas *et al.*, 2003). Also, hypometabolism in the posterior cingulate gyrus or parietal–temporal area as measured with Positron Emission Tomography (PET) scanning was associated with an increased risk for dementia although not in all studies (Berent *et al.*, 1999; Arnaiz *et al.*, 2001; Chetelat *et al.*, 2003; Drzezga *et al.*, 2003; Nestor *et al.*, 2004).

Electrophysiological predictors. A combination of different background frequencies accurately identified subjects with dementia at follow-up with an overall accuracy of 82% in one small study (Jelic *et al.*, 2000). Another small study showed that event-related potentials may be useful for the prediction of dementia with an overall diagnostic accuracy of 85% (Olichney *et al.*, 2002).

Biochemical predictors. The most promising biochemical predictors of dementia are the levels of tau protein (either total tau or phosphorylated tau) and β-amyloid ending at amino acid 42 (Abeta42) in the cerebrospinal fluid. These proteins are thought to reflect the neurodegeneration caused by AD (Blennow and Hampel, 2003). An elevated concentration of total tau protein had a high sensitivity for detecting subjects with Alzheimer-type dementia at follow-up (Arai *et al.*, 1997; Maruyama *et al.*, 2004). The sensitivity of the combination of an elevated concentration of total tau protein and a decreased concentration of Abeta42 for AD-type dementia at follow-up was about 90% (Andreasen *et al.*, 1999; Riemenschneider *et al.*, 2002). The odds ratio

Table 3 Pooled estimates of predictive accuracy for dementia

	OR	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Age (>75 versus 60–75)	2.0	47	70	54	67
Functional impairment (mild versus very mild)	6.8	77	66	51	86
MMSE (<27 versus >26)	3.8	57	73	49	81
Memory (impairment *yes* versus *no*)	7.6	74	73	59	85
MTL atrophy (*yes* versus *no*)	4.6	59	79	61	81
APOE (e4 allele carrier versus *no* e4 allele carrier)	3.4	61	67	45	81

OR, odds ratio; PPV, positive predictive value; NPV, negative predictive value; MMSE, mini-mental state examination; MTL, medial temporal lobe; APOE, apolipoprotein E genotype.
Data are based on a meta-analysis of prospective MCI studies from a clinical setting with a follow-up of on average 3 years (Visser *et al.*, unpublished data).

of this combination for AD-type dementia at follow-up was between 18 and 64 and the positive predictive value between 60 and 94% (Riemenschneider *et al.*, 2002; Zetterberg *et al.*, 2003). In one study, the level of tau phosphorylated at threonine 231 was predictive of dementia (Buerger *et al.*, 2002). Preliminary data indicate that an elevated level of F2-isoprostane 8,12-iso-iPF$_{2\alpha}$-VI in cerebrospinal fluid, plasma, or urine and the level of sulfatide in cerebrospinal fluid may be predictors of dementia as well (Pratico *et al.*, 2002; Han *et al.*, 2003).

It can be concluded that there is no single variable that can accurately identify subjects with dementia at follow-up from among subjects with mild cognitive impairment that will not become demented. The meta-analysis of variables that have been investigated in at least five studies indicated that no variable has an Odds Ratio (OR) higher than 8. Several new promising predictors of dementia have been investigated in small studies, but larger studies are needed to further assess the diagnostic value of these predictors.

Predictive Accuracy of a Combination of Variables

In the previous section, we showed that there is no single variable that can accurately predict progression to dementia. Several studies have suggested that a combination of variables may have a higher accuracy for Alzheimer's disease in subjects with MCI than a single variable (Okamura *et al.*, 2002; Visser *et al.*, 2002b). In the present section, we will discuss one of these multivariable approaches in more detail: the Predementia Alzheimer's disease Scale (PAS) (Table 4) (Visser *et al.*, 2002b). The PAS combines six markers for Alzheimer's disease: age, MMSE score, degree of functional impairment, cognitive test performance, medial temporal lobe atrophy, and the apolipoprotein E genotype. Each variable is scored on a three- to four-point scale and the total sum score indicates the risk for predementia Alzheimer's disease. A retrospective validation study of the PAS in two samples of subjects with MCI who were older than 55 years indicated that the best cutoff score was 6 for the full PAS and 5 for the PAS without the neuroimaging variable. The odds ratio at the best cutoff score was 25, the sensitivity 82% and the positive predictive accuracy 75%. Subjects with a score of 7 or higher had a very high risk (93%) for Alzheimer's disease in both samples, subjects with a score lower than 4 had a very low risk (7%) for Alzheimer's disease, while subjects with a score between 3 and 7 had an intermediate risk for Alzheimer's disease (46%). These intermediate scores were seen in 38% of the subjects. This means that the diagnosis remains uncertain in a substantial number of subjects.

CONCLUSIONS

MCI is a heterogeneous condition. The risk for dementia, typically Alzheimer-type dementia, is high but at longer follow-up intervals, a subset of patients do not develop dementia.

Table 4 Predementia Alzheimer's disease scale (PAS)

	−1	0	1	2	Score
A. *Age*	≤59	60–64	65–74	≥75	
B. *MMSE*[a]	–	≥28	26,27	≤25	
C. *Functional impairment*[b]					
C.1 GDS					
C.2 CDR	–	GDS 1	GDS 2	GDS 3	
C.2.1. Total box score	–	<0.5	0.5–1	≥1.5	
C.2.2. Final score	–	CDR = 0	–	CDR = 0.5	
C.3 CAMDEX	–	–	–	Min Dem	
D. *Neuropsychological tests*[c]	Memory ≥50 perc	Other	1 test impaired	2 tests impaired	
E. *MTL atrophy*[d]					
E.1 Qualitative rating					
Age <75 years	–	0	1	2	
Age ≥75 years	0	1	2	3	
E.2 Volumetry	≥66 perc	33–66 perc	10–33 perc	≤10 perc	
F. *ApoE genotype*	–	Other	e2e4/e3e4	e4e4	
				TOTAL SCORE	

The table indicates which score corresponds with the test result. The total score is an indication for the risk of predementia AD. More information can be found in (Visser *et al.*, 2002b), and at www-np.unimaas.nl/scales/pas.

MMSE, mini-mental state examination; GDS, Global Deterioration Scale (Reisberg *et al.*, 1982); CDR, Clinical Dementia Rating scale (Morris, 1993); MTL, medial temporal lobe; ApoE, apolipoprotein E; Min Dem, minimal dementia; perc, percentile; CAMDEX, Cambridge Mental Disorders of the Elderly Examination (Roth *et al.*, 1986).

[a]The MMSE should be corrected for age and education: if age is 75 or higher or if the period of education has been 8 years or less, one point should each time be added to the observed score; if the period of education has been 14 years or more, one point should be subtracted from the observed score. [b]One option should be used. The CDR can be scored using the Sum of Boxes score (preferred) or the final rating. [c]At least two and maximal four tests including one memory test for delayed recall or learning. An impairment is a score below the 10th percentile or above the 90th percentile (for speed related tasks) after correction for age, sex, and education. [d]One option should be used. A qualitative score can be performed on a CT scan or a MRI scan (Scheltens *et al.*, 1992; de Leon *et al.*, 1993). Volumetry should measure the hippocampus (preferred), parahippocampal gyrus, or entorhinal cortex. The percentile score is relative to age, sex, and intracranial volume.

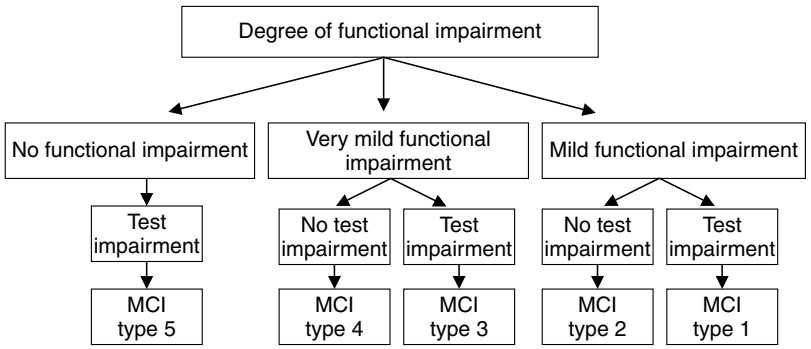

Figure 2 Classification scheme for subjects with mild cognitive impairment. The classification should be performed for each cognitive domain separately (examples of cognitive domains are memory, language, executive function, abstract reasoning/problem solving, and attention). See also www-np.unimaas.nl/scales/cirs. The functional rating is based on a clinical assessment of the performance in daily living. Very mild functional impairments mean that complaints are present and that more effort may be needed to perform tasks. The overall presentation, however, is not impaired and there is no notable deficit in employment or social situation as observed by colleagues or family members. Mild functional impairments mean that complaints are present, impairments are noticeable to colleagues, family members, or the physician, impairments may slightly affect social or occupational functioning, but does affect self-care and does not cause need for assistance from others. The impairment indicates a decrease in functioning that cannot be attributed to normal aging. Test impairment means that performance on cognitive tests is not normal as evidenced by a mild but consistent impairment on a number of tests or a severe impairment on one or more tests

Therefore, MCI should be considered as a description of the severity of cognitive impairment rather as a specific disease.

The lack of standardization of MCI definitions and terminology is confusing and makes it difficult to compare studies. In clinical practice, it may be more informative to classify subjects within the MCI spectrum instead of using a specific MCI definition. An approach for such a classification is shown in Figure 2. More information regarding this classification system can be found at www-np.unimaas.nl/scales/cirs.

There is no single predictor of Alzheimer's disease, but a multivariable approach such as the PAS may provide good diagnostic accuracy. Low-risk and high-risk subjects can be accurately identified by a multivariable approach, but there remains a substantial group of subjects with an intermediate risk for Alzheimer's disease in whom the diagnosis remains uncertain. It is expected that the diagnostic accuracy for these subjects will increase if new predictors for Alzheimer's disease such as the concentration of tau and Abeta42 in cerebrospinal fluid are included in the multivariable approach.

In clinical practice, it seems advisable to keep subjects at intermediate or high risk for dementia under clinical supervision. There is no evidence that subjects at high risk for dementia will benefit from pharmacological treatment. Preliminary data from trials that aimed to prevent progression from MCI to Alzheimer-type dementia with acetylcholine esterase inhibitors, vitamin E, piracetam, or rofecoxib showed lack of efficacy (data presented at the 9th International Conference on Alzheimer's Disease and related disorders in Philadelphia, 19–22 July 2004).

Since subjects continue to develop dementia at longer follow-up studies, studies that investigate predictors of long-term outcome are needed to improve the identification of subjects with MCI who will become demented.

KEY POINTS

- There are no standard criteria for MCI.
- MCI is not related to one specific disorder.
- Subjects with MCI have a high risk for Alzheimer-type dementia, but even in the long term, a substantial number of subjects do not develop dementia.
- A combination of variables may be useful to identify subjects with MCI who are at high risk for Alzheimer-type dementia.
- MCI should be considered as a syndrome rather than as a disease.

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Vascular Dementia

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BACKGROUND

Cognitive function declines with increasing age. This decline differs between individuals probably due to genetic predisposition, and educational, and professional background. The decline may be accelerated by different insults to the brain, such as Alzheimer's disease (AD), cerebrovascular disease (CVD), other brain disorders, and different peripheral disorders such as cardiovascular diseases. When the cognitive function reaches a certain threshold, giving rise to difficulties in everyday life, the term dementia is used. The two most common causes of dementia are AD and cerebrovascular disorders. The latter cause of dementia is often subsumed under the term vascular dementia (VaD). AD and CVD often coexist in the same patient, and is then labeled mixed dementia (Langa *et al.*, 2004).

Current criteria for dementia and its subtypes are old, more than 10 years, and often show inconsistencies in their descriptions (Skoog and Copeland, 2002). Criteria such as those of the ICD-10 (World Health Organization, 1993) and diagnostic and statistical manual of mental disorders (DSM-IV) (American Psychiatric Association, 1994), describe dementia as a global decline in intellectual function affecting memory, orientation, visuospatial abilities, executive function, language, and thinking. It is often accompanied by changes in personality and emotions. These criteria also state that the decline in cognitive function must include significant memory dysfunction. This concept is based on the symptoms seen in AD. However, CVD may cause significant cognitive dysfunction with relatively preserved memory function. The term vascular cognitive impairment has therefore been introduced during recent years (Bowler and Hachinski, 1995). This term includes both VaD and other forms of cognitive decline caused by cerebrovascular and cardiovascular diseases.

VaD can thus be regarded as one manifestation of CVD, together with, for example, focal motor and sensory symptoms. There are many different etiologies of VaD, including stroke, silent infarcts, ischemic white-matter lesions (WMLs), hereditary cerebral hemorrhage with amyloidosis, granular cortical atrophy, hypertensive encephalopathy, cerebral amyloid angiopathy, and cerebral vasculitis. Most cases of VaD exhibit a combination of vascular changes (Munoz, 1991). The two most common causes of VaD are, however, stroke and WMLs. Cerebrovascular disorders are also associated with the overall cognitive decline observed in elderly populations (Breteler *et al.*, 1994a,b,c; Skoog *et al.*, 1996). Several causes of VaD or vascular cognitive impairment are potentially preventable, and can even be treated.

Diagnostic Criteria

The Hachinski Ischemic Score (Hachinski *et al.*, 1975) was the most widely used instrument for the diagnosis of VaD, or multi-infarct dementia (MID) as it was called, from the 1970s to the early 1990s. It comprises a symptom check list which incorporates some symptoms that are believed to be essential in the stroke-related form of VaD, such as abrupt onset, stepwise deterioration, fluctuating course, a history of stroke, and focal neurological symptoms and signs. It also incorporates risk factors such as hypertension and cardiovascular diseases. The assumption was that MID was caused by embolic phenomena, so that the onset would be sudden and acute. Subsequent further emboli would produce other sudden deteriorations, perhaps followed by some improvement.

Memory impairment is mandatory for the diagnosis of VaD in the ICD-10 (World Health Organization, 1993), DSM-III-R (American Psychiatric Association, 1987) and DSM-IV (American Psychiatric Association 1994) criteria. This is not ideal as cognitive dysfunction in CVD may be substantial while memory dysfunction is mild (Bowler and Hachinski, 1995). The ICD-10 requires that "deficits in higher cognitive functions are unevenly distributed" and DSM-III-R that there is "a patchy distribution of deficits (i.e. affecting some functions, but not others) early in the course." The latter was, however, no longer included in the DSM-IV.

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Although stroke increases the risk of developing dementia several-fold (Tatemichi *et al.*, 1992; Pohjasvaara *et al.*, 1997; Linden *et al.*, 2004), the contributions of a stroke or an infarct for the clinical symptoms of dementia are not always easy to elucidate. Most criteria leave it to the clinician to make the decision whether the CVD "may be judged to be etiologically related to the dementia" (Skoog and Copeland, 2002).

In most criteria for VaD, the definition of CVD is based on the history or findings of focal neurological motor symptom/signs, or brain imaging findings of CVD. DSM-IV gives examples of signs, while the ICD-10 specifically requires that at least one should be (1) unilateral spastic weakness of the limbs, (2) unilateral increased tendon reflexes, (3) extensor plantar response, or (4) pseudobulbar palsy.

The DSM-IV specifies that there should be signs AND symptoms OR laboratory evidence indicative of CVD (e.g brain imaging findings of multiple infarctions involving the cortex and subcortical white matter) that are judged to be etiologically related to the disturbance, while ICD-10 requires that there should be evidence from history, examination OR tests of a significant CVD, which may be reasonably judged to be etiologically related to the dementia (e.g history of stroke or evidence of cerebral infarction). In the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (Román *et al.*, 1993), a diagnosis of probably VaD requires that focal signs consistent with stroke AND relevant CVD by brain imaging should be present. Tatemichi, one of the authors of the NINDS-AIREN criteria published a modified version (Tatemichi *et al.*, 1994b) in which this criterion was changed to focal signs consistent with stroke OR relevant CVD by brain imaging. The first criterion is probably too strict and underestimates the occurrence of VaD (Skoog and Copeland, 2002), especially since individuals with silent infarcts or WMLs without stroke symptoms will not be considered. In a study on 85-year-olds (Skoog *et al.*, 1993), 13% of the demented had VaD based on the criteria "focal signs consistent with stroke AND relevant CVD by brain imaging" while 47% had VaD with the criterium "focal signs consistent with stroke OR relevant CVD by brain imaging". The NINDS-AIREN criteria allows a diagnosis of "possible" VaD in the presence of dementia with focal neurological signs in patients in whom brain imaging studies are missing; or in the absence of a clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course. This means that if CVD is present in a patient with dementia, a diagnosis of VaD will be made. Furthermore, the interpretation of a single stroke leading to dementia likely differs between centers, and may be one reason for the disparate results regarding the prevalence of VaD.

The temporal relationship between stroke and the onset of dementia is often thought to strengthen the possibility that the two disorders are etiologically related. The NINDS-AIREN criteria suggest an arbitrary limit of 3 months for the onset of dementia after stroke. However, a stroke which occurred years before may still indicate the presence of CVD.

Epidemiology

Almost all epidemiological studies reporting on the frequency of VaD are concerned with the subtype related to clinically manifest stroke or transitory ischemic attacks (TIA). As may be seen in Table 1, the proportion of VaD vary widely between studies. The differences might be due to differences in diagnostic criteria, differences in the rate of cerebrovascular disorders, or constitutional or environmental factors. It may also reflect the efforts done to diagnose CVD and whether brain imaging has been used. Although the prevalence of dementia is similar in most parts of the world, there are differences regarding the type of dementia. MID is reported to be more common in Finland, the former Soviet Union, and Asian countries, including Japan and China, than in western Europe and the United States, where AD is generally reported to be the most common type of dementia. However, more recent studies from China and Japan report similar proportions of VaD as in western countries (Zhang *et al.*, 2005). Also, the proportion diagnosed with VaD in autopsy studies vary (Table 2), probably due to different samples and the importance given to CVD as a cause of the dementia. It is noteworthy that few patients in autopsy studies were regarded as having pure VaD.

Table 1 Proportion of vascular dementia in population studies

	Country	Sex	Proportion (%) with vascular dementia among the demented
Fratiglioni *et al.* (1991)	Sweden	Male	26
		Female	24
Ott *et al.* (1995)	Holland	Male	18
		Female	15
Rocca *et al.* (1990)[a]	Italy	Male	40
		Female	35
O'Connor *et al.* (1989)	Britain	All	21
Aevarsson and Skoog (1997)[a]	Sweden	Male	44
		Female	45
Livingston *et al.* (1990)			
Manubens *et al.* (1995)	Spain	Male	16
		Female	11
Brayne and Calloway (1989)	Britain	Female	31

[a]CT, scan aided in diagnosis of vascular dementia.

Table 2 Proportion of vascular dementia in autopsy studies

Study	Sample size	VaD%	Pure VaD, %	Setting
Galasko *et al.* (1994)	170	9	2	AD research centers
Ince *et al.* (1995)	69	6	NA	Nursing home
Drach *et al.* (1997)	59	27	12	Nursing home
Holmes *et al.* (1999)	80	29	9	Dementia register
Lim *et al.* (1999)	134	34	3	AD patient registry
Barker *et al.* (2002)	384	18	3	Memory clinics, GP

Stroke-related Dementia

All criteria for VaD include history of stroke due to cerebral infarcts. Most cerebral infarcts are due to thromboembolism from extracranial arteries and the heart, and are often related to large vessel disease. The typical patient has a history of stroke or TIA with acute focal neurological symptoms and signs. The main risk factors for stroke are hypertension, diabetes mellitus, atherosclerosis, atrial fibrillation, smoking, and hypercholesterolemia (Qiu *et al.*, 2002). All these risk factors are potentially treatable.

Stroke is a component of most criteria for VaD or vascular cognitive impairment, but is stroke related to an increased frequency of dementia? According to Tatemichi *et al.* (1992, 1993, 1994a), subjects with ischemic stroke had at least nine times greater risk for dementia than stroke-free controls. Pohjasvaara *et al.* (1997) also reported an increased prevalence of dementia in stroke victims, as well as a decrease in independent living for those with dementia. Linden *et al.* (2004) recently reported that stroke victims had 2–3 times increased risk for dementia. The relative risk for dementia compared to population controls was larger in younger age-groups, but the frequency of dementia was higher after the age of 80, approximately 35%. Furthermore, 60% of nondemented stroke victims had some cognitive dysfunction. In the population studies from Gothenburg, Sweden, Liebetrau *et al.* (2003) reported that stroke increased the risk for dementia 2–3 times in 85-year-olds.

However, cerebral infarcts may occur without focal symptoms, so-called silent infarcts. Silent infarcts become more common with increasing age (Vermeer *et al.*, 2002). Silent infarcts have long believed to be benign incidental findings on brain imaging. Recently, researchers from the Rotterdam Study reported that individuals with silent infarcts have an increased risk for clinical stroke (Vermeer *et al.*, 2002) or dementia (Vermeer *et al.*, 2003) during follow-up. Liebetrau *et al.* (2004) reported that 10% of 85-year-olds had silent infarcts on computerized tomography (CT) and that these lesions were related to a twofold increased prevalence of dementia.

If focal symptoms occur in connection with the onset of dementia, it is considered to strengthen the diagnosis of VaD (Román *et al.*, 1993). However, the recent reports that silent infarcts are common in the elderly and that they are related to an increased risk for dementia may question this statement. The typical clinical course of VaD includes sudden onset, stepwise deterioration, and a fluctuating course. In the early stages, the cognitive impairment may have a large variability depending on the site of the lesions. However, a large group of patients with CVD have a gradual onset of dementia with a slowly progressive course (Fischer *et al.*, 1990) and without focal signs or infarcts on brain imaging, which makes it difficult to differentiate from AD. It has been suggested that individuals with cortical strokes show less decline in cognitive function than those with subcortical CVD (Gunstad *et al.*, 2005). Other cardiovascular manifestations, including myocardial infarction and hypertension, are common in the patients.

The pathogenesis behind stroke-related dementia is not clear. It has been suggested that the dementia may be related to the location or the volume of the infarcts, but there are also other possibilities. The risk factors suggested for VaD are similar to those in stroke, including male sex, hypertension, diabetes mellitus, smoking, and cardiac diseases (Skoog, 1998). Non-stroke-related risk factors are similar to those found in AD (Skoog, 1998), including higher age, lower level of formal education, family history of dementia, and the presence of cerebral atrophy, supporting the view that "poststroke dementia" is a combination of the direct consequences of stroke, and preexisting AD pathology. Pure VaD, without any AD brain changes, is probably rare.

Subcortical White-matter Lesions

The other dominating CVD associated with dementia and cognitive decline are subcortical WMLs (Fernando and Ince, 2004), which has been suggested to be the most common form of VaD. The neuropathological findings include marked or diffuse ischemic demyelination and moderate loss of axons with astrogliosis and incomplete infarction in subcortical structures of both hemispheres and arteriosclerotic changes with hyalinization or fibrosis and thickening of the vessel walls and narrowing of the lumina of the small penetrating arteries and arterioles in the WM (Román, 1987; Brun and Englund, 1986). The cortex is generally well preserved, as are the subcortical U fibers and corpus callosum, probably due to a different blood supply.

The main hypothesis regarding the cause of WMLs is that long-standing hypertension causes lipohyalinosis and thickening of the vessel walls with the narrowing of the lumen of the small perforating arteries and arterioles that nourish the deep WM (Román, 1987). Episodes of hypotension, related to, for instance, aging, drugs, or cardiac failure, may lead to hypoperfusion and hypoxia-ischemia, leading to loss of myelin in the WM. The deep WM has few collaterals, which makes it more vulnerable to ischemia than the cortex when a penetrating vessel occludes. Furthermore, myelin is probably more vulnerable to ischemia than axons are (Englund and Brun, 1990). It has been suggested that the arterial changes are due to exposure of vessel walls to increased pressure over time. The greater the pressure and/or lifespan, the more likely are these changes to be present. This may be one reason for the observed increase with age reported in most studies.

WMLs appear as low density areas on CT scans and as hyperdense areas on magnetic resonance imaging (MRI). In 15 studies or case reports on the clinicopathologic correlations of subjects with WMLs on CT, the histopathologic picture described above had been reported in 53 out of 55 autopsied cases (Skoog *et al.*, 1994). WMLs on MRI are often reported as being the same entity as WMLs on CT. However, WMLs on MRI correspond to several different histological findings, most often état crible, and often show no correlation with cognitive decline and dementia. MRI is more sensitive than CT to detect changes in the white matter, but has a lower specificity, and WMLs on MRI may bear little relationship to the hypodensities seen on CT.

MRI studies have generally reported substantially higher rates of WMLs than CT studies. The population study from Rotterdam (Breteler *et al.*, 1994b) reported that 11% in the age strata 65–69 years, 21% in those aged 70–74 years, 27% in 70–79-year-olds and 54% in those aged 80–84 years had WMLs, and the Helsinki Aging Brain Study (Ylikoski *et al.*, 1995) reported periventricular hyperintensities in 21% of those aged 55–75 years and 65% in those above that age. In the latter two studies severity also increased with age. A recent population-based neuropathological study reported that 94% of demented subjects had WMLs (Fernando and Ince, 2004).

The cognitive decline in subjects with WMLs has been suggested to be caused by a disconnection of subcortical–cortical pathways, producing a decline in abilities related to subcortical or frontal lobe structures. Individuals with WMLs generally exhibit psychomotor slowness (Skoog *et al.*, 1996; Junqué *et al.* 1990; Ylikoski *et al.*, 1993; Breteler *et al.*, 1994c) and deficiencies in frontal lobe skills (Boone *et al.*, 1992), such as executive dysfunction.

Dementia associated with WMLs often has an insidious onset and a slowly progressive course (Román, 1987; Gunstad *et al.*, 2005), which makes it difficult to distinguish from AD. In the initial stage, there may be transient and fleeting attacks of focal neurological deficits, with a subacute accumulation of focal deficits. The typical picture includes subcortical symptoms with extrapyramidal signs, especially psychomotor retardation, and a frontal lobe syndrome with executive dysfunction, apathy, loss of drive, and emotional blunting. Other features may include bilateral or unilateral pyramidal tract signs, and hemi- or motoranesthesia, pseudobulbar palsy, urinary incontinence, and gait dysfunction. However, WMLs seldom occurs as the sole cause of dementia, and the clinical picture may vary depending on what other causes contribute to the dementia. Recently, it was reported that punctate WMLs on MRI do not progress, while confluent white-matter abnormalities are progressive, and thus more malignant in the long-time (Schmidt *et al.*, 2003).

The main risk factor for WMLs is hypertension, and hypertension-clustering factors.

Mixed Dementias

The common coincidence of AD and VaD is becoming increasingly recognized (Langa *et al.*, 2004; Fernando and Ince, 2004), and this may even be the most common form of dementia. Although CVD increases the risk of developing dementia (Tatemichi *et al.*, 1992; Pohjasvaara *et al.*, 1997; Linden *et al.*, 2004; Liebetrau *et al.*, 2003; Skoog *et al.*, 1994), the contribution of CVD for the clinical symptoms of dementia are not always easy to elucidate. CVD may be the main cause of dementia in an individual, it may be the event that finally overcomes the brain's compensatory capacity in a subject whose brain is already compromised by Alzheimer pathology, albeit not yet clinically manifest, and in many instances minor manifestations of both disorders which individually would not be enough to produce dementia may produce it together (Erkinjuntti and Hachinski, 1993a,b). On a clinical basis, it is, however, difficult to differentiate mixed dementia from VaD. CVD as a contributing cause of dementia may be under-diagnosed as sometimes the onset is insidious, the course gradual, the infarctions clinically silent, and the infarcts not detectable by CT or MRI of the brain (Skoog, 1994; Fischer *et al.*, 1990). Pure VaD may also be overdiagnosed as the presence of stroke, WMLs, or other CVD does not necessarily mean that they are the only cause of the dementia (Skoog, 1994). Often AD becomes a diagnosis by exclusion, and the diagnosis of VaD will be assigned if the patient has a history of CVD. This leads to a situation where the dementias will not infrequently be divided into one group with stroke and one without. Even the histopathological diagnoses of AD and VaD are uncertain. Extensive histopathological signs of AD (Tomlinson *et al.*, 1970; Arriagada *et al.*, 1992) and CVD (Del Ser *et al.*, 1990; Tomlinson *et al.*, 1970) have been found in persons who show no clinical signs of dementia during life. In fact, the MRC-FAS study (Neuropathology Group. Medical Research Council Cognitive Function and Aging Study, 2001), and the Nun Study (Snowdon *et al.*, 1997) reported that only about 50% of those fulfilling neuropathological criteria for AD were demented during life. This shows that AD alone does not always lead to dementia. A considerable proportion of subjects fulfilling the diagnosis of probable NINCDS-ADRDA criteria for AD or probable NINDS-AIREN for VaD have mixed pathologies (Holmes *et al.*, 1999; Lim *et al.*, 1999). WMLs have been described on both brain imaging and at autopsy in cases of Alzheimer's disease (Brun and Englund, 1986; De la Monte, 1989; Skoog *et al.*, 1994). The Nun Study showed that CVD increased the possibility that individuals with AD lesions in their brains will express a dementia syndrome (Snowdon *et al.*, 1997). Furthermore, patients with VaD may exhibit cholinergic deficits, similar to that seen in AD, due to ischemia of basal forebrain nuclei and of cholinergic pathways (Erkinjuntti *et al.*, 2004; Roman, 2005). Also other markers of AD, such as cerebrospinal tau (Skoog *et al.*, 1995) and β-amyloid (Skoog *et al.*, 2003) may show similar patterns in VaD as in AD. In addition, vascular risk factors may also be important for the development of AD (Skoog and Gustafson, 2003).

DIAGNOSIS

The first step in the diagnostic work-up is to determine whether the patient has cognitive dysfunction, and to evaluate the nature of this dysfunction. Such examination should be performed on all elderly patients with a recent stroke. For this purpose, a simple screening instrument may be used, for example, the widely used Mini Mental State Examination. Examples of other tests include examinations of executive function, the clock test, word fluency, naming ability, and five-items memory test. Individuals with dementia related to CVD may often be difficult to test because of language dysfunction.

In the second phase, a possible cerebrovascular cause of the dementia is identified. Auxiliary investigations, including brain imaging are necessary in this step, not only to identify CVD but also to diagnose other conditions that might contribute to the cognitive decline, for example, cardiovascular diseases, low-pressure hydrocephalus, subdural hematoma, brain tumors, deficiency states, infections, and depression. It is important to note that in the elderly there are often multiple causes of dementia, and that every contributing treatable cause that can be diagnosed may be important in the treatment of the patient. The examinations include careful history-taking, neurological, psychiatric, and physical examinations, interview of a close informant, brain imaging such as CT scan or MRI of the head, a chest X ray, ECG and biochemical screening including vitamin B12 level, a thyroid function test and, in selected cases, cerebrospinal fluid examinations. Brain imaging is important to detect WMLs and cerebral infarcts. An ECG should be performed to detect arrhythmias. Traditionally, AD has been a diagnosis of exclusion and the diagnosis of VaD has often been assigned if the patient has a history of stroke thought to be related to dementia onset. However, from a clinical standpoint, it is neither important nor possible to differentiate between AD and VaD in most cases. Most cases of VaD are probably of a mixed etiology (see Table 2), and older patients with AD may often have concomitant CVD, which needs treatment. Therefore, treatment should be directed both to the CVD and the AD.

TREATMENT POSSIBILITIES

The general strategy in the treatment of VaD is to prevent new strokes or infarcts. Although no formal studies have been performed, the use of anticoagulant agents, for example, low-dose treatment with salicylates, is often used. Treatment of cardiac arrhythmias, high blood pressure, and hypercholesterolemia is also essential. Regarding white-matter dementia, antihypertensive treatment may potentially prevent the changes in the small vessels. VaD often have concomitant AD. In these cases, one should initiate treatment with an acetylcholinesteras inhibitor (Erkinjuntti *et al.*, 2002, 2004).

KEY POINTS

- Vascular cognitive impairment is a relatively new term that embraces both vascular dementia and other forms of cognitive decline caused by cerebrovascular and cardiovascular diseases.
- Stroke-related dementia is likely to be more common than previously reported and may occur in patients with silent cerebral infarcts and the absence of focal symptoms.
- Subcortical white-matter lesions (WML) linked to long-standing hypertension appear to be an important pathogenetic mechanism in vascular dementia.

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Other Dementias

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INTRODUCTION

Dementia is an acquired syndrome in which there is impairment of cognitive abilities, severe enough to interfere with the individual's occupational, social, and functional abilities. As conventionally used, the term dementia implies "degenerative" and "progressive", but it is also often used in the context of static conditions (such as poststroke cognitive impairment) or reversible conditions (such as depression or medication-related cognitive impairment). Table 1 provides a list of the many causes of dementing illnesses that can occur in older individuals.

Results of different epidemiological studies indicate that Alzheimer's disease (AD) is by far the commonest cause of dementia worldwide (Green, 2001). It may be tempting for clinicians to routinely make this diagnosis without systematically considering alternative or additional diagnoses. Such a practice is time-saving and probably fortuitously correct most of the time. However, it risks a great disservice to a significant proportion of patients as it fails to detect reversible diseases affecting cognition (which often occur concomitantly with degenerative diseases like AD) and by extension, fails to provide appropriate treatment and accurate prognoses.

In population-based studies, the commonest reported dementia etiology after AD is vascular dementia (VaD) (Lobo *et al.*, 2000; von Strauss *et al.*, 1999; Andersen *et al.*, 2000), especially in Asian populations like the Japanese (Ikeda *et al.*, 2001) and Chinese (Wang *et al.*, 2000). Recent reports also indicate that when actively sought for with standard criteria, the prevalence of dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) may be higher than previously thought. For example, the Islington study of dementia subtypes in community-dwelling elderly revealed the following distribution of dementia subtypes: AD–31.3%; VaD–21.9%; DLB–10.9%; and FTD–7.8% (Stevens *et al.*, 2002).

Specialized memory clinic–based estimates differ somewhat from population-based studies in having a relatively higher prevalence of non-AD etiologies, and concomitant potentially reversible conditions, especially depression and metabolic abnormalities. Larson *et al.* (1986) evaluated 200 older persons with dementia and found that 33.7% had metabolic abnormalities. Generally, however, only a small percentage of these have been found to be completely reversible (Clarfield, 1988; Walstra *et al.*, 1997; Siu, 1991), most notably in conditions such as hypothyroidism and vitamin B12 deficiency. The prevalence of etiologies in demented patients presenting to private practitioners has not been estimated, but would likely reflect values intermediate between population and specialized outpatient-based estimates (Green, 2001).

The rest of this chapter seeks to discuss some conditions that are commonly encountered in clinical practice, and concludes with a general approach to the evaluation of dementia in older persons.

VASCULAR DEMENTIA

One of the most controversial and difficult areas in the pathology of dementing disorders is the role of cerebrovascular disease (CVD) in dementia. In the early 1900s, it was erroneously held that the most frequent cause of late-onset dementia was arteriosclerosis (arteriosclerotic insanity). Pioneering work in the 1960s and early 1970s challenged this assumption, establishing that only stroke-related loss of brain tissue exceeding 50 to 100 ml resulted in dementia, and that Alzheimer pathological changes were important in the majority of cases (Tomlinson *et al.*, 1970). In 1974, the term *multi-infarct dementia* (MID) was coined to reflect dementia due to multiple large and small strokes (Hachinski *et al.*, 1974). It has since been realized that the contribution of CVD to VaD is more than MID, since VaD can arise from a single

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Table 1 Causes of dementia other than Alzheimer's disease

1. Other degenerative dementias
   a. Dementia with parkinsonism
      i. Diffuse Lewy body disease
      ii. Parkinson's disease dementia
      iii. Progressive supranuclear palsy
      iv. Others for example, corticobasal degeneration, multiple system atrophy
   b. Frontotemporal dementia
   c. Huntington's disease
   d. Hallervorden–Spatz disease
   e. Kufs' disease
2. Vascular dementia
3. Other CNS causes
   a. Normal pressure hydrocephalus
   b. Epilepsy
   c. Traumatic dementia
      i. Acute and chronic subdural hematoma
      ii. Dementia pugilistica
      iii. Craniocerebral injury
   d. Tumors
      i. Primary CNS tumors: gliomas, meningiomas
      ii. Metastatic tumors, lymphoma, leukemia
      iii. Paraneoplastic limbic encephalitis
4. Psychiatric disorders
   a. Depression
   b. Others: schizophrenia, mania, other psychoses
5. Inflammatory
      i. Cerebral vasculitis
         • Primary angiitis of the CNS
         • Part of systemic involvement: disseminated lupus erythematosus, temporal arteritis, Behcet's, Wegener's granulomatosis, Churg–Strauss disease
      ii. Multiple sclerosis
6. Metabolic
   a. Endocrinopathies
      i. Hyper- and hypothyroidism
      ii. Glucose disorders: HHNK
      iii. Cushing's disease
      iv. Addison's disease
   b. Electrolyte abnormalities
      i. Hypo- and hypernatremia
      ii. Hypercalcemia
   c. Inherited
      i. Wilson's disease
      ii. Mitochondrial disorders
      iii. Adult lysosomal diseases (particularly metachromatic leukodystrophy)
      iv. Peroxisomal disorders
7. Nutritional deficiency
      i. Thiamine deficiency
      ii. Vitamin B12 deficiency
      iii. Folate deficiency
      iv. Vitamin B6 deficiency (pellagra)
8. Infective
   a. Neurosyphilis
   b. Human prion disease
   c. HIV-associated dementia
   d. Progressive multifocal leukoencephalopathy
   e. Postmeningitic/postencephalitic dementia
9. Drugs (remembered by the mnemonic: ACUTE CHANGE IN MS[a])
   a. **A**ntiparkinsonian drugs
   b. **C**orticosteroids
   c. **U**rinary incontinence drugs
   d. **T**heophylline
   e. **E**mptying (motility) drugs
   f. **C**ardiovascular drugs
   g. **H**2 blockers
   h. **A**ntimicrobials
   i. **N**SAIDs
   j. **G**eropsychiatric drugs
   k. **E**NT drugs
   l. **I**nsomnia drugs
   m. **N**arcotics
   n. **M**uscle relaxants
   o. **S**eizure drugs
10. Toxins
   a. Alcohol
   b. Heavy metals: lead, aluminum, mercury
   c. Carbon monoxide poisoning
11. Others
   a. Obstructive sleep apnea
   b. Whipple's disease
   c. Neurosarcoidosis

HHNK, hypoglycemia, hyperglycemic hyperosmolar nonketotic syndrome.
[a]Flaherty JH. Clin Geriatr Med 1998;14(1): 101–27.

strategic stroke, lacunar infarcts, or incomplete white matter ischemia.

Epidemiological studies in the West indicate that VaD is second in prevalence to AD, accounting for 12–20% of dementia cases (Roman, 2003a). The incidence of VaD increased with age, but much less steeply than AD. Unlike AD, men are disproportionately more affected, especially at the younger ages. Interestingly, international comparative studies reveal a comparatively higher frequency of VaD in some Asian countries, especially Japan and China. Among ethnic Japanese, the ratio of AD to VaD ranged from 0.5 in Japan to 1.5 in Hawaii, indicating possible interactions between genes and environment (Chui, 2000). The ratio of AD to VaD varied from 1.4 in Beijing, China, to 2.8 in Korea, compared with the ratio of 3.4 in Europe (Morris *et al.*, 2004).

Dementia may occur in 25–33% of ischemic stroke cases at ages 65 and older. Predictors of the occurrence of dementia following stroke include: older age, lower education level, non-White race, preexisting cognitive decline, diabetes, lower blood pressure or orthostatic hypotension, "silent" infarcts on neuroimaging, ischemic rather than hemorrhagic strokes, hemispheric rather than brainstem or cerebellar lesions, left rather than right hemispheric lesions, larger and recurrent strokes, a more severe neurological deficit on admission, and complications of acute stroke, including hypoxic and ischemic events (seizures, cardiac arrhythmias, aspiration pneumonia, hypotension) (Roman, 2003b). In addition, periventricular white matter lesions of significant size and hippocampal atrophy have been associated with increased risk of VaD (Liu *et al.*, 1992; Mungas *et al.*, 2001). Interestingly, apolipoprotein $\varepsilon 4$ has been associated with increased risk for AD, but not VaD (Frank *et al.*, 2002).

VaD encompasses several clinicopathologic subtypes, ranging from hemorrhagic (including hypertension, cerebral amyloidal angiopathy, subarachnoid hemorrhage, posthemorrhagic obstructive hydrocephalus, subdural hematoma, and hematological causes) to ischemic, and combinations of ischemia and hemorrhage (such as cortical vein and sinus

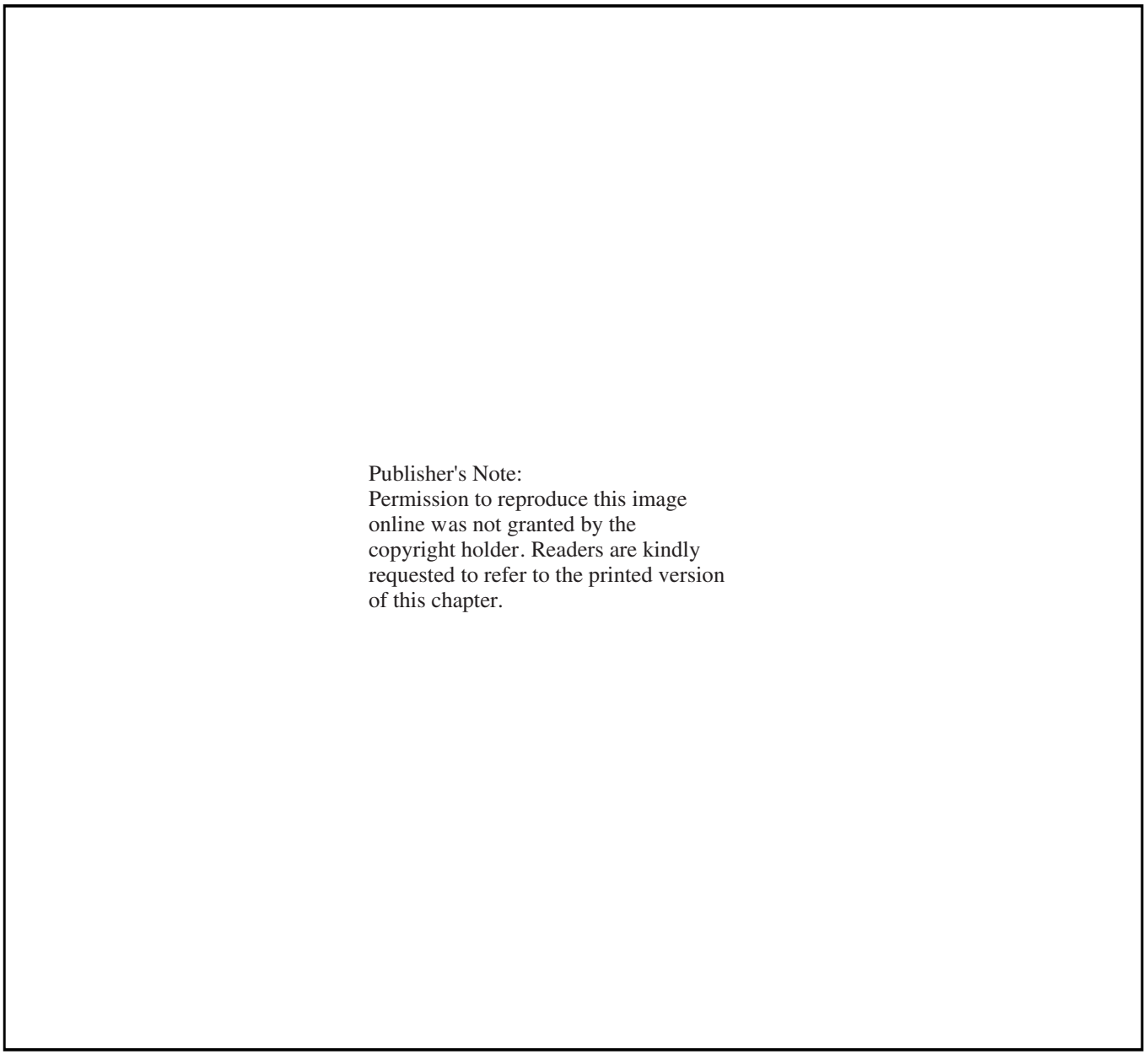

Figure 1 Heterogeneity of clinical presentation of vascular dementia. (a) Heterogeneity of ischemic vascular dementia and (b) differentiation of clinical features by vessel size

thromboses). The ischemic forms of VaD can be further divided into large-vessel, small-vessel, and strategic infarct subtypes (Figure 1a). Strategic stroke VaD results from a single stroke in a strategic location critical to cognitive function, and can occur in large-vessel (usually right posterior cerebral artery, anterior cerebral artery or left gyrus angularis) or small-vessel arterial territory (in the capsular genu, intraluminary nuclei of the thalamus, or head of caudate nucleus). The term *multi-infarct dementia* is now reserved for the combination of multiple cortical and subcortical vascular lesions.

Although there is some degree of overlap, large-vessel strokes tend to yield a clinical picture of cortical dementia, as opposed to the subcortical dementia of small-vessel forms (Figure 1b). These can be reasonably differentiated by a combination of cognitive features, neurological features, and clinical course (Table 2) (Roman, 2002). Subcortical ischemic vascular dementia (SIVD) typically causes a clinically slow, subacute-onset dementia, that is characterized by executive dysfunction, impaired attention, and impaired processing speed, with a comparatively milder memory deficit (Looi and Sachdev, 1999). There may be "lower-half parkinsonism"

Table 2 Characteristics of cortical and subcortical dementia

	Cortical	Subcortical
Cognitive deficits	Memory impairment Heteromodal cortical symptoms Neuropsychological syndromes Executive dysfunction	Executive dysfunction Memory deficit milder Perseveration Mood changes (depression, emotional lability, apathy)
Neurological symptoms	Field cut Lower facial weakness Upper motor neuron signs Dominant/ nondominant lobe signs	Imbalance/falls Gait disturbance Altered urine frequency Mild upper motor neuron signs Dysphagia Extrapyramidal symptoms
Clinical course	Abrupt onset, stepwise deterioration, fluctuating course, plateaus	60%: slow, less abrupt onset 80%: slow progression with and without acute deficits

producing characteristic gait changes of hesitation, *marche a petit pas* (walking with hurried small steps) and diminished step height. In fact, the triad of dementia, urinary incontinence, and gait disturbance is more often produced by VaD than normal pressure hydrocephalus (NPH). SIVD includes the lacunar state and Binswanger's disease, characterized, respectively, by multiple lacunes and periventricular leukoencephalopathy that typically spares the arcuate subcortical U fibers. Included in this group is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetically transmitted small-vessel disorder which has been mapped to chromosome 19q12 with mutations in the Notch 3 gene.

To make a diagnosis of VaD, three elements are necessary: presence of dementia, presence of cerebrovascular lesions, and a temporal relationship between the two. There are two sets of criteria currently available for the diagnosis of VaD (Bowler and Hachinski, 2002). The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 1994) and the *Classification of Mental and Behavioural Disorders*, 10th Revision, under the International Classification of Diseases (ICD-10) (World Health Organization, 1993) are general diagnostic tools that outline criteria without operationalizing them. The second set, such as the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche at L'Enseignement en Neurosciences (NINDS-AIREN) (Roman *et al.*, 1993) criteria (Table 3), is a development of the first two and offers operational criteria. Autopsy studies (Gold *et al.*, 1997; Gold *et al.*, 2002) have shown that while these criteria are generally able to exclude about 90% of AD, they have only modest sensitivity (50–70%) in diagnosing VaD. There is also a tendency to misclassify mixed dementia (AD with CVD) as VaD (54% for ADDTC and 29% for NINDS-AIREN), especially in the "possible VaD" category (Gold *et al.*, 1997).

Table 3 NINDS-AIREN diagnostic criteria for definite, probable, and possible vascular dementia (VaD)

Definite VaD
Clinical criteria for probable VaD
Autopsy demonstration of appropriate ischemic or hemorrhagic brain injury and no other cause of dementia

Probable VaD
Dementia
Cerebrovascular disease
- Focal neurological signs consistent with stroke
- Neuroimaging evidence of clinically relevant vascular lesions

Relationship between dementia and cerebrovascular disease, as evidenced by one or more of the following:
- Onset of dementia within 3 months of a recognized stroke
- Abrupt deterioration or fluctuating or stepwise progression of the cognitive deficit

Clinical features consistent with diagnosis:
- Subtle onset and variable course of cognitive deficits
- Early presence of gait disturbance
- History of unsteadiness, frequent and unprovoked falls
- Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease
- Pseudobulbar palsy
- Personality and mood changes, abulia, depression, emotional incontinence, and subcortical deficits, including psychomotor retardation and abnormal executive function

Possible VaD
Dementia with focal neurologic signs but without neuroimaging confirmation of definite cerebrovascular disease
Dementia with focal signs but without a clear temporal relationship between dementia and stroke
Dementia and focal signs but with subtle onset and variable course of cognitive deficits

Alzheimer's disease with cerebrovascular disease
Clinical criteria for possible Alzheimer's disease
Clinical and imaging evidence of cerebrovascular disease

Reference: Roman GC *et al. Neurology* 1993; **43**:250–60.

Not surprisingly, CVD often coexists with other age-related neurodegenerative pathology such as AD, Parkinson's disease and Lewy body disease (LBD), to yield "mixed dementia". It has been reported that 10–15% of poststroke dementia actually has significant preexisting cognitive impairment. These "pre-stroke" dementia patients probably have underlying AD worsened by stroke (i.e. mixed dementia) (Hénon *et al.*, 2001). Mixed AD with CVD should be considered in patients with a prior diagnosis of AD or amnestic mild cognitive impairment (MCI), or if there is preexisting insidiously progressive cognitive impairment. The Nun Study showed that patients with lacunar strokes had 20 times increased risk of clinical dementia and required fewer senile plaques and neurofibrillary tangles to exhibit signs of dementia (Snowdon *et al.*, 1997). Thus, in patients with AD plus CVD, both conditions require treatment, even if the vascular component appears trivial (for example, one or two lacunes).

Nonetheless, VaD and AD can often be distinguished on the basis of differences in onset, progression, domains of cognitive impairment, and gait disturbances (Table 4) (Roman, 2003b). The features that best distinguish VaD from AD are stepwise deterioration, fluctuating course, history of stroke,

Table 4 Characteristics of vascular dementia and Alzheimer's disease

Characteristic	Vascular dementia	Alzheimer's disease
Onset	Sudden or gradual	Gradual
Progression	Slow, stepwise fluctuation	Constant insidious decline
Neurological findings	Evidence of focal deficits	Subtle or absent
Memory	Mildly affected	Early and prominent deficit
Executive dysfunction	Early and severe	Later and less severe
Neuroimaging	Infarcts and/or white matter lesions	Normal; hippocampal atrophy
Gait	Often disturbed early	Usually normal
Cardiovascular history	Transient ischemic attacks, strokes, vascular risk factors	Less common

Source: Modified from Roman GV. *J Am Geriatr Soc* 2003; **51**:S296–304 with permission of Blackwell Publishing Ltd.

and focal neurological symptoms (Moroney *et al.*, 1997). Neuropsychiatric disturbances such as depression, anxiety, agitation, disinhibition, and apathy are more common in VaD than in AD, and delusions tend to be less common in VaD. Depression in the acute phases following stroke is associated with left frontal lesions, while depression in more chronic poststroke patients is more likely to occur with right posterior lesions (Shimoda and Robinson, 1999). Brain imaging, typically magnetic resonance imaging (MRI) or computed tomography (CT), usually demonstrates with varying degrees of sensitivity, vascular lesions such as a single strategic stroke, multiple cortico-subcortical strokes, and periventricular white matter ischemia. Neuroimaging has come to play such an important role in diagnosing and evaluating VaD that the absence of vascular lesions identified on neuroimaging virtually excludes the diagnosis.

Nomenclature-wise, there has been a recent movement to more accurately define the contribution of CVD in cognitive disorders (Roman *et al.*, 2004). The term *vascular cognitive impairment* (VCI) is now proposed to refer to the subset with ischemic brain injury producing less severe cognitive impairment that do not meet the criteria for VaD (i.e. vascular cognitive impairment no dementia, VCI-ND), analogous to the concept of amnestic MCI, currently considered the earliest clinically diagnosable stage of AD. This is to emphasize the preventable nature of VaD, and the importance of early diagnosis. In addition, the current requirement of memory loss as the *sine qua non* for the diagnosis of VaD may result in oversampling of patients with AD worsened by stroke (i.e. mixed dementia). Thus, the definition of dementia in VaD has been proposed to be modified to the presence of *executive dysfunction* of sufficient degree to interfere with social or occupational functioning. Lastly, the term, *vascular cognitive disorder* (VCD) (Sachdev, 1999), has been proposed as the global diagnostic category for cognitive impairment of vascular origin, ranging from VCI to VaD. It includes specific disease entities such as poststroke VCI, poststroke VaD, CADASIL, Binswanger's disease, and AD plus CVD.

Pharmacologic management of VaD involves a multiprong approach addressing specific treatment for cognition, management of neuropsychiatric disturbances, management of stroke-related disabilities such as spasticity, parkinsonism and incontinence, and prevention strategies centered around the prevention of stroke. The latter involves anticoagulation in patients at risk of cardioembolism, antiplatelet agents, and targeting modifiable risk factors such as hypertension, diabetes, hyperlipidemia, negative lifestyle factors (habitual cigarette smoking, inactivity, obesity), and hyperhomocysteinemia. There is some evidence that treatment of hypertension may reduce the risk of dementia (Pantoni *et al.*, 2000; PROGRESS Collaborative Group, 2001). Despite the benefit of statins in reducing stroke by 30%, this did not translate into benefits in cognition in a recent trial with cognition as the primary endpoint (Shepherd *et al.*, 2002).

It has been postulated that there is a cholinergic deficit in VaD, akin to AD, resulting from interruption of cholinergic pathways by vascular lesions. This hypothesis has been borne out in the results of recent randomized controlled trials of cholinesterase inhibitors, which show modest benefits in global response, cognition, activities of daily living and behavior after 24 weeks, compared with placebo (Erkinjuntti *et al.*, 2004). These benefits were seen in both mixed dementia and VaD patients. Interestingly, the cognitive scores in untreated patients with VaD did not deteriorate over the study period, in contrast to the worsening typically observed in the control group in AD trials, suggesting that VaD patients may be distinct from AD (Figure 2) (Wilkinson *et al.*, 2003). More importantly, it suggests that the treatment aims in the two groups may possibly differ. In VaD, the cognitive effect is dependent on absolute improvement over baseline, representing an *improvement* in cognition, unlike the *stabilization* of cognition observed in AD, where the cognitive effect is mostly dependent on continuing deterioration in the placebo group. There is also evidence that memantine, an *N*-methyl-D-Aspartate (NMDA) receptor antagonist that protects against glutamate-mediated excitotoxicity, shows modest benefits in mild to moderate VaD (Orgogozo *et al.*, 2002).

DEMENTIA WITH PARKINSONISM

General Approach

The concomitant presentation of cognitive impairment with Parkinsonism is not uncommonly encountered in clinical practice, and presents a diagnostic conundrum to most clinicians. The principal causes in the elderly are listed in Table 5. A detailed clinical history and physical examination, coupled with relevant investigations, is indispensable in navigating through the labyrinth of differential diagnoses.

It is important to ascertain the onset, duration, and progression of the illness. A younger age of onset would alert

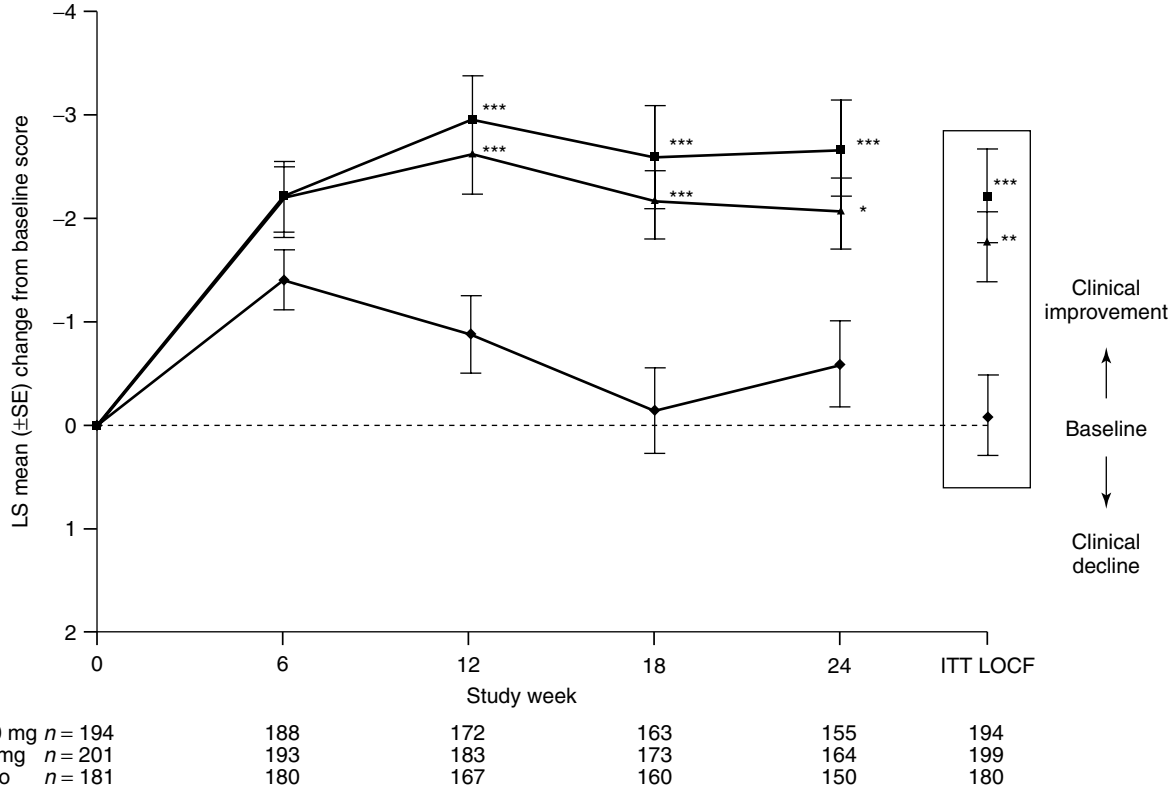

Figure 2 Alzheimer disease assessment scale–cognitive subscale least squares mean change from baseline score in donepezil- and placebo-treated patients. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ versus placebo. —■— = Donepezil 10 mg/day; —▲— = donepezil 5 mg/day; —◆— = placebo (Reproduced from Wilkinson D, *et al.*, Donepezil in vascular dementia, *Neurology*, **61**, 479–86, Copyright 2003, with permission from Lippincott Wiliams and Wilkins)

Table 5 Principal causes of parkinsonism with cognitive impairment in the elderly

Parkinson's disease
- Idiopathic
- Familial

Parkinsonism in other neurodegenerative diseases
- Dementia with Lewy bodies
- Progressive supranuclear plasy
- Frontotemporal dementia with parkinsonism
- Multiple system atrophy
  - Olivopontocerebellar degeneration
  - Shy–Drager syndrome
  - Striatonigral degeneration
- Corticobasal degeneration
- Hallervorden–Spatz disease

Vascular dementia with parkinsonism

Postencephalitic parkinsonism
- Encephalitis lethargica
- Other encephalitides eg, syphilis

Secondary parkinsonism
- Pharmacologic: antipsychotic agents, especially the high potency conventional agents, and other dopamine blocking drugs
- Toxins: carbon monoxide intoxication, cyanide poisoning, methanol, ethanol
- Postanoxic parkinsonism
- Dementia pugilistica
- Normal pressure hydrocephalus
- Space-occupying lesions: tumors, blood clot, abscess, and so on
- Metabolic, for example, Wilson's disease

the clinician to familial syndromes, hereditary illnesses (e.g. Wilson's disease), and certain neurodegenerative causes (e.g. FTD and multiple system atrophy). Cognitive decline without significant progression for several years, is not, in general, likely to be secondary to a neurodegenerative disease since once symptomatic, these tend to be progressive. Chronology of presenting symptoms, in particular, the temporal relationship between the onset of Parkinsonism and dementia, can yield useful information. For instance, dementia onset more than 12 months after the initial motor symptoms of Parkinsonism, favors the diagnosis of Parkinson's Disease dementia (PDD) rather than DLB (McKeith *et al.*, 1996). Marked fluctuations in cognition, attention, and alertness are pathognomonic of DLB and PDD, although it is prudent to exclude delirium and its myriad causes if the duration is short. A history of frequent falls early in the course of disease suggest progressive supranuclear palsy (PSP), although this can also be seen in idiopathic Parkinson's disease (PD), DLB, multiple system atrophy (MSA) and NPH. Early dysphagia or dysarthria is characteristic of PSP. Compared to AD, the degree of memory impairment in the group of dementias with Parkinsonism is comparatively milder by disease stage, and there are usually more neuropsychiatric features at the time of presentation. Frontotemporal dementia patients are more likely to manifest euphoria and disinhibition, while visual hallucinations, delusions, and misidentifications are

more common in DLB and PDD. A detailed family history and medication review cannot be overemphasized. Other relevant history includes occupational history (e.g. dementia pugilistica results from recurrent significant head trauma and this typically occurs in boxers), ethanol ingestion, and significant illnesses (e.g. strokes, encephalitis).

Pertinent pointers during physical examination include examination of the eyes (impairment of vertical gaze with intact oculocephalic reflex in PSP, and nystagmus suggestive of olivopontocerebellar degeneration), cerebellar signs (olivopontocerebellar degeneration), pattern of extrapyramidal involvement (PSP is characterized by predominantly axial as opposed to distal rigidity), postural blood pressure (orthostatic hypotension from autonomic dysfunction is a feature of MSA, but can also occur in DLB and PD; it can also be secondary to drug treatment with levodopa and dopamine agonists), higher cortical function (asymmetrical limb apraxia and cortical sensory loss in corticobasal degeneration), and gait (apraxic gait typically in NPH, but also seen in Binswanger's disease and SIVD).

Structural neuroimaging with CT or MRI can yield useful information about the differential diagnosis: hydrocephalus; space-occupying lesions; evidence of vascular parkinsonism such as lacunar infarcts, periventricular, and white matter hyperintensities; midbrain atrophy which is typical of PSP; pontine and cerebellar changes evident in olivopontocerebellar degeneration; and mixed low and high signal intensity in the putamen evident in striatonigral degeneration. Hypointensity of the striatum on MRI is generally against the diagnosis of idiopathic Parkinson's disease (Cummings, 2003).

In summary, the cardinal task of the clinician when confronted with a patient with Parkinsonism and cognitive impairment is first, to exclude easily identified secondary causes, and then determine if the clinical picture supports a diagnosis of Parkinson's plus syndrome as opposed to idiopathic Parkinson's disease. Useful discriminating features in favor of Parkinson's plus syndrome are symmetrical onset of Parkinsonism, absence of resting tremors, and the presence of concomitant atypical features (history of poor response to levodopa, predominantly axial involvement, early severe dementia, early marked autonomic disturbance, gaze palsies, and upper motor neuron findings). When patients with two out of the three classic signs of parkinsonism (tremors, rigidity, and bradykinesia) were compared with postmortem pathologic diagnosis of Parkinson's disease (Hughes *et al.*, 1992), the strongest additional bedside argument for PD (positive likelihood ratio = 4.1; negative likelihood ratio = 0.4) is the combination of (1) asymmetrical onset, (2) no atypical features, and (3) no alternative diagnosis. This can then direct the clinician to further investigations and management.

DEMENTIA WITH LEWY BODIES

There is growing appreciation that LBD may be a single disease spectrum comprising DLB at one end and PDD at the other (Figure 3). Accumulating evidence favors this unified school of thought, as opposed to the thinking that they are independent diseases ending in a similar common pathway (McKeith and Mosimann, 2004). The hallmark of both diseases is the presence of Lewy bodies, which contain α-synuclein and suggest neurobiological links with other synucleinopathies such as MSA (Baba *et al.*, 1998). In Parkinson's disease, Lewy bodies are prominent in the brain stem and rare in the cortex, whereas in DLB, they are common in the brainstem, limbic system, and neocortex. Although concomitant AD pathology (β-amyloid plaques, and to a lesser degree, neurofibrillary tangles) may be present, clinicopathologic correlations reveal that the severity of cognitive impairment is significantly associated with α-synuclein rather than AD pathology (Gomez-Tortosa *et al.*, 1999). In DLB, cortical LB density has been associated with cognitive impairment and visual hallucinations, while better correlates with visual hallucinations are found with Lewy neurites (LN), neurone loss, dopaminergic, and cholinergic deficits (Perry *et al.*, 2003). The cholinergic deficit in DLB is better defined and more pronounced then AD.

Onset of DLB is between 50 and 90 years of age, and the duration of illness varies between 6 and 10 years. Risk factors include older age, male sex, and the presence of apolipoprotein-ε4 allele. DLB accounts for approximately 15–20% in autopsy series. Clinically, DLB is marked by a progressive dementia syndrome with fluctuating cognition and alertness, recurrent, well formed visual hallucinations and parkinsonism (Table 6). Autopsy validation studies have shown the criteria for DLB to have high specificity (80–100%), but more limited sensitivity (35–80%)

Table 6 Concensus guidelines for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

Central feature
Progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function
Core features (two core features essential for a diagnosis of probable, one for possible DLB)
Fluctuating cognition with pronounced variations in attention and alertness
Recurrent visual hallucinations that are typically well formed and detailed
Spontaneous motor features of parkinsonism
Supportive features
Repeated falls
Syncope
Transient loss of consciousness
Neuroleptic sensitivity
Systematized delusions
Hallucinations of other modalities
REM sleep behavior disorder
Depression
Features less likely to be present
History of stroke
Any other physical illness or brain disorder sufficient enough to interfere with cognitive performance

Source: Modified from McKeith IG *et al.* Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB), *Neurology* 1996; **47**:1113–24, with permission of Lippincott Williams & Wilkins.

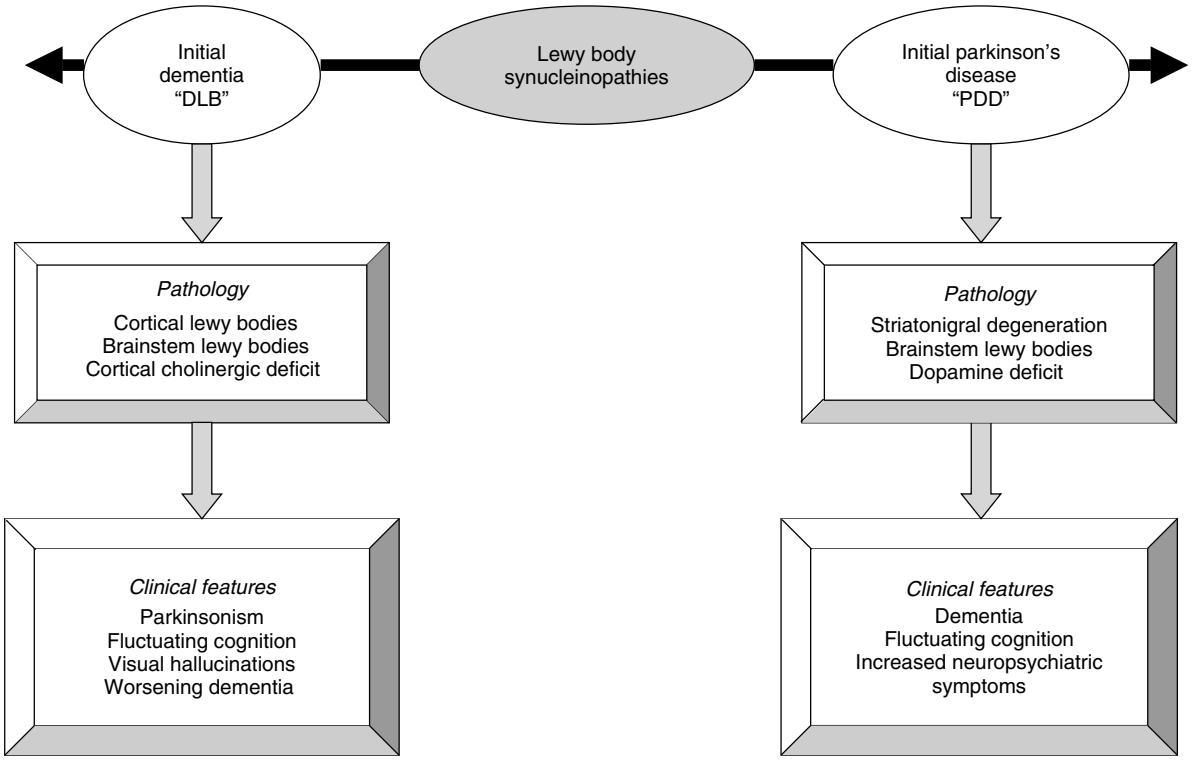

Figure 3 Schematic representation of the spectrum of clinical presentation of dementia Lewy bodies, based on the premise that Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are actually different representations of the same neurobiological process with different initial manifestations

(McKeith, 2002). It is the identification of cognitive fluctuation that poses clinicians the greatest difficulty, and the most frequent clinical misdiagnosis of DLB is AD.

Prominent or persistent memory impairment may not necessarily occur in the early stages, but is usually evident with progression. The characteristic neuropsychological profile in early LBD is that of prominent executive, attentional, and visuospatial dysfunctions with relatively preserved memory functions. Fluctuation in cognitive performance, attention, and level of consciousness is the most characteristic feature of DLB. The marked amplitude between best and worst performances distinguishes it from the minor day-to-day variations that commonly occur in dementia of any cause. Transient disturbances of consciousness in which patients are found mute and unresponsive for periods of several minutes, may represent the extreme of fluctuation in arousal, but are often mistaken for transient ischemic attacks, despite a lack of focal neurological signs. One study (Ferman *et al.*, 2004) reported that informant endorsement of at least three items out of four composite features of fluctuations (daytime drowsiness and lethargy, daytime sleep of 2 or more hours, staring into space for long periods, episodes of disorganized speech) yielded a positive predictive value of 83% for DLB against the alternate diagnosis of AD.

Prominent neuropsychiatric symptoms at time of presentation are among the defining features of DLB. Although not unique to DLB, the behavioral alterations occurring in DLB are present at a much higher frequency than in other dementias (Cummings, 2003). The visual hallucinations typical of DLB are typically recurrent, well formed and detailed, and usually involve people and animals that appear to be real but make no noise. Depressive symptoms are common and 40% have a major depressive episode, which is significantly greater than in AD (McKeith, 2002). Other common behavioral manifestations include hallucinations in other modalities, misidentifications (such as Capgras syndrome), systematized delusions, and rapid eye movement (REM) sleep disorders.

Extrapyramidal motor symptoms (EPS) of DLB, present in about 80% of DLB patients, consist primarily of bradykinesia and rigidity, with resting tremors seen in less than 50%. When present, these symptoms can be as severe as in PD, although progression of EPS is uncommon. It is reported that 70% of DLB patients have at least a transient beneficial response to levodopa treatment (Louis *et al.*, 1997). Recurrent falls and syncope occur in a third, presumably reflecting autonomic dysfunction.

Differential diagnosis include other dementia syndromes such as AD and VaD; other causes of delirium; other neurological syndromes such as Parkinson's disease, PSP, or Creutzfeld–Jakob disease; and other psychiatric disorders such as late-onset delusional disorders, depressive psychosis, and mania. There are as yet no clinically applicable genotypic or cerebrospinal fluid (CSF) markers to support a DLB diagnosis, though neuroimaging investigations may be helpful.

These include relative preservation of hippocampal and medial temporal lobe volume on MRI, and occipital hypoperfusion on single photon emission computerized tomography (SPECT), compared with posterior parietal-temporal hypoperfusion in AD (Lobotesis *et al.*, 2001).

Forty percent to 50% of DLB patients show neuroleptic sensitivity reactions with a 2–3-fold increase in mortality (McKeith *et al.*, 1992). These range from sedation, increased confusion, and worsening of parkinsonism, to more deleterious effects like irreversible parkinsonism, impaired consciousness, and marked autonomic disturbances *à la* neuroleptic malignant syndrome. Conventional neuroleptic medications are best avoided, while atypical newer agents (such as clozapine, olanzepine, risperidone, and quetiapine) should be used judiciously. In addition, medications with anticholinergic or dopaminergic antagonism (e.g. tricyclic antidepressants, low potency neuroleptics, antiparkinsonian anticholinergic drugs and antispasmodics) should be avoided, as they have the potential to impair cognition, exacerbate psychotic symptoms and may be associated with orthostatic hypotension. There is evidence that cholinesterase inhibitors are effective and relatively safe for the treatment of neuropsychiatric and cognitive symptoms in DLB, with major side effects similar to those reported in AD; mainly gastrointestinal symptoms with nausea, vomiting, and diarrhea (McKeith *et al.*, 2000).

PARKINSON'S DISEASE DEMENTIA

It is now recognized that crude prevalence figure of 20–40% from earlier cross-sectional surveys of movement-disorder clinic populations, underestimated the frequency of PDD. Subsequent long-term follow-up studies showed that 60–80% of PD patients will develop dementia, typically after 10–15 years of motor disability (Aarsland *et al.*, 2003). Older age, at PD onset, duration of motor symptoms, akinetic-rigid profile (as opposed to the tremor-predominant subtype), reduced verbal fluency (naming number of items belonging to a specific category, for example, animals, in 1 minute), early hallucinations, and depression are predictive factors of dementia development (Emre, 2003).

There are four pertinent issues related to the management of PDD. Firstly, from a diagnostic standpoint, there is a need to review the current concept of the dementia syndrome, such as those found in the DSM-IV and ICD-10, which often are heavily AD-based (McKeith, 2004). Unlike AD, the initial impairment in PDD typically involves attention, executive function, and visuospatial performance with only mild memory impairment in the initial stages. Moreover, it can be difficult to judge the extent to which functional impairment is attributable to cognitive dysfunction rather than motor disability.

Secondly, it is imperative for the managing clinician to be cognizant of attendant sleep and neuropsychiatric issues, and to actively screen for their presence. The former consists of longer sleep latency, poor quality sleep with frequent awakenings, restless leg syndrome, excessive daytime sleepiness and REM sleep disorders. The latter is more common in PD patients with dementia than those without, and corresponds with the severity of cognitive impairment. In a study of community-dwelling PD patients, the most common behavioral issues were dysphoric mood (38%), hallucinations (27%) and anxiety (20%) (Cummings *et al.*, 1994). Risk factors for depression include early onset of PD, presence of hallucinations or delusions, the akinetic-rigid clinical syndrome, greater degree of cognitive impairment, and right-sided parkinsonism (due to greater left brain involvement) (Tandberg *et al.*, 1997). Anxiety disorders are common in PD, especially in the "off" period of treatment, and usually coexist with depression. Mood fluctuations are also common in PD patients with the "on–off" phenomenon, with increased depression and anxiety during the "off" state and increased elation during the "on" state (Richard *et al.*, 2001).

Thirdly, managing clinicians should be mindful of treatment-associated neuropsychiatric symptoms, occurring with levodopa, dopamine agonists, anticholinergic agents, and amantadine. These include sleep disturbances, hallucinations, delusions, mania/euphoria, and hypersexuality/sexual paraphilias. The most important determinant of which individuals will develop psychiatric phenomena following therapy initiation, is individual susceptibility (the presence of cognitive impairment is the most influential among these factors), rather than drug dosage. The syndrome of *hedonistic homeostatic dysregulation* (HHD) has been described, typically in men with early onset PD who exhibit drug induced dyskinesias. HHD is an addiction syndrome to levodopa characterized by excessive use beyond that required to alleviate motor impairment, increasing dose requirements as drug tolerance develops, withdrawal reactions, and classic substance abuse behaviors of drug hoarding and denial. Frequently associated symptoms include punding (this refers to repetitive, purposeless motor acts), hypersexuality, psychomotor restlessness, pathological gambling and shopping, and anorexia.

Lastly, with regard to therapeutic options, there is evidence from three randomized controlled trials of PDD patients (Emre *et al.*, 2004; Aarsland, 2002; Leroi *et al.*, 2004) that cholinesterase inhibitors can offer modest improvements in memory mirroring the degree seen in AD, as well as attention and neuropsychiatric features (especially hallucinations). Tremors occurred more frequently with treatment, but the overall motor function did not decline. Further trials are needed to ascertain which subgroup responds best to cholinergic enhancement, and at which stage cholinesterase inhibitors should be offered. Although improved cognition has been reported in patients with mild Parkinson's disease following the administration of levodopa, mixed results have been found in moderately to severely affected PD patients (Morrison *et al.*, 2004). In an evaluation of 800 patients studied in the Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism (DATATOP) trial, no clear benefit was noted with either deprenyl or tocopherol, alone or in combination

(Kieburtz *et al.*, 1994). Finally, the role of memantine, a novel NMDA receptor antagonist, needs to be established; it has been shown to improve cognition in moderate to severe AD (Reisberg *et al.*, 2003), and may also ameliorate motor symptoms (the parkinsonian drug, amantadine, is a related compound) and apathy.

PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy is a tauopathy characterized neuropathologically by marked midbrain atrophy, neurofibrillary tangles, or neuropil threads in the basal ganglia and brainstem, as well as tau-positive astrocytes. Clinically, it is the degenerative disorder most commonly confused with PD. According to the National Institute of Neurological Diseases and Stroke-Society for Progressive Supranuclear Palsy (NINDS-SPSP) criteria, key clinical features for probable PSP are onset at age 40 or later, a gradually progressive course, paralysis of vertical gaze, and prominent postural instability with falls in the first year of disease onset (Litvan *et al.*, 1996). Typically, there are limitations of volitional vertical downgaze followed by decreased vertical upgaze, with vertical pursuit and lateral movements affected next. Oculocephalic reflexes remain intact through most of the disease course. There is symmetrical rigidity that is predominantly axial with extensor posturing resulting in retrocollis. Other pertinent features include early dysphagia and dysarthria leading to unintelligibility of speech, and poor response of parkinsonism to levodopa therapy. Cognitive impairment is primarily one of the executive dysfunctions involving the frontal-subcortical circuits, with slower processing speed, diminished free recall but relatively preserved recognition memory, impairment in abstract thought and verbal fluency (Bak and Hodges, 1998). Compared with PD patients, those with PSP have significantly more apathy and disinhibition while those with PD exhibit more delusions, hallucinations, and depression (Aarsland *et al.*, 2001). Sleep abnormalities are common in PSP, and include shortened sleep time, lower percentage of time spent in REM sleep, and awakenings. Unfortunately, PSP is a treatment resistant condition and prognosis is generally poor (Kompoliti *et al.*, 1998). Parkinsonism may respond to dopaminergic agents, especially dopamine receptor agonists in some cases (Jackson *et al.*, 1983). Patients are intolerant of anticholinergic compounds, which should be avoided. Local treatment with botulinum toxin injections may relieve blepharospasm or painful spasms in affected limbs (Polo and Jabbari, 1994).

CORTICOBASAL DEGENERATION

Corticobasal degeneration (CBD) is a tauopathy which has substantial overlap with FTD (Kertesz *et al.*, 2000). The cardinal neuropathological features are asymmetrical cortical degeneration involving primarily the frontal and parietal regions, severe neuronal loss in the substantia nigra, ballooned achromatic cells as well as tau-positive neurofibrillary tangles and neuropil threads in the cortex, subcortex, and brainstem (Schneider *et al.*, 1997). Patients have a parkinsonian syndrome manifested by asymmetrical rigidity, dystonia, and reflex myoclonus. Cognitive features include apraxia, cortical sensory loss and alien limb phenomenon, which refers to actions performed by the affected limb that are not consciously intended by the patient. The apraxia of CBD is of the ideomotor type, referring to inability to perform movements on command that is not explained by motor or sensory abnormalities. The apraxia is typically most severe in the limb affected by dystonia or myoclonus, and rarely, can involve buccofacial structures. The low sensitivity but relatively high specificity of the diagnosis of CBD means that most patients with a clinical diagnosis of CBD have the diagnosis confirmed at autopsy, but autopsy also detected many cases not suspected clinically (Riley and Lang, 2000). CBD has a unique cognitive profile of combined cortical and frontal-subcortical cognitive deficits that is marked by executive dysfunction, visuospatial disturbances, retrieval memory deficit, and aphasia. Behaviorally, depression and apathy are frequent and often prominent, while most other symptoms are less common. MRI may reveal asymmetrical frontoparietal atrophy, while functional neuroimaging such as positron-emission tomography (PET), show asymmetrical changes that are most severe on the side contralateral to the affected limb (Hirono *et al.*, 2000).

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy is a synucleinopathy characterized by α-synuclein containing cytoplasmic inclusions in glial cells and affected neurons. It is a sporadic, progressive, adult-onset disorder that includes striatonigral degeneration (when parkinsonian features predominate), olivopontocerebellar atrophy (when cerebellar features predominate) and Shy–Drager syndrome (when autonomic failure is predominant) (Concensus Committee of the American Autonomic Society and the American Academy of Neurology, 1996). Cognitive changes are typically mild and represent executive dysfunction. Diagnostic features for MSA have high specificity but low sensitivity and many patients go unrecognized; it is most commonly misdiagnosed as PD or PSP (Litvan *et al.*, 1997). The features that discriminate MSA from PD are an earlier age of onset (50–55 years of age), rapid progression, and the presence of autonomic dysfunction preceeding or within 2 years of the onset of the motor symptoms. Progression is more rapid than idiopathic PD, with 40% of patients markedly disabled or wheelchair-bound within 5 years of onset (Wenning *et al.*, 1994). Treatment is mainly supportive. Fludrocortisone or midodrine may be used for treating symptomatic postural hypotension.

FRONTOTEMPORAL LOBAR DEGENERATION

Frontotemporal lobar degeneration (FTLD) denotes a progressive dementia syndrome characterized by behavioral change, prominent aphasia, or both. It is the commonest form of primary degenerative dementia in middle age after AD, accounting for up to 20% of presenile dementia cases (Snowden *et al.*, 2002). Only a minority of patients exhibit Pick-type histological changes, hence the more generic term FTLD is preferred to "Pick's disease". FTLD is superior to "dementia" as a generic term for this group of disorders, since patients may have progressive neurological dysfunction for substantial periods of time before meeting criteria for a dementia syndrome.

Onset occurs most commonly between the ages 45 and 65, although the disorder can present before the age of 30 as well as in the elderly. There is an equal gender distribution. The mean duration is 8 years, ranging from 2 to 20 years. A family history of dementia is present in about 40% of first-degree relatives. Ten percent of the familial cases and 0–3% of sporadic cases have been linked to specific mutations. Most of these mutations occur in the tau gene on chromosome 17, although rare cases of both familial motor neurone disease with FTLD and familial FTLD, have been linked to chromosome 9 and 3 respectively (Brown *et al.*, 1995; Hosler *et al.*, 2000).

Three main neuropathological findings have been identified in FTLD (Lund and Manchester Groups, 1994; McKhann *et al.*, 2001). The most common (microvacuolar) type, accounting for 60% of cases, displays microvacuolation, neuronal loss, mild gliosis, and the lack of distinctive changes (swellings or inclusions). In this disorder, there is a loss of tau protein function ("tauless tauopathy") (Zhukavera *et al.*, 2001), which may be functionally related to abnormal tau aggregation. The second histological pattern (Pick-type) is seen in 25% of cases, including Pick's disease and FTLD with parkinsonism linked to chromosome 17; it is characterized by neuronal loss with widespread gliosis, minimal or no microvacuolation, inclusions that are positive for both tau and ubiquitin, and greater involvement of the limbic system, and striatum. Tau-positive inclusions are also evident in CBD and PSP. In about 15% of cases, neuronal loss and gliosis with ubiquitin positive and tau-negative inclusions are present. These changes have been described in FTLD with motor neurone disease and FTLD with marked striatal degeneration.

There are three distinct clinical syndromes in FTLD (Neary *et al.*, 1998): the commonest (at least 70%) is FTD, followed by semantic dementia (SD) (about 15%), and progressive nonfluent aphasia (PNA) (about 10%). There can be substantial overlap between the three syndromes, as well as with other clinical disorders, notably CBD and PSP. Motor neurone disease has been seen in combination with all three subtypes, but is most common with FTD and PNA (Neary *et al.*, 1998). All eventually worsen and produce a dementia syndrome. The clinical syndrome does not predict histological type, so that clinical distinctiveness itself does not imply etiological difference.

In general, three behavioral subtypes of FTD have been described (Snowden *et al.*, 2002). The *disinhibited* type is characterized by jocularity, unconcern, breakdown of social and interpersonal behaviors, easy distractability, and purposeless overactivity. At the other extreme is the *apathetic* subtype, featuring inertia, aspontaneity, loss of volition, unconcern, mental rigidity and perseveration; the *stereotypic* type has pronounced behavioral stereotypes, compulsions, and ritualistic behavior. These broad behavioral subtypes reflect regional involvement. The disinhibited subtype corresponds to orbital frontal and anterior temporal dominance; the apathetic form occurs when there is extensive frontal involvement extending into the dorsolateral frontal cortex, and the stereotypic type is most strongly related to marked striatal changes with variable cortical involvement, often with emphasis on temporal rather than frontal lobe pathology. Clinical presentation often reflects asymmetrical hemispheric involvement, with the right-sided disorders manifesting primarily marked neuropsychiatric disturbances, whereas the left-sided disorders tend to exhibit more language dysfunction.

Frontotemporal Dementia

The salient clinical characteristic is an early and profound alteration in personality and social conduct, occurring in the context of relative preservation of memory, spatial skills, and praxis. Clinical features are summarized in Table 7 (Neary *et al.*, 1998).

There is difficulty modulating behavior to the social demands of a situation, and is often associated with disinhibition, impulsivity, undue jocularity, inappropriate sexual behavior, distractability, and impersistence. Rigidity and inflexibility are common, and often accompanied by repetitive and compulsive behaviors, ranging from simple verbal or motor mannerisms to more elaborate routines, such as tapping each wall twice upon entering a room, rereading the same book, walking to the same location repeatedly, as well as clock-watching and adherence to a fixed routine. However, FTD patients do not typically experience the feelings of anxiety and release from anxiety characteristic of obsessive-compulsive disorder. Dietary changes typically take the form of overeating, food fads, and a preference for sweet foods. There is a loss of concern for one's personal appearance, and the patient may be increasingly unkempt early in the disease. Utilization and imitation behaviors are common in the later stages; the former refers to stimulus-bound behavior in which patients grasp and use an object in their visual field, despite its contextual inappropriateness (e.g. drinking from an empty cup). All of this occurs in the setting of loss of insight, indifference, and unconcern for one's actions. Although there may be memory complaints, cognitive changes reflect frontal lobe dysfunction (inattention, poor abstraction, difficulty shifting mental set, and perseverative tendencies) rather than a true amnestic syndrome. Speech output is attenuated, with progressive reduction of speech to

Table 7 Clinical diagnostic features of frontotemporal dementia

Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well preserved

Core features
Insidious onset and gradual progression
Early decline in social interpersonal conduct
Early impairment in regulation of personal conduct
Early emotional blunting
Early loss of insight

Supportive features
Behavioral disorder
- Decline in personal hygiene and grooming
- Mental rigidity and inflexibility
- Distractibility and impersistence
- Hyperorality and dietary changes
- Perseverative and stereotyped behavior
- Utilization behavior

Speech and language
- Altered speech output:
  - Aspontaneity and economy of speech
  - Pressure of speech
- Stereotype of speech
- Echolalia
- Perseveration
- Mutism

Physical signs
- Primitive reflexes
- Incontinence
- Akinesia, rigidity, and tremor
- Low and labile blood pressure

Investigations
- Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
- Electroencephalography: normal on conventional electroencephalography despite clinically evident dementia
- Brain imaging (structural and/or functional): predominant frontal and/or temporal abnormality

Source: Modified from Neary D *et al.* Frontotemporal lobar degeneration: a concensus on clinical diagnostic criteria. *Neurology* 1998; **51**:1546–54, with permission from Lippincott Williams & Wilkins.

Table 8 Distinguishing features between frontotemporal dementia (FTD) and Alzheimer's disease (AD)

Clinical feature	Frontotemporal dementia	Alzheimer's disease
Cognitive		
Amnesia	Delayed until later in the course	Occurs early, *sine qua non* of AD
Executive dysfunction	Early, progressive	Less early in most cases
Language	Reduction of speech output	Anomia with fluent aphasia; speech output preserved
Visuospatial skills	Relatively preserved	Involved early
Calculation	Relatively preserved	Involved early
Behavioral		
Disinhibition	Common	Occurs, but is less severe
Euphoria	Common	Rare
Stereotyped behavior	Common and marked	Less common
Apathy	Common and severe with marked emotional blunting	Common, less severe
Dietary changes	Hyperorality and food fads (high carbohydrates) common	Anorexia more common then overeating
Self-neglect	Common	Rare until late
Psychosis	Occurs, but is less common	Delusions and hallucinations more common

a mute state. Also common are verbal stereotypies, involving repeated use of a word, phrase, or complete theme. Patients may tell the same joke over and over again, or retell the same story many times a day.

Table 8 summarizes the distinguishing features of FTD from AD. In one study, the behavioral features of loss of social awareness, hyperorality, stereotyped and perseverative behavior, reduced speech output, and preserved spatial orientation had good specificity (97–100%), but lower sensitivity (63–73%) for the diagnosis of FTD compared with AD (Miller *et al.*, 1997). Other useful discriminating features include dietary changes and loss of affective response (generalized blunting of emotions), which is typically more severe than in AD.

Physical examination–wise, primitive reflexes, such as grasping, pouting, and sucking reflexes, occur earlier in the course of FTD then AD. Parkinsonian signs of akinesia, rigidity, and tremor develop with disease progression. A minority of FTD patients develop fasiculations, wasting, and weakness typical of motor neurone disease. Structural imaging with MRI is more sensitive then computed tomography in showing atrophy of the frontal and anterior temporal lobes. In some cases, these alterations show a striking asymmetry, which is most sensitively picked up by functional imaging techniques such as SPECT.

Rational treatments for FTD are currently limited. The cholinergic system is not implicated in FTD in neurochemical studies, unlike in AD (Wenning *et al.*, 1994). Nonetheless, there is some evidence that behavioral symptoms such as disinhibition, overeating, and compulsions may benefit from treatment with selective serotonin reuptake inhibitors (SSRIs), suggesting that a modicum of symptomatic improvement can be achieved at least in some cases (Swartz *et al.*, 1997).

Progressive Nonfluent Aphasia

Progressive nonfluent aphasia is the FTLD syndrome corresponding to degeneration of the left frontal cortex. The dominant feature initially and throughout the course is disorder of expressive language, presenting as progressively worsening nonfluent spontaneous speech with agrammatism (omission or incorrect use of grammatical terms including

articles, prepositions, etc.), phonemic paraphasia with sound-based errors, and anomia (Neary *et al.*, 1998). There is often accompanying stuttering, impaired repetition with paraphasic intrusions, alexia, and agraphia. In the early stages, comprehension is preserved for word meaning, but impaired for syntactic relationships. Behaviorally, there is early preservation of social skills, although evolution to dementia with behavioral features of FTD is common after several years of progressive linguistic changes (Weintraub *et al.*, 1990). PNA can usually be distinguished from the fluent aphasia of AD. Unlike AD, amnesia and perceptuospatial disorders are also noticeably absent in the early stages.

Semantic Dementia

The term semantic dementia typically refers to patients with progressive fluent aphasia associated with visual agnosia (Neary *et al.*, 1998). These patients have impaired inability to understand the meaning of words (semantics), manifested by impaired word naming and comprehension, such that speech, although fluent, is progressively devoid of content. Semantic paraphasic errors are common, and there may be associated surface dyslexia and dysgraphia, although syntax and phonology, visual perceptual and visuo-skills, single-word repetition, calculation, and nonverbal problem-solving abilities are often preserved. In fact, an unusual number of SD patients have an emergence of artistic talent in their dementia syndrome, reflecting the integrity and possibly, disinhibition of right hemispheric activity (Miller *et al.*, 1998). Other cognitive functions such as episodic memory are relatively well preserved in the early stages; typically, there is preservation of episodic events and semantic facts from very recent life compared with other time periods. Perceptual disorders are characterized by prosopagnosia (impaired recognition of identity of familiar faces) and/or associative agnosia (impaired recognition of object identity).

The main differential diagnosis is AD, which can also manifest as a progressive fluent aphasic disorder. However, AD patients exhibit a greater degree of amnesia, and concomitant visuospatial and calculation dysfunction. In addition, although both groups exhibit medial temporal lobe atrophy, there is asymmetrical hippocampal atrophy (left greater than right) and greater atrophy of the temporal poles in SD patients compared with AD (Galton *et al.*, 2001).

DEPRESSION

Depression is common among the elderly. The term *pseudodementia* was coined to reflect the impairment in thinking and memory that frequently accompany depression. The cognitive domains affected in depression include slowed mental processing and deficits in attention and executive function (Porter *et al.*, 2003). Individuals with late-onset depression have more significant cognitive impairment (van Reekum *et al.*, 1999).

Confirming the diagnosis of depression in a patient presenting with cognitive impairment can be difficult, since the patient may not complain of classical mood changes or have comorbid medical conditions that confound interpretation of "physical" symptoms of sleep, appetite/weight, psychomotor change, and energy disturbance. Although certain clinical features can be helpful in the differential diagnosis of dementia and depression (Table 9), none are diagnostic and frequent exceptions and overlaps exist. This is confounded by three possible relationships that can exist between depression and dementia.

Firstly, the two conditions often coexist. Epidemiological data indicates prevalence rates of 30–50% for depressive symptoms among AD patients, especially in the earlier stages of dementia where insight is often retained (Olin *et al.*, 2002). Studies have generally found an absence of effect of depression on cognitive performance in early stage AD (Powlishta *et al.*, 2004). Thus, it is often the experience that while antidepressant treatment of concomitant depression in dementia can result in impressive improvement in mood and

Table 9 Comparison of clinical presentations of depression (presenting as memory difficulties) and mild Alzheimer's Disease

Feature	Depression without underlying dementia	Alzheimer's disease without depression
Age of onset	Common below and above age 60	Uncommon below age 60
Onset	Subacute or insidious	Insidious
Course	Fluctuations may be present	Progressive decline
Insight	Almost always present	Sometimes present, usually in earlier stages
Cognitive domains		
Memory	Less prominent	Prominent and early
Executive function/ psychomotor speed	Prominent and early, proportional to dementia severity	Less prominent in earliest stages
Language/praxis	Uncommon unless depression is severe	Uncommon in mild stages but common in moderate and severe stages
Mood	Sad, stoic, or agitated	Sad, stoic, agitated or euthymic
Sleep-wake cycle	Often disturbed; early morning awakening	Sometimes disturbed
Response to cholinesterase inhibitor	Improvement in cognitive status not expected	Modest improvement in cognitive status can occur
Response to antidepressant	Significant improvement likely	Mild improvement in mood or behavior may occur

Source: Modified from Green RC. *Diagnosis and management of Alzheimer's Disease and other dementias.* Caddo, OK: Professional Communications, Inc; 2001, with permission.

quality of life, the cognitive impairment remains relatively unchanged.

Secondly, there is a growing body of evidence that depression at baseline is a risk factor for incident dementia and cognitive decline (Jorm, 2000). Thus, dementia needs to be entertained as a differential diagnosis in cases of long-standing depression where there is lack of cognitive improvement, despite adequate treatment of the underlying affective disorder.

Thirdly, owing to the considerable overlap in symptoms, some individuals with dementia may be erroneously diagnosed as having depression instead. Features of depression such as loss of interest, decreased energy, psychomotor changes, and decreased concentration lose diagnostic specificity in the presence of dementia (Burke and Wengel, 2003). Affective symptoms such as guilt, expressions of worthlessness and suicidal thoughts, if present, are more useful in distinguishing depression from dementia. It is also important to give appropriate consideration to the proxy informant's subjective reports of symptoms of depression in a demented patient, as the latter tends to minimize or underreport depressive symptoms, particularly when there is lack of insight into the underlying cognitive deficits (Burke *et al.*, 1998).

Since depression in the elderly is not always easily recognizable, many clinicians maintain an appropriate readiness to try antidepressants empirically or even as a therapeutic challenge to evaluate the response. A 6–8-week treatment trial of an appropriate antidepressant without significant anticholinergic properties, such as the SSRIs, is relatively safe and can sometimes provide considerable improvement (Green, 2001).

HUMAN PRION DISEASES

Prion diseases (also known as *transmissible spongioform encephalopathies*) are progressive and invariably fatal neurodegenerative diseases occurring in a wide range of mammals, including humans. They are defined by four cardinal neuropathological features: spongioform change, neuronal loss, reactive gliosis, and accumulation of the prion protein (PrP). According to the prion hypothesis, the infectious agent (termed PrP^{sc}) is an altered form of prion protein (termed PrP^{c}). PrP^{sc} results from the conversion of PrP^{c}, a host-encoded soluble protein of as-yet indeterminate function (Prusiner, 1982).

Prion diseases are unique amongst human neurodegenerative disorders in that they occur in sporadic, familial, and acquired forms (Table 10). Several point mutations and insertional mutations of the human prion protein gene (PRNP) on the short arm of chromosome 20 have been described in the familial forms. In the sporadic forms, either spontaneous somatic mutations or conformational change to PrP^{sc} occurs. The polymorphisms at codon 129 (methionine/valine) and 219 (glutamic acid/lysine) are thought to influence disease susceptibility in sporadic and variant Creutzfeld–Jakob disease (CJD) (Windl *et al.*, 1996). With regard to the iatrogenic forms, transmission can occur via inoculation of PrP^{sc} from contaminated surgical instruments, tissue grafts (corneal and dural) and human pituitary gland extracts from affected donors.

Table 10 Classification of human prion diseases

Idiopathic
Sporadic Creutzfeld–Jakob disease
Sporadic fatal insomnia
Inherited
Familial Creutzfeld–Jakob disease
Gerstmann–Straussler–-Scheinker (classical and variant forms)
Fatal familial insomnia
Acquired
Human source: kuru
Iatrogenic Creutzfeld–Jakob disease
Bovine source: variant Creutzfeld–Jakob disease

Sporadic Creutzfeld–Jakob disease (sCJD) is the commonest form of human prion disease, occurring in a worldwide distribution with an annual incidence of 0.5–1.0 per million population. Most cases occur in the elderly, with peak onset in the 70s. Homozygotes for the codon 129 genotype, tend to have a significantly younger age of onset (Alperovitch *et al.*, 1999). Males and females are equally affected. The median duration of sCJD is 4 months and around 65% of cases have an illness duration of less than 6 months. In 14% of cases, there is a relatively long duration of 12 months or more; durations of more than 2 years are rare (5% of cases). Clinically, the classical triad of rapidly progressing dementia, myoclonic jerks, and characteristic electroencephalographic (EEG) findings should alert the clinician to consider the possibility of CJD. Other commonly associated symptoms include pyramidal and extrapyramidal signs, visual manifestations (restriction of visual field, homonymous hemianopsia, metamorphosia, palinopsia, and optic atrophy), and cerebellar gait disturbances. However, there can be a wide spectrum of clinical presentation, including (1) nonspecific symptoms such as asthenia, disturbances of sleep and eating patterns, (2) mental deterioration only, (3) predominantly neurological symptoms, usually of visual (the Heidenhain variant) or cerebellar (the Brownell–Oppenheimer variant) origin. Conditions that can mimic the initial presentation of CJD include Hashimoto's encephalitis, intracranial vasculitis, paraneoplastic limbic encephalitis, AIDS dementia complex, chronic meningitis, subacute sclerosing panencephalitis and myoclonic epilepsy with Lafora bodies.

Characteristic EEG findings in CJD, consisting of periodic lateralized or generalized bursts of spike-wave complexes, may be absent in the initial stages of the disease. However, as the disease evolves, periodic activity often becomes apparent. Periodic EEG activity is not specific to CJD, but can also be seen in postanoxic encephalopathy, Hashimoto's encephalitis, AIDS dementia complex, MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) syndrome, severe metabolic derangement, multiple cerebral abscesses, and AD.

Among the brain associated proteins in CSF, 14-3-3 has high sensitivity and specificity of 90–97% and 84–96%

respectively (Zerr *et al.*, 2000). False-positive results can be found in patients with extensive central nervous system (CNS) damage, including recent stroke, subarachnoid hemorrhage, viral encephalitis, paraneoplastic CNS syndromes, AD and dementia with Lewy bodies. The CSF picture is otherwise bland, aside from occasional elevated total protein. MR brain imaging shows increased signals in the basal ganglia, (particularly caudate nucleus and the putamen), in the diffusion weighted image (DWI), fluid-attenuated inversion recovery (FLAIR), and T2-weighted sequences. In particular, diffusion weighted changes may be seen as early as 1 month after symptom onset (Bahn *et al.*, 1999).

Neuropathological examination is required for a definite diagnosis of CJD. Brain biopsy is carried out less frequently nowadays, largely due to the better-defined clinical diagnostic criteria for human prion diseases (Table 11). However, accurate and definitive diagnosis from brain biopsy can exclude an underlying treatable condition, aid caregivers in planning of care, as well as facilitate community surveillance of future transmission (See *et al.*, 2004). Biopsy of the nasal epithelium has recently been reported as a reliable and less invasive way of obtaining tissue (Zanusso *et al.*, 2003).

In 1996, a new variant form of CJD (vCJD) was reported in the United Kingdom, which, on the basis of epidemiologic, biochemical, and experimental transmission evidence, is strongly linked to human exposure to bovine spongioform encephalopathy (BSE), indicating that vCJD is the first example of a zoonotic form of prion disease in humans (Ironside and Head, 2004). There are distinct clinical features from sporadic CJD. It occurs in a younger age-group (mean age 28 years) with a prolonged duration of illness (mean 13 months), and is characterized by marked neuropsychiatric features (depression, anxiety, apathy, withdrawal, delusions) at onset and the prominence of sensory abnormalities (dysesthesias involving the face, arms, back, or legs), in addition to ataxia, movement disorders (myoclonus, dystonia or chorea), and dementia (Will *et al.*, 1999). Investigation-wise, the characteristic EEG changes of sCJD are absent, while the CSF 14-3-3 protein is elevated in only 50%, although it retains its specificity (Green *et al.*, 2001). The MRI scans show hyperintensities mainly in the posterior thalamus. Microscopic examination of the brain shows widespread spongioform change characterized by numerous florid plaques throughout the cerebrum and cerebellum.

Table 11 Clinical diagnostic criteria for sporadic and iatrogenic Creutzfeld–Jakob disease (CJD) and familial prion disease (from www.cjd.ed.ac.uk)

1. Sporadic
   a. Rapidly progressive dementia
   b. i) Myoclonus
      ii) Visual or cerebellar problems
      iii) Pyramidal or extrapyramidal features
      iv) Akinetic mutism
   c. Typical EEG
2. Iatrogenic
   2.1 Definite:
   Definite CJD with a recognized risk
   2.2 Probable
      2.2.1 Progressive cerebellar syndrome in human pituitary hormone recipients
      2.2.2 Probable CJD with recognized risk
3. Familial prion diseases[a]
   3.1 Definite
   Definite TSE plus definite or probable TSE in a first-degree relative
   3.2 Probable
      3.2.1 Probable TSE plus definite or probable TSE in a first-degree relative
      3.2.2 Progressive neuropsychiatric disorder plus disease-specific mutation

TSE, transmissible spongioform encephalopathy.
[a]Includes Gerstmann–Straussler–Scheinker and familial fatal insomnia.

HUNTINGTON'S DISEASE

The prevalence of Huntington's disease in Europe is approximately 0.5–8/100 000 (Harper, 1992). It is caused by the expansion of a CAG trinucleotide repeat sequence on the huntington gene located on the short arm of chromosome 4. The number of repeats correlates inversely with age of onset, with 40 repeats being the pathological threshold, beyond which disease will most likely develop (Harper, 1996). Inheritance is autosomal dominant with complete penetrance. New mutations are rare and most apparently sporadic cases in fact reflect either an incomplete family history or nonpaternity. Histopathologically, it is characterized by neuronal loss and gliosis mainly affecting the frontal lobes and caudate nucleus, and the presence of polyglutamine nuclear inclusions.

Onset is generally in middle life (mean age 40 years). The course is one of inexorable progression of cognitive, behavioral and motor decline, with death occurring 12–15 years from the time of symptomatic onset. Neuropsychiatric symptoms of depression, apathy, aggression, disinhibition, and social disintegration are common, and may predate the hallmark chorea, other extrapyramidal signs, and gaze apraxia (Paulsen *et al.*, 2001). A subcortical dementia marked by executive dysfunction, cognitive slowing, apathy, and typically, inattention develops. Bilateral atrophy of the head of caudate nucleus may be seen on brain imaging. Genetic testing is a powerful diagnostic tool that should be offered only if recommended provisions can be followed (International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea, 1994).

CEREBRAL VASCULITIS

Vasculitis can affect the CNS, usually as part of a systemic involvement. The differential diagnosis is wide and includes primary vasculitides such as Wegener's granulomatosis, temporal arteritis, Churg–Strauss syndrome and polyarteritis nodosa; systemic diseases that can

produce vasculitis such as systemic lupus, sarcoidosis, Henoch–Schonlein papura and Behcet's disease; infectious agents such as Lyme's disease; and other rare conditions such as intravascular lymphoma. These conditions can be easily distinguished by the clinical picture, elevated inflammatory markers, autoantibodies, and histopathological findings. However, it is important to be aware of the condition of primary angiitis of the CNS, where there is isolated CNS involvement. Pathologically, it is characterized by patchy inflammation (granulomatous, necrotizing, or lymphocytic), preferentially affecting small leptomeningeal and parenchymal vessels. Clinical presentations range from acute confusion to relapsing-remitting fluctuations to an indolent subcortical dementia. Headache is common but not universal, and seizures may occur. Inflammatory markers and autoantibodies are usually negative, however. Besides mild pleocytosis, the CSF is otherwise bland. MRI may show nonspecific white matter lesions. Cerebral angiogram can be useful, although beading of vessels is found in only approximately a third of patients with histologically confirmed CNS vasculitis, as well as in CNS infection, atherosclerosis, cerebral embolism, and vasospasm; multiple microaneurysms, often seen on visceral angiography in systemic vasculitis, are distinctly rare in CNS vessels (Younger, 2004). In many cases, the definitive diagnosis is clinched by histopathology, and unconfirmed suspicion of cerebral vasculitis remains one of the few indications for brain biopsy before committing the patient to immunosuppressive therapy.

ALCOHOL-RELATED DEMENTIA

The Liverpool Longitudinal Study of mental health of community-dwelling elderly, found that dementia was 4.6 times more likely to occur in men aged 65 and above who had a lifetime history of heavy drinking (Saunders *et al.*, 1991). However, the concept of a distinct entity of alcohol-related dementia remains a source of nosological confusion because of the considerable overlap with concomitant conditions, such as Wernicke–Korsakoff syndrome (thiamine deficiency), other nutritional deficiencies (e.g. B12 deficiency, pellagra), and hepatic encephalopathy. Nonetheless, the observation in epidemiological studies of the considerable number of demented alcoholics, even when these causes have been excluded, supports a case for the direct vindicative role of alcohol on the development of dementia (Harper and Scolyer, 2004). Diagnostic criteria for alcohol-related dementia have been proposed (Oslin *et al.*, 1998).

Histopathological findings reveal region-specific neuronal loss (the frontal lobe, hypothalamus, and cerebellum) and white matter–associated brain atrophy. Some of the white matter loss appears to be reversible in that, after prolonged abstinence, the brain shrinkage reverts towards normality (Liu *et al.*, 2000). There is a wide spectrum of effects of alcohol on the brain, depending on individual susceptibility, drinking pattern, and comorbid factors like recurrent head injury, seizures, and polydrug abuse. Typically, chronic alcohol abuse can lead to progressive intellectual deterioration resulting in long-term cognitive and neuropsychiatric sequelae. Executive function and autobiographical memory appear especially vulnerable, and confabulation may occur. Brain imaging shows nonspecific generalized cerebral atrophy with frontal predominance.

HUMAN IMMUNODEFICIENCY VIRUS–ASSOCIATED DEMENTIA

The spectrum of human immunodeficiency virus (HIV) cognitive involvement range from the nonspecific "aseptic meningitis" during the viremia of primary infection, to "minor cognitive motor disorder" which confers a worse prognosis for a similar HIV disease stage, to the most severe form, HIV-associated dementia (HAD) (Working Group of the American Academy of Neurology AIDS Task Force, 1991). HAD is believed to be the direct result of central nervous HIV infection, and it is a diagnosis of exclusion in patients with known AIDS who develop cerebral symptoms. It generally presents as a subcortical dementia with cognitive and motor slowing, and accompanying behavioral changes, seizures, and gait ataxia. Brain MRI reveals diffuse cerebral atrophy and white matter hyperintensities. It is associated with a relatively low CD4 count and the control of HIV viral load through intensive combination antiretroviral therapy is associated with significantly lower risk of progression to HAD (Childs *et al.*, 1999). Recent comparisons of neuropsychiatric performance with the addition of protease inhibitor (PI) drugs demonstrate better performance in subjects treated with a PI compared to those receiving less intensive HIV therapy (Ferrando *et al.*, 1998). Epidemiologic studies support the declining incidence of HAD with the advent of more effective and intensive retroviral therapy (Clifford, 2000). More recent studies have focused on the role of neuroprotective strategies (nimodipine, antioxidant agents, *N*-methyl-D-aspartate antagonist, tumor necrosis factor antagonist) in the treatment of HAD.

PARANEOPLASTIC LIMBIC ENCEPHALITIS

This condition arises from the autoimmune response to tumor antigens, and usually precedes the diagnosis of the underlying malignancy. The most commonly associated primaries are in the lung, testis, and breast. The characteristic histopathological finding is that of inflammatory infiltrates and neuronal loss typically in the mesial temporal area, and also the extralimbic areas such as the hypothalamus and brainstem. Clinically, it is characterized by changes in mood and personality, hallucinations, seizures, and cognitive impairment.

There may be symptoms and signs referable to other areas of the CNS, such as ataxia and sensory neuropathy. Supportive features include focal temporal lobe abnormalities on MRI and electroencephalography, and an inflammatory CSF yield; the presence of oligoclonal bands in the CSF but not the serum indicates local immunoglobulin synthesis, in a high proportion. It is associated with positive antineuronal antibodies (predominantly anti-Hu) in about 60% of cases (Gultekin *et al.*, 2000). An underlying primary may be uncovered by an exhaustive workup, usually including thoracoabdominal computed tomography or whole-body positron-emission tomography, if available. Therapeutic options are limited but some patients improve after treatment of the underlying malignancy.

NORMAL PRESSURE HYDROCEPHALUS

The underlying pathophysiology in NPH is believed to be due to impaired CSF absorption and increased intraventricular pulse pressure. The resultant increase in ventricular size exerts a pressure on surrounding white matter tracts to produce the classical triad of gait instability, urinary incontinence, and cognitive impairment. The diagnosis is clinched by the radiological finding of enlarged ventricles out of proportion to the degree of cerebral atrophy. Estimated to cause no more than 5% of cases of dementia, NPH is often treatable, and careful evaluation of symptoms coupled with radiographic evidence yields vital information of likely responders to shunting. A good prognosis is indicated by short duration of symptoms, onset of gait abnormality before or at same time as dementia, duration of cognitive impairment of less than 2 years, the presence of secondary causes (e.g. subarachnoid hemorrhage, meningitis, head injury, previous brain surgery), the absence of aphasia and alcohol abuse, and an improvement in gait following drainage of 30–50 cc of CSF (Graff-Radford, 1999). Radiologically, less favorable prognostic factors include concomitant sulcal enlargement and hippocampal atrophy (which may indicate underlying AD), and extensive white matter lesions. MRI flow void studies and cisternography have not been proven to reliably predict shunting outcome (Verrees and Selman, 2004). CSF diversion by ventriculoperitoneal shunting remains the treatment of choice, although, the highly variable success rate of 33–90% emphasizes the importance of careful patient selection. In one review (Hebb and Cusimano, 2001), 59% of NPH patients reported improvement after shunting with a persistent improvement in only 29%.

MEDICATIONS

Strictly speaking, medications cause a state of cognitive impairment secondary to chronic confusion or delirium rather than an actual dementia. As with depression, cognitive impairment due to medications is often superimposed upon other dementing disorders. Virtually any medication, including many over-the-counter drugs, has been implicated. The commonest culprits are drugs affecting the cholinergic, dopaminergic, serotonergic, and noradrenergic systems, and can be remembered by the mnemonic ACUTE CHANGE IN MS (mental status) (Flaherty, 1998). (refer Table 1) Medications are potentially reversible causes of cognitive impairment, hence a high index of suspicion is required, especially if there is a clear temporal relationship between the onset of symptoms and change in type or dosage of medications. Removing or reducing unnecessary medications may improve cognition, even in patients with underlying neurodegenerative diseases such as AD.

APPROACH TO THE DIAGNOSIS OF DEMENTIA IN OLDER PERSONS

The evaluation of dementia should be targeted at patients in whom there is some suspicion of cognitive impairment. These include: subjects with memory and other cognitive complaints (such as forgetfulness and confusion), either self-reported or by a reliable collateral source; subjects who arouse suspicion of cognitive impairment during the clinical encounter despite absence of memory complaints; those who are at increased risk of dementia (such as those with a strong family history of dementia); and medico-legal situations where the subject's mental competency is called into question (such as financial matters or making a will).

A four-step evidence-based approach is recommended in the evaluation (Chong and Sahadevan, 2003). *Firstly*, it is imperative to determine whether the cognitive symptoms are acute or chronic in onset. If acute, delirium needs to be ruled out using a well-validated instrument like the confusion assessment method (CAM) (Inouye *et al.*, 1993).

Secondly, if the forgetfulness or confusion is of a chronic nature, the clinician needs to determine if this is due to underlying dementia, or other conditions such as depression, late-onset psychiatric disorders, or partial epilepsy. Dementia is a clinical diagnosis, and the DSM-IV (American Psychiatric Association, 1994) criteria are useful for this purpose. The criteria require the presence of memory impairment, as well as deficits in one other cognitive domain (aphasia, apraxia, agnosia, and executive dysfunction), which should be of sufficient severity to cause perceptible impairment in social or occupational functioning. Table (12a) gives examples of questions that can be asked to elicit these criteria. It cannot be overemphasized that the clinical diagnosis of dementia is established purely by history-taking, and therefore, a corroborating history from a reliable collateral source should always be obtained. Objective tests like mental status tests (brief cognitive screening instruments) or more detailed neuropsychological tests administered by psychologists, can yield useful adjunct information in the diagnosis of dementia. These tests, however, are prone to floor and ceiling effects, require subject cooperation, can be difficult to administer with concomitant hearing impairment and aphasia, and

Table 12 Approach to assessment of dementia

(a) DSM-IV clinical criteria for diagnosis of dementia

Symptom	Questions
Amnesia	Is there forgetfulness? Was onset sudden or gradual? Is there a progressive course? If so, is the decline gradual, stepwise or fluctuating? Does amnesia affect short (e.g. appointments, misplacing, medications) or long-term domains? Is there undue repetition?
Plus impairment in at least one of the following domains:	
Aphasia	Any difficulty in word-finding, comprehension (e.g. conversations, television programs), or reading?
Apraxia	Any difficulties with buttoning, dressing, brushing teeth? Any problems using utensils during mealtimes?
Agnosia	Any difficulty recognizing familiar faces or familiar items?
Executive dysfunctioning	Any problems handling money (e.g. loose change, tip, paying bills, balancing accounts)? Any change in general problem-solving abilities? Is one's "work" (occupation, social activities, housework) getting more disorganized?
The above cognitive deficits, if present, must represent:	
A decline from a previously higher level of functioning	Does the cognitive deficit (e.g. forgetfulness) represent a change from one's baseline level, and is this change a decline?
Sufficient severity to cause significant impairment in social or occupational functioning	As a result of the above, is one therefore less independent in his community affairs, home and hobbies, and personal care?

Source: Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Copyright 2000. American Psychiatric Association.

(b) Behavioral, functional, and social assessment in dementia

Variable	Questions
Behavioral	
Depression	Has patient been noted to be sad, tearful, having thoughts of worthlessness or inappropriate guilt, exhibiting diminished interest in work, hobbies, or recreational activities? Is there poor sleep, early morning awakening, change in appetite/weight, or impaired concentration?
Anxiety	Does patient get worried easily?
Agitation	Is patient easily agitated or irritable? Is there undue restlessness, overactivity, or aggressive behavior? Is the agitation related to certain times of the day (sundowning pattern)?
Paranoia	Is patient suspicious of others, accusing others of causing him harm or stealing his possessions (when in fact they have been misplaced)?
Hallucinations	Does patient see, hear, or smell things that are not present?
Sleep problems	Does patient have problems falling asleep or have sleep-wake reversals?
Functional	
Community functioning	Can patient find his way around in unfamiliar surroundings, manage his finances, shop, or participate in social activities independently?
Home-care functioning	Can he prepare his own food, help in housework and cooking? Is he able to choose proper attire to dress himself? Is he safe to be left at home alone?
Self-care functioning	Is he able to bathe and dress himself? Is he able to go to toilet, transfer, or feed himself? Is he continent of bladder and bowels?
Social	
Coping difficulties	How are caregivers coping? What is their level of stress? Are they also depressed? Are there features of elder abuse?
Financial issues	Are the financial costs of care manageable?
Legal issues	Are there any legal issues that require the assessment of decision-making capacity for example, will-making, placement decisions
Driving safety	Can the patient be persuaded not to drive? (Otherwise, he may require regular assessments of fitness to drive)

Table 12 (*continued*)
(c) Canadian consensus conference criteria[a] for performing cranial CT in patients with dementia

Criteria:
<60-years old
Rapid (e.g. over 1 to 2 months), unexplained decline in cognition or function
Dementia of relatively short duration (<2 years)
Recent, significant head trauma
Unexplained neurologic symptoms (e.g. new onset of severe headache or seizures)
History of cancer, especially of a type or at a site associated with metastasis to the brain
Use of anticoagulants or history of bleeding disorder
History of urinary incontinence and gait disturbance early in the disease (suggestive of normal pressure hydrocephalus)
Presence of any new localizing signs on physical examination (hemiparesis, Babinski's sign)
Unusual or atypical cognitive symptom or presentation (e.g. progressive aphasia)
Gait disturbance
CT is recommended if one or more of these criteria are present

Source: Modified from Chong MS, S Sahadevan. *Ann Acad Med Singapore* 2003; **32**:740–8.
CT, computed tomography.
[a]Patterson CJ *et al.* CMAJ 1999;160:S1–5.

require adjustments for age and education. It should be appreciated that these tests can only identify cognitive impairment and not dementia *per se* – the definitive diagnosis of dementia is still clinical.

Thirdly, if dementia is present, what are the complications? Behavioral, functional, and social problems are often amenable to treatment or palliation and should be assessed in all patients with dementia. These areas can be evaluated by a semistructured clinical approach (refer Table 12b) or by the use of validated scales such as the Geriatric Depression Scale (GDS) (Yesavage *et al.*, 1983), the Cornell Depression Scale in Dementia (Alexopoulos *et al.*, 1988), the neuropsychiatric inventory (NPI) (Cummings *et al.*, 1994), and the Bristol Activities of Daily Living Scale (Bucks *et al.*, 1996). The reader is referred to the excellent review article by Burns *et al.*, (2002), for more information on commonly used rating scales in geriatric psychiatry.

Lastly, if dementia is present, what is the etiology? The main aim of determining the etiology is to rule out potentially reversible causes of dementia and it begins with a focused history and physical examination, followed by selected laboratory tests and neuroimaging.

The most commonly recommended hematological tests are easy to perform and of a relatively low cost: complete blood count, urea and electrolytes, liver function test, serum calcium, serum glucose, thyroid function tests, vitamin B12 level, and sedimentation rate. Given the problems in interpreting the serum and CSF serology for neurosyphilis, routine testing is not advocated. Serum Venereal Disease Research Laboratory (VDRL) testing detects only 75% of cases of tertiary syphilis and CSF VDRL may be negative in 30–70% of neurosyphilis. Thus, the diagnostic utility of serum VDRL and treponemal antibody is optimized in situations where patients are already manifesting some of the clinical features of neurosyphilis (i.e. the "pretest probability" is sufficiently high to warrant a confirmatory test) (Jacobs, 2000).

The principal value of neuroimaging in the evaluation of dementia is the identification of cerebral infarcts and clinically important surgical brain lesions (SBLs), such as subdural hematomas, cerebral tumors, and NPH (Engel and Gelber, 1992). There is currently no consensus with regard to routine neuroimaging for all patients, versus selective usage based on judicious application of certain clinical indicators. One reasonable approach is to use a well-validated criteria like the Canadian Consensus Conference on the Assessment of Dementia (CCCAD) criteria (Table 12c) (Patterson *et al.*, 1999), with the additional consideration of the functional stage of dementia (Chong and Sahadevan, 2003). In cases of advanced dementia, caregivers are often not looking to the doctor for a precise etiological diagnosis; rather, they seek the doctor's help in managing the attendant's behavioral, functional, and social problems. Thus, in a patient with advanced dementia of a long duration (>2 years based on the CCCAD recommendation) not fulfilling any of the CCCAD criteria, a brain scan is of limited benefit. Conversely, if the dementia is of mild to moderate severity (even after 2 years), there is still a role for neuroimaging evaluation of dementia.

KEY POINTS

- Non-Alzheimer dementias constitute a significant proportion of dementia etiologies in epidemiologic studies. The major degenerative subtypes are vascular dementia (VaD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), and frontotemporal dementia (FTD). These conditions have distinct clinical features and can often be reliably distinguished clinically from Alzheimer's disease (AD) through the use of standard criteria.
- It is important to accurately diagnose non-Alzheimer's dementia, as they often carry different prognoses, and entail different treatment considerations from AD. For instance, FTD generally carries a worse prognosis and is not amenable to cholinesterase

inhibitor treatment, unlike AD. Accurate diagnosis of DLB would alert the physician to the dangers of neuroleptic sensitivity when deciding on the course of treatment for the management of attendant neuropsychiatric problems. Aggressive treatment of vascular risk factors and secondary stroke prevention may impede progression of cognitive decline in VaD, even if the stroke lesions appear insignificant.

- In patients presenting with confusion of forgetfulness, it is important to exclude delirium, either in isolation (acute/subacute presentation) or in combination with an underlying neurodegenerative process (acute on chronic presentation).
- In the evaluation of dementia, it is vital to evaluate the behavioral, functional, and social complications, as these are often amenable to treatment or palliation.
- Through a four-step systematic approach involving comprehensive history-taking, targeted physical examination, and selected investigations, the clinician can confidently evaluate the diagnosis, complications, and etiology of older persons presenting with memory problems or confusion.

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Treatment of Behavioral Disorders

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INTRODUCTION

Behavioral disorders in elderly individuals are most commonly caused by a dementing process. Individuals who suffered from lifelong psychiatric diseases, such as schizophrenia, might continue to exhibit symptoms of these diseases even in old age, but management of these symptoms follows general psychiatric practice. Therefore, this chapter will concentrate on behavioral disorders caused by a progressive degenerative dementia.

Problem behavior is a serious problem in progressive dementias and is the most common reason for institutionalization (Phillips and Diwan, 2003). The most common progressive dementias are Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. A behavioral disorder may also be caused by a delirium that is induced by an acute medical or surgical condition (e.g. infections, dehydration, metabolic disorder) or by adverse effects of medications (e.g. drugs that have anticholinergic effect such as diphenhydramine, thioridazine, and benztropine, by cardiac medications such as digoxin and antihypertensive agents, and by drugs used to treat peptic ulcers such as cimetidine). Individuals with dementia are more sensitive to development of delirium and occurrence of delirium in cognitively intact individuals is an indication that the individual is at high risk of developing dementia.

Delirium is characterized by an acute onset of mental status change, fluctuating course, decreased ability to focus, sustain and shift attention, and either disorganized thinking or an altered level of consciousness that resolves if the precipitating causes are removed (*see* **Chapter 90, Delirium**). However, diagnosis of delirium is not easy because some of these diagnostic criteria are not unique for delirium. Acute onset of mental status change may be caused also by a vascular dementia, and fluctuating course of cognitive impairment is an important clinical diagnostic feature of dementia with Lewy bodies (McKeith *et al.*, 1996). Delirium is also not always a transient cognitive impairment because cognitive impairment resolves within 3 months in only 20% of patients with diagnosis of delirium. The specific symptoms of reversible dysfunction include plucking at bedclothes, poor attention, incoherent speech, abnormal associations, and slow vague thoughts. Delirium superimposed on dementia ranges from 22%–89% of hospitalized and community populations aged 65 and older with dementia and has several adverse effects including accelerated decline, need for institutionalization, and increased mortality. Therefore, the possibility that delirium is responsible for the onset of new behavioral symptoms should be always considered.

The diagnostic criteria for Alzheimer's disease include multiple cognitive deficits manifested by both memory impairment and at least one other cognitive disturbance (aphasia, apraxia, agnosia, or disturbance of executive functioning). These cognitive deficits have to be severe enough to cause significant impairment in social or occupational functioning and has to represent a significant decline from a previous level of functioning. The course of the Alzheimer's disease is characterized by a gradual onset and continuing cognitive decline. The cognitive impairment cannot be due to other brain disease, to systemic disturbances that can cause dementia, or to drug-induced effects. Clinical diagnosis of the Alzheimer's disease is tentative and needs to be supported by neuropathological examination of the brain after the patient dies. Thus, the most definite clinical diagnosis of Alzheimer's disease is "Probable Alzheimer's disease", which is made when there are no other possible etiological factors and "Possible Alzheimer's disease" when other possible etiological factors are also present.

There are several diagnostic sets of criteria for vascular dementia and they differ from each other (Verhey *et al.*, 1996) (*see* **Chapter 95, Vascular Dementia**). Most criteria require an abrupt onset of dementia, focal neurological findings (abnormal reflexes or nerve functions), low-density areas (indicating vascular changes in the white matter) and/or the presence of multiple strokes on CT (computerized tomography) or MRI (magnetic resonance imaging) scans. Other criteria also include fluctuation of impairment, unchanged personality, emotional lability, and a temporal relation between

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a stroke and development of dementia. However, it has to be recognized that vascular changes are often present together with Alzheimer changes during brain autopsy. Thus, it is difficult to exclude the possibility that a patient has Alzheimer's disease even when several criteria for vascular dementia are met.

Dementia with Lewy bodies (also sometimes called *diffuse Lewy body disease*) is characterized by a fluctuating course of cognitive impairment that includes episodic confusion with lucid intervals similar to delirium (McKeith *et al.*, 1996) (*see* **Chapter 96, Other Dementias**). In addition, there must be at least one of the following: (1) visual and/or auditory hallucinations resulting in paranoid delusions, (2) mild extrapyramidal symptoms (muscle rigidity, slow movements) or adverse extrapyramidal response to standard doses of antipsychotics, or (3) repeated unexplained falls. The clinical features of dementia with Lewy bodies persist over a long period of time in contrast to delirium that is usually shorter and usually does not progress to severe dementia. As with Alzheimer's disease, other causes of the progressive cognitive decline have to be excluded.

The diagnosis of frontotemporal dementia is based on personality changes and the presence of atrophy of the frontal brain areas in neuroimaging studies (CT scan, or MRI). The personality changes in frontotemporal dementia are similar to changes induced by the damage of frontal lobes by other causes (injury, stroke) and include behavioral disinhibition, loss of social or personal awareness, or disengagement with apathy. Patients with frontotemporal dementia differ from Alzheimer patients because they maintain some abilities (e.g. elementary drawing and calculations) into the later stages of dementia. Pick's disease is a pathological subtype of frontotemporal dementia, which is characterized by specific neuropathological findings: Pick bodies inside nerve cells and ballooned nerve cells.

PHYSICAL CAUSES OF BEHAVIORAL SYMPTOMS

Before any behavioral symptoms are ascribed to underlying dementia, possible physical causes have to be eliminated. Behavioral symptoms may be induced by an acute illness or an exacerbation of a chronic condition. These conditions include cardiovascular disease, brain tumors, sensory deprivation (*see* **Chapter 103, Disorders of the Eye**; **Chapter 105, Auditory System**), metabolic disorders, chronic obstructive pulmonary disease, and anemia. Acute illness can be an infection, acute abdominal conditions, or an injury. Unrecognized pain is a common cause of behavioral symptoms and treatment of behavioral symptoms with acetaminophen may decrease the inappropriate use of psychoactive medications (*see* **Chapter 84, Control of Chronic Pain**). The pain could result from fecal impaction, urinary retention, or unrecognized fracture, but the most common cause of chronic pain in nursing home residents is arthritis, followed by old fractures, neuropathy, and malignancy. Detection of pain is difficult in individuals with dementia who cannot describe the pain and its location. A comprehensive evaluation of pain in noncommunicative individual relies on the observation of facial expression, vocalization, and body movements and tension and may use a recently developed scale (Warden *et al.*, 2003).

CONCEPTUAL FRAMEWORK OF BEHAVIORAL SYMPTOMS OF DEMENTIA

Although progressive degenerative dementias differ in their early presentation, the behavioral disorders that they cause in later stages of dementia are very similar. Several conceptual frameworks were developed to classify and describe behavioral symptoms of dementia on the basis of nursing, psychological, or psychiatric concepts (Volicer and Hurley, 2003). A model integrating all these approaches postulates a hierarchy of causes of behavioral symptoms (Figure 1). At the core of these symptoms is the dementing process itself that may be modified by the underlying personality of the individual. Primary consequences of dementia are functional impairment, mood disorders, and delusions/hallucinations. These primary consequences, alone or in combination, lead to secondary consequences that are inability to initiate meaningful activities, dependence in activities of daily living (ADLs), spatial disorientation, and anxiety. Primary and secondary consequences of dementia cause peripheral symptoms: agitation, apathy, insomnia, interference with other residents, resistiveness to care, food refusal, and elopement. Peripheral symptoms may be caused by more than one of the primary and secondary consequences, and each primary and secondary consequence can generate several peripheral symptoms. For instance, functional impairment may lead to an inability to initiate meaningful activities, dependence in

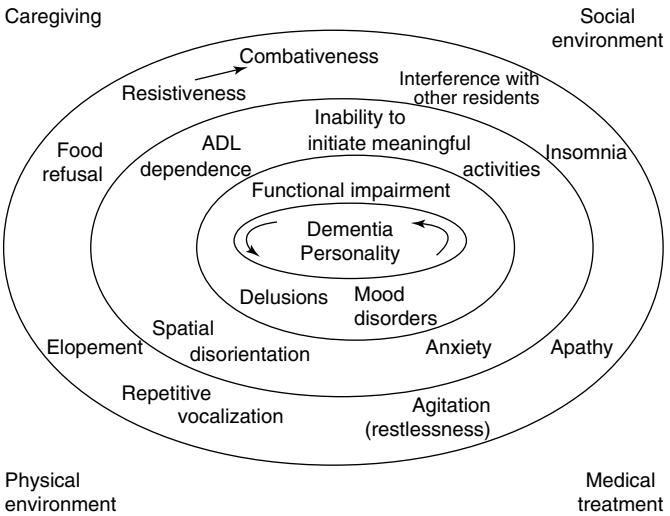

Figure 1 Comprehensive model of psychiatric symptoms of progressive degenerative dementias. (From Mahoney, Volicer and Hurley (2000). *Management of challenging behaviors in dementia* (p. 2). Baltimore: Health Professions Press; reprinted by permission)

ADLs, and anxiety and agitation if stressful demands are made, or agitation/apathy and repetitive vocalization if meaningful activities are not provided. Similarly, depression may lead to anxiety, worsening of the ability to initiate meaningful activities and to engage in ADLs, to food refusal, agitation, insomnia, and worsening of resistiveness to care. Therefore, it is important to analyze the cause(s) of peripheral behavioral symptoms of dementia and treat effectively the primary or secondary consequences that are causing these symptoms instead of treating each peripheral symptom in isolation.

Behavioral symptoms of dementia are influenced by four environmental factors. Caregiving approaches are most important for the resistiveness/combativeness continuum (see below). Social environment is important because it eliminates problems related to interaction with cognitively intact nursing home residents. Physical environment should prevent elopement and provide for safe ambulation and wandering. And finally, medical interventions may aggravate behavioral symptoms because demented individuals do not understand the need for these interventions and do not cooperate with diagnostic and therapeutic procedures. The rest of this chapter will describe in more detail elements of this model and therapeutic approaches that can be used.

DEMENTIA AND PERSONALITY

Dementia is at the core of behavioral disorders. There is some evidence that premorbid personality traits are related to subsequent psychiatric symptoms. Patients who were more neurotic and less assertive before developing dementia are more likely to become depressed, while patients who were more hostile before developing dementia are more likely to have paranoid delusions. Patients who were neurotic and extroverted before developing dementia are more likely to engage in aggressive behavior while previous agreeableness decreases the probability of aggression.

Unfortunately, there is no treatment currently available that would stop or reverse the course of progressive degenerative dementias. However, there are currently two classes of medications approved for the treatment of Alzheimer's disease (Table 1). There is some evidence that cholinesterase inhibitors may be also useful for treatment of vascular dementia (Kumar *et al.*, 2003) and dementia with Lewy bodies (Wesnes *et al.*, 2002). Although the primary effect of cholinesterase inhibitors is the improvement of cognitive function, their administration also leads to some improvement in behavioral symptoms of dementia. Metanalysis of published reports regarding the efficacy of cholinesterase inhibitors showed that the behavior of patients treated with cholinesterase inhibitors improved significantly according to the Neuropsychiatric Inventory (Trinh *et al.*, 2003). There was no difference in efficacy among cholinesterase inhibitors. Memantine was found to decrease agitation (Areosa and Sherriff, 2003).

Table 1 Drugs for treatment of dementia

Drug	Mechanism of action	Daily doses (mg)	Maintenance dose
Donepezil (Aricept)	Inhibition of AChE	5, 10[a]	10 mg QD
Galantamine (Reminyl)	Inhibition of AChE Nicotinic receptor modulation	8, 16, 24[b]	8–12 mg BID
Rivastigmine (Exelon)	Inhibition of AchE Inhibition of BChE	3, 6, 9, 12[b]	4.5–6 mg BID
Memantine (Namenda)	Modulation of NMDA receptors	5, 10, 15, 20[c]	10 mg BID

AChE, acetylcholine esterase; BChE, butyrylcholine esterase; NMDA, *N*-methyl-d-aspartate.
[a]The dose should be increased after 4–6 weeks. [b]The dose should be increased if lower dose is tolerated for 4 weeks. [c]The dose should be increased every week.

Cholinesterase inhibitors may not be effective enough to control all behavioral symptoms of dementia, but they may be useful as a first line treatment. Donepezil was found to potentiate the antipsychotic effect of perphenazine (Bergman *et al.*, 2003) and caregivers of individuals with dementia treated with donepezil report lower level of behavioral disturbances than caregivers of individuals not receiving this treatment. Donepezil patients were described as significantly less likely to be threatening, destroy property, and talk loudly. Cholinesterase inhibitors are usually well tolerated, with diarrhea and nausea being the most common adverse effects.

FUNCTIONAL IMPAIRMENT

Presence of functional impairment that interferes with daily activities is necessary for the diagnosis of dementia. Functional impairment is a result of several deficits affecting both cognitive and physical functions. Memory impairment causes inability to remember appointments and prevents the individual from participating in social games, for example, bridge. Speech impairment interferes with social contact and may result in an inability to understand spoken or written language. Apraxia leads to the inability to use tools and continue engagement in previous hobbies. Spatial disorientation leads to the inability to take independent walks. Executive dysfunction leads to deficits in problem solving and judgment and prevents the individual from planning and executing an activity.

Functional impairment may cause three secondary consequences of dementia: dependence in ADLs, inability to initiate meaningful activities, and anxiety if a person with dementia recognizes his/her limitations, or if a caregiver has unrealistic expectations about abilities of the care recipient. These secondary consequences may cause several peripheral symptoms: resistiveness to care, agitation, repetitive vocalization, apathy, and insomnia. Functional impairment may involve both cognitive and physical components.

Treatment of cognitive component of functional impairment involves both behavioral and pharmacological approaches. Because of the progressive nature of dementia, the deficits cannot be reversed. However, they can be minimized and the function maintained for as long as possible by creating an environment in which the individual with

dementia can experience positive emotions and by preventing excess disability that may be induced either by expecting too much or by expecting too little from the individual (*see* **Chapter 158, Geriatric Occupational Therapy: Focus on Participation in Meaningful Daily Living**). In the mild to moderate stage of dementia, memory aids may be helpful. Cueing and creating connections to familiar things, and simplifying and breaking tasks into small parts may be useful to maintain dressing behavior (Beck *et al.*, 1997). Practice may also help maintain cognitive skills. Patients who performed exercises that included word fluency, immediate and long-term verbal and nonverbal recall and recognition, and problem solving, improved their cognitive function and had less behavioral problems while control group continued to decline. These results indicate that procedural learning can occur in individuals with dementia and that the rate of decline can be slowed by the prevention of excess disability. Individuals may also maintain ability to perform an activity (e.g. playing dominoes) even after they lose the ability to explain the rules.

Pharmacological management of cognitive component of functional impairment involves drugs used for treatment of dementia described above. There is good evidence that both cholinesterase inhibitors and memantine improve temporarily functional abilities or slow down the rate of their loss. Multifactorial approaches to maintenance of cognitive function were also developed. In a study involving administration of ginkgo biloba, vitamin C, vitamin E, and low fat diet, and including meditation, mind-body exercises, physical exercises, stress reduction techniques and cognitive rehabilitation exercises, experimental group improved in verbal fluency, controlled oral word association test, and paired association (Bender *et al.*, 2002).

Physical component of functional impairment includes decreased ability to ambulate and eat. Individuals with dementia become unable to ambulate independently because they cannot recognize objects in their path and because neurological impairment leads to unsteady or narrow-based gait (*see* **Chapter 112, Gait, Balance, and Falls**). Both of these consequences lead to an increased risk for falls. If the risk for falls is managed by restraints, the individuals deteriorate further because of deconditioning and forgetting how to walk. It is important to maintain ambulatory ability for as long as possible because walking represents meaningful activity and because inability to walk increases the risk of intercurrent infections and pressure ulcers. Ability to walk can be promoted by a regular walking program and by assistive devices, such as Merry Walker (Trudeau *et al.*, 2003).

MOOD DISORDERS

Mood disorders that can occur in individuals with dementia include depressive disorders and bipolar disorder. Depressive disorders are major depression with or without psychosis, dysthymic disorder, and minor depressive disorder (*see* **Chapter 100, Depression in Late Life: Etiology, Diagnosis and Treatment**). Depression is very common in community dwelling individuals with dementia and should be considered even in individuals with advanced dementia. Depression can cause or aggravate the inability to initiate meaningful activity and dependence in ADLs, and often has an anxiety component. These secondary consequences may lead to several peripheral symptoms, such as apathy, agitation, food refusal, and repetitive vocalization. Depression may also aggravate resistiveness to care because depressed individuals ignore ADLs. Depression also increases the propensity for escalation of resistiveness into combativeness because even cognitively intact depressed individuals are angry and do not tolerate others. Depression was significantly more common among residents with dementia who manifested physical or verbal aggression than in those without such behaviors (Menon *et al.*, 2001). Depressive symptomatology may be improved by providing sufficient meaningful activities, but often requires treatment with antidepressants.

The first line drugs to use for treatment of depression in individuals with dementia are selective serotonin reuptake inhibitors (SSRIs) (Table 2). These medications are usually well tolerated with the most common adverse effect being diarrhea. Since many individuals with dementia suffer from

Table 2 Selected antidepressants for treatment of depression in individuals with dementia

Drug class[a]	Name (trade name)	Dose range (mg)	Frequency[b]	Elimination half-life (hours)
Tricyclics	Amitryptyline (Elavil, Endep)	25–100	TID	24
	Nortryptyline (Aventyl, Pamelor)	25–50	BID–QID	26
SSRIs	Citalopram (Celexa)	20–60	QAM/HS	35
	Escitalopram (Lexapro)	10–20	QAM/HS	27–32
	Fluoxetine (Prozac)	10–40	QAM	168
	Fluvoxamine (Luvox)	50–300	QHS	15
	Paroxetine (Paxil)	20–50	QHS	24
	Sertraline (Zoloft)	50–200	QAM	24
Other	Bupropion (Wellbutrin)	150–300	BID–TID	14
	Mirtazepine (Remeron)	15–45	QHS	30
	Trazodone (Desyrel)	50–300	TID, QHS	8
	Venlafaxine (Effexor)	25–75	BID–TID	11

[a]SSRIs, selective serotonin reuptake inhibitors; [b]QD, once a day; BID, twice a day; TID, three times a day; QID, four times a day; QAM, every morning; QHS, every evening.

constipation, this usually is not a problem. SSRIs have some differences in their effects. Fluoxetine is the most stimulating of them and may result in increased agitation while paroxetine is sedating. Both fluoxetine and paroxetine, and to a lesser extent sertraline affect cytochrome P450 isoenzymes and interfere with metabolism of several drugs. Escitalopram may be an improvement over the first generation SSRIs because it is faster acting than citalopram (Valuck, 2004).

In individuals who do not tolerate SSRIs, venlafaxine, or bupropion may be used. Another option is mirtazepine, which may promote food intake in individuals with decreased appetite. Tricyclic antidepressants are used infrequently because they cause significant adverse effects that are partly mediated by an anticholinergic activity. Because of this activity, they are contraindicated in individuals treated with cholinesterase inhibitors. Trazodone is a relatively weak antidepressant but is useful for treatment of insomnia as will be discussed below. Electroshock therapy is effective in the treatment of depression in elderly individuals but may increase memory loss caused by dementia. Treatment of psychotic depression requires addition of antipsychotics to the antidepressant therapy. However, addition of an antipsychotic may be also effective in the treatment of resistant depression without psychotic features (Shelton *et al.*, 2001).

The prevalence of manic episodes in individuals with Alzheimer's disease and other dementias is relatively low and most of the individuals who exhibit them have a history of mania before the onset of Alzheimer's disease. Manic episodes are more common in people with cerebrovascular disease, especially when it involves the right hemisphere and orbitofrontal cortex. Manic symptomatology can be a significant cause of agitation and may also lead to interference with other residents, for example, unwelcome sexual advances.

Manic symptomatology is best treated with mood stabilizers (Table 3). Lithium is a drug of choice for the treatment of bipolar disorder in young individuals but its use in older individuals is questionable because the elderly may have age-related decreased kidney function or diseases and drug treatments that affect lithium excretion. Lithium is less effective in older adults with "organic manic disorder"; dementia, or mania complicated by serious medical conditions or by other psychiatric diagnoses. Carbamazepine is effective in the treatment of agitation in nursing home residents with dementia, but it has significant adverse effects that include rash, sedation, ataxia, agranulocytosis, hepatic dysfunction, and electrolyte disturbance.

The most commonly used mood stabilizers in dementia are valproic acid and gabapentin. Valproic acid, or its better tolerated enteric-coated derivative, divalproex sodium, was shown to be effective in dementia in several trials and this effect may be partly mediated by a neuroprotective effect (Tariot *et al.*, 2002). However, a recent metanalysis of these trials concluded that low doses of valproate may not be effective and high doses are associated with unacceptable rate of adverse effects, mainly sedation (Lonergan *et al.*, 2004). Other potential adverse effects of valproic acid include weight gain, hair loss, thrombocytopenia, and hepatic dysfunction.

Gabapentin is used increasingly in the management of behavior problems in individuals with dementia despite lack of randomized control studies. An open label study found that gabapentin was well tolerated and decreased caregiver stress. The advantages of gabapentin over other mood stabilizers are the relative lack of adverse effects and no need to monitor plasma levels. Several newer anticonvulsants are also sometimes used for treatment of behavioral symptoms of dementia but there are no data about their effectiveness and side effect profiles.

DELUSIONS AND HALLUCINATIONS

Delusion is a false belief, based on incorrect inference about an external reality that is firmly sustained despite evidence to the contrary. Delusions are often combined with hallucinations, which are sensory perceptions occurring without the appropriate stimulation of the corresponding sensory organ. Delusions occur in about half of individuals with Alzheimer's disease. Most of them have only delusions, some have both delusions and hallucinations, while isolated hallucinations are rare. Isolated hallucinations are more common in dementia with Lewy bodies. Delusions and hallucinations could be caused by other conditions. The most common one is delirium, which was described above.

Delusions may be divided into two types: simple persecutory delusions and complex, bizarre, or multiple delusions (*see* **Chapter 98, Geriatric Psychiatry**). Simple persecutory delusions include delusions of theft or suspicion. Suspicions involve beliefs such as being watched or having an unfaithful spouse. Complex delusions may include a conviction about a family member or a pet being injured, about plots against individuals of certain religious faith, and about wild parties happening on a nonexisting floor of the

Table 3 Selected mood stabilizers used in dementia

Name (trade name)	Dose range (mg)	Frequency[a]	Elimination half-life (hours)	Therapeutic level
Lithium (Eskalith, Lithobid, etc.)	100–300	BID–QID	22	0.6–1.2 m Eq l^{-1}
Valproic acid (Depakene); divalproex sodium (Depakote)	100–300	BID–QID	9–16	50–125 μg ml^{-1}
Carbamazepine (Tegretol)	100–200	BID	25–65 (12–17)[b]	4–12 μg ml^{-1}
Gabapentin (Neurontin)	300–900	TID[c]	5–7	Not measured

[a]BID, twice a day; TID, three times a day; QID, four times a day; [b]After chronic administration. [c]After titration phase (during titration, 300 mg once a day of BID).

nursing home. An example of complex delusion is Capgras syndrome that consists of a false belief that significant people have been replaced by identical-appearing impostors. Complex delusions may also present as grandiose delusions often connected with euphoria and hypomanic mood.

The most common delusions in Alzheimer patients are paranoid delusions, and the most common of those are delusions of theft that occurred in 28% of patients. The cause of these delusions may be memory problem of the patient, who forgets where he or she has put personal belongings. Delusions of suspicion were seen in 9% of the patients and more complex delusions in 3.6%. A common delusion of suspicion is that other patients in a long-term care facility are criticizing the patient behind his or her back. A stimulus for this delusion may be an innocent conversation in the hallway that is not heard very well by the patient and is misinterpreted. A very common delusion is the belief that the patient is much younger than his or her actual age. This delusion may be connected with misidentification, for example, of the patient's wife as his mother.

Onset of hallucinations in Alzheimer's disease is usually later in the disease progression, more than 5 years after the onset of dementia or more than a year after diagnosis. In approximately half of the patients the hallucinations are temporary, while in other patients hallucinations persist until death. Therefore, it is important to frequently reevaluate the need for pharmacological treatment in demented individuals. Hallucinations and delusions are associated with greater functional impairment and are more common in individuals who have extrapyramidal signs, such as muscle rigidity, and in individuals who have myoclonus.

Delusions and hallucinations may cause several secondary and peripheral behavioral symptoms of dementia. They may induce anxiety and spatial disorientation, and they may also interfere with ADLs because the individual does not believe that the activity is needed. Delusions and hallucinations are related to resistiveness to care and "aggression" (Kunik *et al.*, 1999), and agitation (Haupt *et al.*, 1998). They may also lead to food refusal if the individual believes that the food is poisoned and to attempts to leave a home or facility if the individual believes that he/she has to go to work or go "home". Misidentification of other residents and staff may lead to interference with other residents or inappropriate behavior toward the staff.

Treatment of delusions and hallucinations should consider their relationship to other behavioral symptoms of dementia. Some individuals with dementia have many delusions or hallucinations but are not bothered by them and they do not affect them behaviorally. In that case, no treatment is necessary. Otherwise, it is important to attempt nonpharmacological management of delusions and hallucinations before initiating treatment with antipsychotic medications. Nonpharmacological management should include attention to sensory perceptions, environmental modifications, and behavior strategies. Improvement of vision or hearing may decrease auditory delusions or visual hallucinations. Increased lighting, decreased noise, safe space for ambulation, and social environment of a dementia special care unit will decrease the need to treat delusions and hallucinations, which cause behaviors that may be distressing to other cognitively intact residents. Behavior strategies should recognize that reasoning cannot change behavior because the individual with dementia does not understand reasoning and does not remember what he/she was told; therefore, caregivers have to change their behavior. Caregivers should avoid the word "no" and instead of arguing, distract the individual from undesirable activity. It is better to accept the individual's reality than to try to orient them to reality. And the person with dementia should always be made comfortable by smiling, by a positive tone of voice, and by answering in a positive way even if the individual's speech does not make sense.

Pharmacological treatment of delusions and hallucinations utilizes administration of antipsychotics (Table 4). Older antipsychotics, represented by haloperidol, were potent antagonists of dopamine receptors. This led to a high incidence of extrapyramidal side effects and akathisia. These drugs are mostly replaced by newer (atypical) antipsychotics that have more beneficial adverse effect profile. This improvement is due to their effect on other than dopamine receptors. The most significant is blockade of the serotonin 2A receptors that prevents extrapyramidal side effects and may also lead to improvement in apathy. This activity is present in risperidone and olanzapine. However, activity at other receptors may lead to other adverse effects. Olanzapine and quetiapine block histamine 1 receptors, resulting in sedation and weight gain. The weight gain is especially troublesome in olanzapine, because it could lead to development of diabetes. Blockade of noradrenergic alpha 1 receptors, that is present in quetiapine and risperidone, may lead to orthostatic hypotension. Aripiprazole has a novel mechanism of action because it is a partial agonist on dopamine receptors. This effect prevents excessive dopamine activity while preserving normal dopamine function.

Table 4 Selected antipsychotics used for treatment in dementia

Name (trade name)	Dose range (mg)	Frequency[a]	Elimination half-life (hours)	Most common adverse effects
Aripiprazole (Abilify)	10–15	QD	75 (94)[b]	Insomnia, somnolence
Haloperidol (Haldol)	0.5–1	QD–TID	18	EPS[a], tardive dyskinesia
Olanzapine (Zyprexa)	2.5–10	QD	30	Weight gain, anticholinergic, sedation
Quetiapine (Seroquel)	25–100	BID–TID	6	Sedation, hypotension
Risperidone (Risperdal)	0.25–1	QD–BID	3–20 (21–30)[a]	EPS, hypotension

[a]QD, once a day; BID, twice a day; TID, three times a day; EPS, extrapyramidal side effects; [b]active metabolite.

Most clinical studies in dementia involved risperidone but usually used agitation or aggression as an outcome because delusions and hallucinations are difficult to measure in individuals with dementia who have limited communication ability (Brodaty *et al.*, 2003). Risperidone administration resulted in lower risk for falls and weight gain than olanzapine. Quetiapine has a broad dose range and its efficacy is somewhat unpredictable although it was found to be effective in an open label study (Tariot *et al.*, 2004). Risperidone was associated with slightly increased incidence of cerebrovascular incidents and other antipsychotics may also increase the risk of strokes. Therefore, it is important to avoid the use of antipsychotics if possible and use the lowest effective dose when they are being used.

DEPENDENCE IN ACTIVITIES OF DAILY LIVING

ADLs are the activities that are needed for self-care and independent living. They include instrumental activities of daily living (IADLs) and physical activities of daily living (PADLs) sometimes called *basic ADLs*. Dependence in ADLs is the result of functional impairment induced by dementia, but depression or delusions may aggravate the dependence, resulting in excess disability. Therefore, it is important to determine carefully the reasons for dependence. If the individual is dependent in PADLs, physical care has to be provided. The individual with dementia might not recognize the reason for this care and might resist the care. This resistiveness may escalate into combative behavior as will be described below. Thus, ADL dependence may lead to significant behavioral changes.

IADLs include shopping, preparing meals, traveling, doing housework and laundry, using telephone, taking medications, and managing money. Continued participation in ADLs is important for the self-esteem of the individual with dementia but safety and stress induced by these activities have to be considered. IADLs should be simplified because the individual with dementia may still be able to participate in some steps but not in the entire activity (Table 5). Supportive services, such as a homemaker or Meals on Wheels, may allow an individual with dementia to continue living in his/her own home. Assistance may come in many forms: encouragement, verbal cues, visual cues (gestures), and physical guidance.

Table 5 Examples of IADL adaptations for individuals with dementia

IADL	Suggested adaptations
Shopping	Plan and go shopping with others
	Continue to help choosing purchases
Meal preparation	Prepare one dish, with steps presented one at a time
Using telephone	Help person list things to talk about before making a call
	Help person call relatives and friends
	Put pictures of people on preprogramed telephone buttons
Money management	Simplify bill-paying routine
	Carry small amount of money
	Make small purchases with assistance on shopping trips

Source: (Adapted from Stehman *et al.*, *Handbook of dementia care* (1996)).

PADLs include bathing, dressing, grooming, toileting, walking, and eating. PADL functional abilities decline in a predictable temporal order according to the complexity of the ADL – bathing, dressing, grooming, toileting, walking, and eating. Bathing is an activity that most often results in resistive behavior. Strategies for bathing dependence will be described below. Dressing is the ADL that has been studied most extensively. A significant improvement in dressing performance can be achieved by implementing strategies that promote independence in dressing by nursing assistants (Beck *et al.*, 1997). Strategies for toileting difficulties include behavioral interventions (prompted voiding), establishing a routine, clothing modifications, making going to the bathroom easier, becoming familiar with and watching for cues indicating that the individual needs to use the bathroom, preserving dignity, and physical assistance to reach a bathroom. Independent eating is promoted by encouraging independence while providing supervision and assistance, by creating a social mealtime environment and by simplifying the eating process. Walking ability can be maintained for as long as possible by the use of assistive devices, such as Merry Walker (Trudeau *et al.*, 2003).

INABILITY TO INITIATE MEANINGFUL ACTIVITIES

This inability is caused by functional impairment but may also be aggravated by depression. Lack of meaningful activities may result in apathy or agitation, repetitive vocalization and insomnia, if the individual with dementia sleeps during the day. Involvement in meaningful activities is important for maintenance of functional abilities, social involvement, feeling of success and accomplishment, improvement in mood, and reduction of disruptive behavior (Volicer and Bloom-Charette, 1999).

Individuals with dementia live in the moment, and there is a widespread agreement among experts that the moment should be pleasurable. Management goals for people with the inability to initiate meaningful activity, therefore, are to prevent disability and to improve their interaction with the environment and their quality of life. Individuals with dementia who are unable to initiate meaningful activities may be unoccupied and appear bored or not engaged with the environment, sitting motionless, or wandering around aimlessly. They spend more time in a state of inner retreat, and this withdrawn behavior may manifest itself as lack of behavior, somnolence, perseveration, or nondirected verbal agitation.

The goal of management of the inability to initiate meaningful activities is to create environment with optimal stimulation and a steady flow of meaningful activities that are adapted to the functional capacity of the individual with

Table 6 Guidelines for planning activities for people with dementia

Principle	Rationale
Focus on enjoyment, not achievement	The goals of therapeutic program are to prevent excess disability and help the person "feel good"
Create "failure-free" environment	Helps person maintain self-esteem
Design therapeutic activities to stimulate multiple senses(Trudeau, 1999)	The ability to experience a range of human responses (emotions, behavior) continues across mild, moderate, and severe stages of dementia
Make activities part of daily routine	Maintain homelike routines Make all activities (including ADLs) meaningful Not an extra burden for the caregiver
Plan structured activities that employ previously learned motor patterns	These tasks require no new learning, yet can make the person feel useful and productive

Source: (Simard, 1999; Stehman *et al.*, 1996).

dementia. Engaging the individual in meaningful activities throughout the course of Alzheimer's disease or any other type of progressive dementia is challenging. Individuals with dementia do not ask for something to do as the more alert residents will, and as their dementia progresses they are increasingly difficult to keep engaged during activities because of their short attention span. An activity program that provides continuous programing throughout the majority of the residents' waking hours is not only an effective way to reduce psychotropic medication, reduce falls and social isolation, but it also helps individuals with dementia to live with some purpose and meaning in spite of the disease. General guidelines for planning activities for individuals with dementia are listed in Table 6.

In an institution, the programming should take into consideration the routine the individual had before admission for long-term care. The continuous programming for moderate dementia should begin with a morning routine that may include the Pledge of Allegiance, patriotic song, newspaper, or weather report discussion. Exercise programs, food and beverages served in a social atmosphere, word games, and spelling bees should follow. All these programs should be "no fail" opportunities to have fun. An individualized program that was found to decrease agitation and improve mood is Simulated Presence Therapy (Camberg *et al.*, 1999). At the end of the day, active participants are tired and ready for a video or a movie, a snack, and a peaceful sleep.

As dementia progresses into the severe stage, it becomes more challenging to engage individuals in meaningful activities. They tend to sleep during programs and may have difficulty communicating. Another level of programming, one that has more individual attention and has less physical activities helps meet their needs at this stage. Activity staff provides more touch, respects when the resident needs to take short "naps" and uses more visual cues. Physical exercise may require the activity staff standing in front of the resident and modeling the movement, or assisting the resident to move their arms or legs. Fewer programs are scheduled but the activity professional is in the room with the residents so that when they are awake, they can be engaged. Music, old musicals, sensory stimulation, and showing items from the past are some ways to engage residents in the severe stage of dementia.

Meaningful activities should be provided even for individuals in the terminal stage of dementia because Alzheimer's disease rarely, if ever, progresses to the persistent vegetative state (Volicer *et al.*, 1997a). Activities useful in that stage include pet therapy, massage, and Snoezelen (Brown, 1999).

ANXIETY

Anxiety is defined as a vague, uneasy feeling, the source of which is often nonspecific or unknown to the individual who is experiencing it. Anxiety is a feeling of distress, subjectively experienced as fear or worry, and objectively expressed through autonomic and central nervous system responses. Anxiety can be a symptom of depression or caused by disturbing delusions and hallucinations. It also can be caused by a primary anxiety disorder such as generalized anxiety disorder, phobia, posttraumatic stress disorder, and obsessive-compulsive disorder. However, new onset primary anxiety disorders are unusual in older adults. In most instances, older people with primary anxiety disorders have a history of them, and it is therefore important to obtain complete personal and family psychiatric history.

Anxiety may be also a symptom of physical illness or caused by medications. It may be induced by decreased delivery of oxygen to the brain caused by cardiac or pulmonary disease and by endocrine disorders such as hyperthyroidism and hypoglycemia. Medications that may cause anxiety as an adverse effect include anticholinergic drugs, caffeine, steroids, decongestants, bronchodilators, alcohol, narcotics, sedative-hypnotics and other psychotropic medications. Anxiety also may be a withdrawal symptom in individuals dependent on alcohol, benzodiazepines, or sedatives/hypnotics.

Anxiety is very common in Alzheimer's disease occurring in 52% of patients in mid and late stages of the disease (Hart *et al.*, 2003). The prevalence of anxiety increases with the progression of the disease (Porter *et al.*, 2003) but it is present together with suspiciousness even in individuals with mild cognitive impairment. Anxiety is even more common in individuals with vascular dementia and frontotemporal dementia than in individuals with Alzheimer's disease (Porter *et al.*, 2003).

Presence of anxiety is associated with reduced functional status in performing ADLs (Schultz *et al.*, 2004) and with sleep disturbances. Over a half of individuals with Alzheimer's disease who were experiencing anxiety woke up their caregivers at least once at night during the past week. The awakenings were associated with higher levels of patient anxiety and impairment in ADLs (McCurry *et al.*, 2004). Anxiety may also lead to agitation and repetitive vocalization.

Table 7 Selected medication for treatment of anxiety

Drug class	Name (trade name)	Dose range and frequency[a]	Elimination half-life (hours)	Side effects
Benzodiazepines	Alprazolam (Xanax)	0.25–0.5 mg TID	12	Sedation, impaired motor coordination, risk of falls, memory loss, respiratory depression, dependence, paradoxical reaction
	Lorazepam (Ativan)	0.5–1 mg BID or TID	15	
	Oxazepam (Serax)	10–20 mg TID or QID	8	
Azapirone	Buspirone (busPIRone)	5–20 mg TID	Onset of action 3–6 weeks	Headache, nausea, drowsiness, lightheadedness
Antidepressants	See Table 2			
Antipsychotics	See Table 4			

Source: Data from Raskind (1998).

Nonpharmacological management of anxiety is based on decreasing the stress level to which the individual with dementia is exposed. This may be accomplished by rest periods that prevent fatigue, positive communication strategies, prevention of overstimulation by providing low stimulation environment, and avoiding unfamiliar situations. Pharmacological management should first consider treatment of the primary consequences of dementia that may cause anxiety: mood disorders and delusions/hallucinations. Only if this approach is not effective or there is a strong evidence that the anxiety is caused by a primary anxiety disorder, anxiolytic medications should be used. These medications include administration of benzodiazepines and buspirone (Table 7). Only short-acting benzodiazepines should be used, and they may be useful also for a short-term treatment of an anxiety-induced catastrophic reaction that usually causes extreme agitation. Trazodone is another medication that may be useful on an as-needed basis because of its antidepressant and sedative effects.

SPATIAL DISORIENTATION

Spatial disorientation is the misperception of immediate surroundings, not being aware of one's setting, or not knowing where one is in relation to the environment. Spatial disorientation may cause misunderstanding of the environment and lead to development of fear, anxiety, suspicions, delusions, and safety problems such as getting lost. Getting lost may also lead to interference with other residents occurring if an individual with dementia invades their space, and the inability to find a bathroom contributes to ADL deficit. In the early stages of dementia, the individual may become confused when in unfamiliar place. In the later stages, the individual becomes confused even in previously familiar places.

Spatial disorientation may be related to a damage of specific brain area-posterior cingulate gyrus, because hypofunction of this area measured by positron-emission tomography was associated with disorientation for place. Another brain area that is necessary for place navigation, and is damaged severely in Alzheimer's disease, is the hippocampus. A healthy hippocampus uses two mechanisms for spatial orientation: cognitive mapping and cue navigation. Cognitive mapping requires cognitive processing to identify and store mental images of the most frequently encountered elements in a particular environment and the ability to make the connections among those elements. Cue navigation works by selection of a single landmark that directs an individual toward a specific location in the environment. Individuals retain these cues longer when they are familiar and are strongly associated with an environmental landmark. Another factor that participates in spatial disorientation in Alzheimer's disease is impaired depth perception. Because of this impairment, a change in color of a carpet or tile may be perceived as a step or obstacle.

Management of spatial disorientation utilizes information from these studies by using pop-up cues and environmental landmarks. Pop-up cues strategy attempts to simplify detection of the cue by providing one salient feature and color contrasts. If the cue is complex, it requires more cognitive processing than a simple cue. Individuals with dementia, who have impaired attention span and cognitive processing, may not recognize complex cues. Color contrast improves detection of the cue. Thus, a white toilet in a red bathroom is easier to find than a white toilet in a white bathroom. Environmental landmark strategy utilizes long-term memory by either keeping the environment unchanged or by using familiar objects as landmarks in a new environment. Personal or emotionally charged objects should be used as orientation devices. It is also important to simplify the environment by removing clutter and scatter rugs. Spatial orientation is promoted by signs on doors of common rooms, personal pictures or effects by the door of individual rooms, adequate lighting that does not cast shadows that may be misinterpreted, and by establishing a walking area with color contrasting borders.

RESISTIVENESS TO CARE

Resistiveness to care is defined as the repertoire of behaviors with which individuals with dementia withstand or oppose the efforts of a caregiver (Mahoney *et al.*, 1999). These behaviors occur primarily during hands-on care that includes bathing, dressing, toileting, eating, and administering medication. They can also occur when the caregiver attempts to redirect the individual with dementia. Resistiveness to care is caused by either misperception of the need for care activity or by misperception of the caregiver's intent (*see* **Chapter 89, Communication Disorders in Dementia**). Thus,

an individual who does not recognize that he/she has soiled clothing will resist caregiver's attempt to change his/her clothes. Communication difficulties may prevent the individual with dementia from recognizing what the caregiver's intent is. In both cases, the individual with dementia does not cooperate with the caregiver but actively resists the caregiver's approach. If the caregiver insists on providing care, the individual with dementia may defend him/herself from this unwanted attention, becomes combative and even strikes out. Such an individual may be labeled "aggressive". However, the patient perceives the caregiver as the aggressor and just defends him/herself. Most individuals with dementia are not aggressive unless provoked and most "aggressive" behaviors reported in the literature occur in the context of personal care.

Several factors increase probability of resistive behavior. Delusions and hallucinations may prevent recognition of the need for care or lead to misidentification of a staff person. Depression increases resistiveness to care because depressed individuals are angry and do not tolerate others. Spatial disorientation may result in increased need for toileting because the individual cannot find a bathroom. Management of these factors may decrease resistiveness to care but the most important factor for its management is the caregiver approach. Therefore, caregiver behavior should always be evaluated when resistiveness of care occurs before initiation of any pharmacological therapy.

The goal of care is to prevent escalation of resistive behavior into combative behavior. The approach used by the caregiver is crucial. Relaxed and smiling caregiver behavior is related to calm and functional behavior of the individual with dementia. It is important to avoid making demands that create stress or are beyond the ability of the individual with dementia, avoid rushing through ADL, avoid touching without warning, avoid painful procedures, avoid overstimulating the individual, and to express respect for the individual with dementia by allowing him/her to maintain some control. Distraction may be also used to direct the individual's attention away from the stressful stimulus. Engaging an individual in conversation on a favorite topic or reminiscing about happy memories that are retained takes the focus away from the task and places it on the person. This person-centered approach is effective even with individuals who have significant cognitive and language impairment. In an institutional setting, distraction may be accomplished by using two caregivers. While one caregiver engages the individual's attention by talking or singing, a second caregiver performs the ADL care.

Another important factor is the environment in which the care is provided. This is especially important for bathing. The bathroom should feel private and personal, it should be warm, have relaxing music, soft light, low noise level, homelike furnishings, aromas to evoke memories, set mood and make the bathing experience pleasant, and the bathing equipment should be comfortable and functional. Very effective strategy for decreasing resistiveness to care is the modification of care procedures. Some individuals prefer to bathe in the morning and some in the afternoon or evening. It is also possible to replace shower or tub bath with a bed bath that is much less stressful for an individual with dementia (Sloane *et al.*, 1995).

Pharmacological management should take into account the possible causes of resistiveness to care. A possibility that resistiveness is induced by pain that the individual experiences during care procedures should be considered and if pain is present premedication with analgesics before a care episode should be instituted. If symptoms of depression are present, antidepressant treatment often decreases the resistive behavior. Delusions are a common cause of resistive behavior and if the behavior cannot be managed by behavioral strategies, antipsychotic therapy may be useful.

FOOD REFUSAL

One important goal of dementia care is to provide adequate nutrition by promoting eating and preventing food refusal. Food refusal may have several causes (*see* **Chapter 26, The Anorexia of Aging**; **Chapter 27, Weight Loss in Older Adults**; **Chapter 73, Communication Disorders and Dysphagia**). An individual with dementia may dislike institutional food especially if he/she is of different ethnic background and was used to eating different food. Food refusal may also be caused by physical reasons, such as fatigue, overstimulation, constipation, medication-induced nausea, dehydration, toothache, or ill-fitting dentures. Food refusal is an important symptom of depression and may be also caused by delusions about food being poisoned. In advanced dementia, when individuals develop swallowing difficulties, food refusal may be a consequence of choking on food and liquids. Finally, in the terminal stage of dementia, some individuals are unable to open mouth and swallow.

Food refusal may lead to weight loss and malnutrition although very often it is only occasional and the individual with dementia makes up for decreased food intake one day by eating more the next day. Management of food refusal should first consider personal and behavioral factors that may contribute to food refusal. It is important to obtain information about foods that the individual with dementia likes or dislikes although sometimes food preferences are significantly changed as dementia progresses. Environmental factors are chaotic or noisy dining area, inadequate staff time or knowledge of how to promote eating, unappealing food presentation, and improper utensils. As dementia progresses, individuals become unable to use utensils and their failure to eat may not indicate food refusal. Serving finger food may allow them to eat independently much longer.

If the behavioral and environmental interventions are ineffective, pharmacological management may be initiated. The most important is to eliminate depression and delusion as causes of food refusal by appropriate treatment with antidepressants or antipsychotics. If that approach is not appropriate or effective, food intake may be enhanced by administration

of megestrol acetate or dronabinol. Megestrol acetate is a progesterone derivative with androgenic properties. It is used for treatment of anorexia and cachexia in cancer and AIDS. Megestrol acetate improved appetite and well-being in nursing home patients but a weight gain occurred only after discontinuation of the treatment (Yeh *et al.*, 2000). Dronabinol is a cannabinoid derivative that is used for treatment of anorexia in AIDS and prevention of vomiting after chemotherapy for cancer. Dronabinol increased body weight of institutionalized individuals with Alzheimer's disease and also improved their problem behaviors (Volicer *et al.*, 1997b).

Tube feeding is not an appropriate strategy for management of food refusal in individuals with advanced dementia. Tube feeding does not have any benefits on these individuals (Finucane *et al.*, 1999). Tube feeding does not prevent malnutrition or infections and it does not increase survival in individuals with progressive degenerative dementia (*see* **Chapter 60, Aspiration Pneumonia**). Nasogastric tube may cause infections of sinuses and middle ear, and gastrostomy tubes may cause cellulitis, abscesses, and even necrotizing fasciitis and myositis. Contaminated feeding solution may cause gastrointestinal symptoms and bacturiuria. Insertion of a tube may actually cause death from arrhythmia during insertion of a nasogastric tube and from perioperative mortality in percutaneous endoscopic gastrostomy tube placement. Occurrence of pressure ulcer is not decreased by tube feeding and it may actually be increased because of the use of restraints and increased production of urine and stool (*see* **Chapter 142, Restraints and Immobility**). There is also no evidence that tube feeding promotes healing of pressure ulcers or improves functional status of individuals with advanced dementia (Finucane *et al.*, 1999).

INSOMNIA

Sleep disturbances are common in elderly and probably even more common in individuals with dementia (*see* **Chapter 63, Sleep Disorders in Elderly People**). A survey of individuals 65 years old or older who were living at home showed that 28% had difficulty falling asleep and 42% had difficulty both in falling asleep and staying asleep. Aging affects sleep structure, resulting in less time spent in deep sleep and slightly more time spent in lighter stages of sleep. The elderly experience frequent nighttime awakenings and fragmentation of sleep. They also sleep less efficiently with their actual time asleep being only 70–80% of the total time spent in bed (Folks and Fuller, 1997).

Insomnia could be a primary condition but it also may be caused by other factors. These factors include medical and psychiatric illness, medication use, specific sleep disorders, psychosocial factors, and circadian rhythm changes. Insomnia is associated with respiratory symptoms, physical disabilities, use of nonprescription medications, depressive symptoms, and poor self-perception of health (Folks and Fuller, 1997). Many medications that are used for treatment of chronic conditions may affect sleep. These medications include decongestants, antiasthmatics, corticosteroids, antihypertensives, alcohol, caffeine, nicotine, and thyroid preparations. Sleep disorders include sleep apnea and periodic limb movement in sleep. Both of these conditions are very common in the elderly (Ancoli-Israel, 2000). Psychosocial factors include loneliness, bereavement, and the lack of physical activity. Circadian rhythm changes differently in normal aging and in Alzheimer's disease. In normal aging, there is an advance of the sleep phase with early evening sleepiness and early morning awakenings. Even if elderly go to bed later, they may wake up early in the morning and be unable to go back to sleep (Ancoli-Israel, 2000).

In Alzheimer's disease, there is a delay in circadian rhythm resulting in inability to go to sleep in the evening. This rhythm shift may be so pronounced that it results in complete reversal of day and night activities with the individual with dementia sleeping during the day and staying up during the night. The delay in circadian rhythm may also participate in increased behavioral disturbances in the afternoon and evening that are often called *sundowning* (Volicer *et al.*, 2001). In contrast, individuals with frontotemporal dementia have no change in circadian rhythm of body temperature but an advanced rhythm of motor activity (Harper *et al.*, 2001). Institutionalized individuals with dementia have extremely fragmented sleep, barely sleeping full hour and barely staying awake for a full hour throughout the day and night.

Management of insomnia should first utilize behavioral modifications. This includes avoiding caffeine, heavy meals, and excessive amount of alcohol before going to sleep, avoiding nocturia by decreased fluid intake in the evening, reviewing medications, and limiting day naps to 30 minutes. If behavioral modifications are not effective in reducing insomnia, use of hypnotic medications may be considered (Table 8). Antihistamines should not be used because they have strong anticholinergic effects that can aggravate memory problems and can also cause other adverse effects. Most common agents used in the management of insomnia are benzodiazepines. Only short-acting benzodiazepines should be used to avoid daytime sedation and increased risk for falls. The shortest acting agent, zaleplon, is especially useful in individuals who have difficulty falling asleep. Trazodone is a nontricyclic sedative antidepressant. Although there are few data to support the use of trazodone in nondepressed individuals (James and Mendelson, 2004), trazodone is useful in the treatment of insomnia

Table 8 Drugs for treatment of insomnia

Name (trade name)	Dose range (mg)	Elimination half-life (hours)
Trazodone	50–300	4–9
Triazolam (Halcion)	0.125–0.25	2–3
Zaleplon (Sonata)	5–10	1
Zolpidem	5–10	1.5–3.5

associated with administration of stimulating antidepressants (Kaynak *et al.*, 2004). Melatonin was not found to be an effective sleep agent in individuals with Alzheimer's disease.

APATHY AND AGITATION

Agitation is sometimes used as a term to label all behavioral symptoms of dementia. However, such a use of this term does not take into consideration the context in which a behavior happens and does not differentiate between behavioral symptoms induced by caregiving activity (resistiveness to care) and symptoms that occur without provocation or environmental triggers. Therefore, it is more useful to limit the term "agitation" to behaviors that communicate to others that the individual with dementia is experiencing an unpleasant state of excitement and that are observable without subjective interpretation, are not strictly behaviors that are invoked by caregiving activities, are unrelated to known physical needs of the patient that can be remedied, and are without known motivational intent (Hurley *et al.*, 1999).

Apathetic individuals appear passive, demonstrate inattention to the external environment (e.g. fixed staring or immobility), and are uninterested in what is happening around them. Apathy and depression are not synonymous and there is no significant correlation between them. Apathy and depression also result in a different pattern of brain blood flow changes.

Both agitation and apathy denote a lack of psychological well-being. The most common cause of agitation and apathy is functional impairment, resulting in inability to initiate meaningful activities. If these activities are not provided, the individuals with dementia experience boredom and become apathetic. Alternatively, the individuals attempt to stimulate themselves and that may result in repetitive behaviors or repetitive vocalization. Therefore, the most important intervention for both apathy and agitation is the availability of meaningful activities. Because lack of meaningful activities may induce both apathy and agitation, both of these symptoms are often present in the same individuals. Treatment of agitation with sedating medications results in an even more apathetic individual.

However, agitation may persist even in the presence of these activities and may actually interfere with participation in activities. In that case, the agitation may be a symptom of depression or a consequence of anxiety that may be induced by delusions or hallucinations. Therefore, careful analysis of the likely causes of agitation and a treatment of the underlying cause is necessary. Agitation may also be induced by changes of circadian rhythms. Delay in circadian rhythm is related to agitation in the afternoon and evening, which is called *sundowning* (Volicer *et al.*, 2001). Resetting of the circadian rhythm by bright light exposure may improve sundowning, although the effect is not very strong (Ancoli-Israel *et al.*, 2003).

ELOPEMENT AND INTERFERENCE WITH OTHERS

Unsupervised wandering away from a home or institution may have severe consequences for the individual with dementia. Elopement exposes the individual to a risk of injury if they walk into traffic, to hypothermia in cold climates, and hyperthermia with dehydration in warm climates. Wandering into rooms of other residents leads to conflict between residents, especially if the other resident is cognitively intact and resents the intrusion.

Wandering commonly describes the ambulating behavior of a person with dementia when that person walks away from one area or walks into an area "without permission". Wandering may be caused by spatial disorientation, or by delusions and hallucinations. An individual may be searching for something, attempting to fulfill unmet needs, escaping a threatening situation, reacting to reminders of departure near an exit, or carrying out a predementia lifestyle function. Wandering occurs in one-third of individuals with dementia living in a community and two-thirds of individuals with dementia living in an institution. It was reported that 26% of nursing home residents elope during the course of their institutionalization and 69% of individuals with dementia living at home experience at least one elopement episode. However, 81% of them do elope repeatedly (G. Flaherty, personal communication).

Some individuals with dementia walk back and forth as if following a rhythm or pattern. In that case, their activity is called *pacing*. Pacing often occurs with speed and a sense of urgency and may seem to represent hyperactivity or restlessness. Pacing may pose a problem for the individual with dementia if it occupies so much walking time that the individual becomes overtired. Pacing may also interfere with sitting down to eat and may result in weight loss. Pacing actually consumes considerable amount of energy and it was estimated that up to additional 1600 calories are required to maintain adequate nutrition in individuals who pace. Another adverse effect of pacing may be foot problems, such as blisters.

Both wandering and pacing should not be a problem if they occur in a safe environment and may actually provide beneficial physical exercise. Interference with other residents may be avoided by providing care for individuals with dementia in a dementia special care unit, where residents may not mind the intrusion because they themselves have spatial orientation difficulties. Thus, the most important intervention for these behaviors is environmental modification. These modifications should provide a safe walking path away from exits, and secure exits by disguising them or by a touch padlocking device. Wandering and pacing may also be a consequence of lack of meaningful activities. Engaging an individual in activity might distract them from seeking an exit from a home or institution. Because an individual with dementia living in a community may wander away from a caregiver in public places and because the individual may elope from a home despite safety measures, it is important to register the individual with both the Alzheimer's Association Safe Return Program and the Medic Alert Program.

KEY POINTS

- Interaction of dementia with personality results in three main consequences: functional impairment, mood disorders, and delusions/hallucinations.
- Continuous programing providing meaningful activities prevents many behavioral symptoms of dementia.
- Environmental influences affecting behavioral symptoms of dementia include caregiving strategies, social environment, physical environment, and medical interventions.
- Caregiving strategies are most important in preventing escalation of resistive behavior into a combative behavior that is sometimes labeled "aggression".
- Medical interventions should be congruent with goals of care and avoid unnecessary aggressive procedures that increase behavioral symptoms of dementia.

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Geriatric Psychiatry

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INTRODUCTION

Over the last two decades, geriatric psychiatry has emerged as an organized subspecialty within psychiatry. Multiple textbooks and subspecialty journals have emerged, such as International Psychogeriatrics, the American Journal of Geriatric Psychiatry and the International Journal of Geriatric Psychiatry. Also, an impressive body of evidence-based clinical knowledge specific to the behavioral health care of older adults is now increasingly available. Psychiatric disorders are profound in their impact upon the economic well-being and quality of life among older adults and their families. Interventions may avoid or delay onset, reduce the initial burden of symptoms and reduce functional impairment over time. Older adults with psychiatric disorders are often precluded from adequate mental health care due to inadequate funding of research, training, and service provision. Clinical and biological complexity is the rule rather than the exception in geriatric psychiatric syndromes. Moreover, behavioral abnormalities, cognitive deficits, and physical symptoms and signs are often manifested by more than one psychiatric, neurological, or medical condition. The quality of psychiatric services for older persons lags behind services for younger adults, despite a growing evidence-base supporting the effectiveness of a variety of interventions and services for late-life psychiatric disorders (Bartels, 2003a). The evidence-base is most developed for interventions addressing late-life depression and dementia, although effective treatments and service models have been identified for a variety of disorders (Bartels *et al.*, 2002).

EPIDEMIOLOGY

One in four older adults has a significant psychiatric disorder (Bartels, 2003a). Most of these individuals have anxiety disorders, followed by mood disorders, cognitive disorders, and alcohol abuse. Future growth of the population of older adults with mental illness in conjunction with the projected shortfall in providers with expertise in geriatrics and the inadequate financing for geriatric mental health services is predicted to create a future health-care crisis (Jeste *et al.*, 1999). Generalized anxiety disorder (GAD) is highly prevalent in older adults with rates of 7.3% reported in the older population. Prevalence rates of phobia range from 3.1 to 12%. Dementia affects around 7% of the general population older than 65 years and 30% of people older than 80 (O'Brien *et al.*, 2003). Twice as many people have cognitive impairment that falls short of diagnostic criteria for dementia (O'Brien *et al.*, 2003). Depression affects about one in 10 people over the age of 65 (Mellow *et al.*, 2003). Approximately 2% of the population older than 54 years have a chronic psychiatric disorder (such as schizophrenia, bipolar disorder, chronic depression) other than dementia (Jeste *et al.*, 1999). Older adults account for 13% of the population but almost a fifth of all suicides. Thirty-three out of every 100 000 older white men commit suicide compared to national rate of 11 for every 100 000. Four older adults attempt suicide for each who succeeds. This compares with 200 attempts per completed suicide among young adults. The prevalence of psychotic disorders in older adults ranges from 0.2 to 5.7% in community-based samples to 10% in a nursing home population. A more recent study found an even higher prevalence (10%) of psychotic symptoms in nondemented individuals aged 85 and older (Ostling and Skoog, 2002). 12 to 25% of healthy older adults report chronic insomnia, with higher rates among those with coexisting medical or psychiatric illness (Montgomery, 2002). 65 to 90% of residents in long-term care (LTC) have a significant psychiatric disorder (American Geriatrics Society and American Association for Geriatric Psychiatry, 2003). Moreover, the majority (89%) of older adults with severe and

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Table 1 CAGE questionnaire

C	"Have you ever felt you ought to CUT DOWN on your drinking?"
A	"Have people ANNOYED you by criticizing your drinking?"
G	"Have you ever felt bad or GUILTY about your drinking?"
E	"Have you ever had a drink first thing in the morning (EYE OPENER) to steady your nerves or get rid of a hangover?"

persistent psychiatric disorder who receive institution-based care are in nursing homes. The prevalence of psychiatric disorders in older adults is expected to double over the next 30 years, making them a priority for health-care and social-care services (Jeste *et al.*, 1999).

THE PSYCHIATRIC INTERVIEW OF AN OLDER ADULT

The foundation of the diagnostic workup of the older adult experiencing a psychiatric disorder is the diagnostic interview. Input from a reliable informant who is familiar with the patient is often crucial for accurate diagnosis. To supplement the clinical interview, use of structured interview schedules and rating scales such as the Confusion Assessment Method (CAM) for delirium (Inouye, 1990), the Mini-Mental State Examinaton (MMSE) (Folstein *et al.*, 1975) for dementia, the CAGE questions (Table 1) for alcohol abuse, the Beck Anxiety Inventory (BAI) (Beck *et al.*, 1988) for anxiety and the Geriatric Depression Scale (GDS) (Yesavage *et al.*, 1983) for depression may be helpful. Because age-related cognitive changes, mood changes, or behavioral changes may signal treatable medical conditions, it is important to take any complaint seriously. Risk factors which should trigger a cognitive and/or depression screen include age older than 65 years, illnesses that increase the possibility of diagnosis of cognitive or mood disorders, for example, diabetes, Parkinson's disease, cerebrovascular disease and so on, a past history of depression or a family history of dementia. A simple screening question asking about the patient's memory and mood state is often informative. Every person aged 65 and older is recommended to be screened for alcohol and prescription drug use/abuse as part of regular medical and psychiatric care and patients should be screened again yearly if certain physical or emotional symptoms emerge or if the person is undergoing major life changes or transitions.

DEPRESSION

Depression can be reliably and easily distinguished from normal aging but is often overlooked. It is extremely treatable if appropriate pharmacotherapy and/or psychotherapeutic interventions are prescribed and accepted by patients and their caregivers. The outcome of depressive disorder in older adults is as good as in other age groups. It is important to follow-up depressed older patients with cognitive impairment for later signs of dementia. Depression is recognized in only a fraction of older primary care patients, and an even smaller fraction of those identified receive appropriate antidepressant treatment (Alexopoulos, 2001). The major impediment to recognition and treatment of depression in older adults is the limited time of general practitioners. Many older adults with clinically significant depressive symptoms do not meet diagnostic criteria for major depressive disorder. However, the cumulative functional morbidity of these subsyndromal disorders actually exceeds that of major depression among the older adults (Lyness, 2004a). Also, evidence to date suggests that major depression may not be pathogenetically distinct from less-severe forms of depression (Lyness, 2004a). Within the emerging concept of vascular depression there is some evidence of a lower response rate to antidepressant monotherapy but the response rate to electroconvulsive therapy (ECT) may be as favorable as for other patients but with an increased risk of ECT-induced delirium (Baldwin *et al.*, 2002).

BEREAVEMENT

Bereavement is associated with declines in health, inappropriate health service use, and increased risk of death (Prigerson and Jacobs, 2001). Identifying and intervening on behalf of bereaved patients may help address these increased risks. Complicated bereavement may be distinct from major depression and formal criteria have been proposed (Prigerson and Jacobs, 2001). Complicated bereavement includes symptoms such as extreme levels of "traumatic distress", numbness, feeling that part of oneself has died, assuming symptoms of the deceased, disbelief, or bitterness, and symptoms endure for 6 months. Immediate attention from a mental health professional should be sought if suicidality is suspected at any time post-loss. For bereaved patients diagnosed with major depression and complicated bereavement, treatment should follow general guidelines including prescription of antidepressants. Brief dynamic psychotherapy, traumatic grief therapy, crisis intervention, and support groups can significantly reduce grief symptoms (Prigerson and Jacobs, 2001).

BIPOLAR AFFECTIVE DISORDER

Most older adults with bipolar disorder have the disorder from their young adulthood although onset as late as in the ninth and tenth decades has been reported (Umapathy *et al.*, 2000). Late-onset bipolar disorder (onset after age 50) is commonly associated with comorbidities such as hypertension, diabetes or coronary artery disease, and neurological disorders. It is less likely to be associated with a family history of mood disorders. Bipolar elderly patients in outpatient treatment were found to use four times the total amount of mental health services and are four times more likely to have had a psychiatric hospitalization over the previous 6 months

compared to older outpatients with unipolar depression (Bartels *et al.*, 2000). Older manic patients seldom display the euphoric or elated mood characteristic of younger adults, and are more likely to appear irritable, angry, paranoid, and disorganized. Older adults often have more frequent episodes of mania and depression, with a shorter (e.g. rapid cycling) duration of symptoms than younger patients. A significant proportion of older bipolar patients exhibit neuropsychological deficits when they are clinically euthymic. Lithium and divalproex have been most studied in older adults, and both may be efficacious in acute treatment of mania, but there are no controlled efficacy or effectiveness trials (Young *et al.*, 2004). Despite lack of systematic data, atypical antipsychotics may be useful in the treatment of older adults with bipolar disorder. There are no systematic studies of the treatment of bipolar depression in older adults and there are no systematic studies using psychosocial interventions to treat bipolar disorder in older adults. Nonetheless, psychopharmacologic treatment of older adults with bipolar depression and use of psychosocial interventions based on extrapolation of research from younger adults can improve functional outcomes in older adults with bipolar disorder. Adjunctive psychotherapy is recommended to help increase adherence to medication, enhance social and occupational functioning, and improve detection of an impending mood episode. Psychosocial interventions that focus on reducing stressful life events and maintaining a stable living environment are helpful for older adults with bipolar disorder. Electroconvulsive therapy (ECT) should be considered in all older adults with severe bipolar depression or mania, especially in those with a history of previous good response to ECT.

LATE-LIFE PSYCHOSES

There is an increased incidence of psychotic symptoms (delusions and hallucinations) in older adults in contrast to younger adults (Desai and Grossberg, 2003). Psychotic disorders in old age have more toxic (e.g. drugs), metabolic (e.g. laboratory abnormalities), and structural (e.g. brain lesions, tumors) associations and a greater association with dementia. New onset of psychotic symptoms in the background of cognitive impairment are most likely to be due to delirium or dementia. Schizophrenia makes up the majority of the diagnoses of older adults with severe and persistent psychotic disorder.

SCHIZOPHRENIA

Although schizophrenia is less prevalent than dementing disorders and depression, the total health expenditures for individuals aged 65 and above with schizophrenia exceed those for individuals aged 65 and above with depression, dementia, or all medical disorders (Bartels *et al.*, 2003b). Onset of illness typically begins in early adulthood, with a small but distinct subgroup of older adults developing the disease after the age of 55. Late-onset schizophrenia has a higher prevalence of the paranoid type, less-severe negative symptoms, overrepresentation of women and requires lower doses of antipsychotic medications as compared to early-onset schizophrenia. The course of schizophrenia in late life appears stable, but most elderly patients remain symptomatic and impaired. In spite of considerable ongoing disability, most older adults with schizophrenia continue to function in the community. Long-term studies have begun to erode the belief that most patients with schizophrenia have a downward course. At least 50 to 60% of early-onset schizophrenia patients over two to three decades significantly reclaimed their lives (Harding, 2003). Many older adults with schizophrenia have spent lengthy periods in hospitals and do not have community living skills. Sustained remission can occur even in older adults with chronic schizophrenia, but its prevalence is lower than that previously thought. Significant cognitive and functional deficits are also commonly seen in older adults with schizophrenia, particularly those whose lifetime course of illness has been chronic. Older adults with schizophrenia are more impaired in most domains of functioning and less impaired in memory than are patients with dementia. Cognitive decline is not uniform across older adults with schizophrenia, with some showing cognitive and functional decline even in brief follow-up periods. Risk factors for decline include less education, advanced age, and more severe positive symptoms of schizophrenia at the time of initial assessment. Poor outcome over the course of the entire life span may be a risk factor for further decline in later life.

Although older adults with schizophrenia may not have more physical problems than age-matched peers, the severity of their medical conditions may be greater (Schoos and Cohen, 2003). It should be remembered that older adults with schizophrenia are even more a group of survivors than are their same-age peers in the general population. Many of these patients have difficulty complying with care regimens for chronic medical conditions such as diabetes and hypertension and have poor dietary habits. Most of the older adults with schizophrenia have been active smokers for many years. Mortality rates among older adults with schizophrenia are higher than those of their same-age peers.

For most adults with schizophrenia, there is evidence of adaptation and compensation with aging. However, countervailing factors such as cognitive deficits, poor physical health, and movement disorders can worsen adaptive functioning. Cognitive impairment, negative symptoms, and social isolation, rather than psychosis, appear to predict the level of care needed. Atypical antipsychotics are the primary form of intervention and have tremendous advantages over older drugs in terms of side effects (Cohen *et al.*, 2000). Psychosocial treatments for older adults with schizophrenia such as cognitive-behavioral therapy, health management intervention, social skills training, and residential alternatives are also recommended. Assertive community treatment and case management greatly increase the success of pharmacological and psychosocial interventions.

COGNITIVE DISORDERS

These primarily include dementing disorders, delirium, cognitive impairment no dementia (CIND), mild cognitive impairment (MCI) and vascular cognitive impairment (VCI).

Dementing Disorders

The dementias are a growing problem in an aging world. Cognitive impairment and functional decline associated with dementia can be reliably differentiated clinically from normal effects of aging in most older adults. Primary care physicians are the first medical contact for most patients with early-stage dementia. Physicians often underdiagnose dementia, and, when dementia is detected, some physicians choose not to disclose the diagnosis to the patient. It is important to formally diagnose the type of dementia. A trial of a cholinesterase inhibitor or/and memantine is recommended for the treatment of Alzheimer's disease and vascular dementia (Cummings, 2003; Doody *et al.*, 2004). Cholinesterase inhibitors may also be useful for dementia with Lewy bodies and Parkinson's dementia. Empirical evidence supports the value of psychosocial interventions in addressing behavioral symptoms of dementia, but there is less agreement on the effectiveness of antipsychotics, anticonvulsant, and antidepressant agents (Bartels *et al.*, 2002). Better matching of the available nonpharmacologic interventions for behavioral symptoms of dementia to patient's needs and capabilities is necessary for consistently successful outcomes (Cohen-Mansfield, 2001). The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) protocol for Alzheimer's disease (AD), a trial developed in collaboration with the National Institute of Mental Health (NIMH), assessing the effectiveness of atypical antipsychotics for psychosis and agitation occurring in AD outpatients has just been completed and its results are expected to clarify the role of atypical antipsychotics in the treatment of psychosis and agitation in older adults with AD.

Delirium

The incidence and prevalence of delirium among hospitalized elderly, those in intensive care units and in emergency departments is high. Postoperative delirium is particularly common among older adults. Preexisting cognitive impairment is a major risk factor for postoperative delirium. Delirium is frequently superimposed on dementia. Although there are many potential causes for delirium, a "final common pathway" involving a concomitant decrease in cholinergic tone and increase in dopaminergic tone in relevant brain regions has been hypothesized (Trzepacz, 2000). Finding and treating the cause of delirium and reducing anticholinergic burden of drug regimens are key to successful functional outcome of older adults with delirium. Management of behavioral disturbances associated with delirium is primarily nonpharmacological using multicomponent interventions such as improved sleep hygiene, range-of-motion exercises, ambulation, reorientation, and cognitive stimulation (Inouye *et al.*, 2003). Low-dose antipsychotics such as parenteral haloperidol may be needed to control severe agitation.

Mild Cognitive Impairment (MCI) and Cognitive Impairment, No Dementia (CIND)

Many conditions cause cognitive impairment, which does not meet current criteria for dementia. Within this heterogenous group, termed *Cognitive Impairment, No Dementia* (CIND), there are disorders associated with an increased risk of progression to dementia (Davis and Rockwood, 2004). MCI describes older adults with subjective complaints of memory loss and objective psychometric measures of memory impairment compared with individuals of the same age. However, these individuals do not have pronounced impairments in daily function and generally do not have impairment of other cognitive functions such as language or abstract thinking. Amongst patients with MCI, especially its amnestic form, many will progress to AD. The occurrence of neuropsychiatric symptoms in MCI and the similarity of these symptoms to those of early AD suggest that these symptoms may assist in identifying patients in the earlier stages of AD and distinguishing them from patients with other disorders. In contrast to clinic-based studies, where progression is more uniform, population-based studies suggest that the MCI classification is unstable in that context. In addition to Amnestic MCI, other syndromes exist and can progress to dementia. For example, an identifiable group with vascular cognitive impairment without dementia shows a higher risk of progression to vascular dementia, AD, and mixed dementia. Also, in some cases, mild vascular cognitive impairment can be reversible if appropriately treated (Borroni *et al.*, 2004).

Vascular Cognitive Impairment (VCI)

Cerebrovascular disease is the second most common cause of acquired cognitive impairment and dementia and contributes to cognitive decline in the neurodegenerative dementias (O'Brien *et al.*, 2003). The current narrow definitions of vascular dementia needs to be broadened to recognize the important part cerebrovascular disease plays in several cognitive disorders, including the hereditary vascular dementias, multi-infarct dementia, poststroke dementia, subcortical ischemic vascular disease and dementia, MCI, and degenerative dementias (including Alzheimer's disease, frontotemporal dementia, and dementia with Lewy bodies). The term Vascular Cognitive Impairment (VCI), which is characterized by a specific cognitive profile involving preserved memory with impairments in attentional and executive functioning has been proposed. Important noncognitive features of VCI include depression, apathy, and psychosis. Diagnostic criteria have been proposed for some subtypes of VCI, and

there is a pressing need to validate and further refine these. Evidence from the available studies support the benefit of cholinesterase inhibitors for the treatment of VCI.

SUBSTANCE ABUSE

Substance use and abuse in older adults is a growing public health issue. Primary care physicians and emergency care providers can play a crucial role in early identification and initial management of addiction problems in older persons. Alcohol use/abuse is the most common form of substance abuse in older adults. Heavy drinking is a well-established factor in causing disability and excessive mortality. However, among elders with chronic medical and emotional health disorders, even modest alcohol consumption can lead to excessive disability and poorer perceived health. Alcohol abuse in older adults is a hidden epidemic because its symptoms often mimic or are masked by common physical and mental infirmities of aging and because health-care providers rarely ask about when and how much their older patients drink or what effect alcohol may have on their lives. In addition, older adults and their relatives are often in denial about the extent and effects of their drinking habits and because the amount of alcohol now causing trouble had no untoward social or physical effects in middle age. Use of screening tools such as the CAGE questionnaire and Short Michigan Alcoholism Screening Test-Geriatric Version (SMAST-G) (Blow *et al.*, 1998) are recommended to minimize this oversight. Older adults with alcohol abuse also face greater risk for suicide (Blow and Oslin, 2003). Alcohol abuse is seen in older men as well as women. Older adults with alcohol abuse are more likely to present with physical symptoms and to be admitted to medical or surgical wards than younger patients with alcohol abuse. A nonjudgmental and tactful approach is recommended in asking about and attempting to treat alcohol abuse, especially in aging women.

There is insufficient evidence to endorse pharmacological interventions for geriatric alcohol abuse (Bartels *et al.*, 2002). In contrast, psychosocial interventions are likely to be effective for older persons with alcohol use disorders. Brief interventions (5 minutes for five brief sessions) targeting a specific health behavior (at-risk drinking) by primary care providers are quite effective. As the post–World War II baby-boom generation ages, providers may begin to see a greater number of elderly patients who use illicit drugs than has been seen in previous cohorts. The abuse of narcotics is rare among older adults, except if they have a history of abuse at a younger age, or in the presence of alcoholism. Older heroin abusers are usually life-long addicts who have survived. With the current epidemic of acquired immunodeficiency syndrome (AIDS) and hepatitis C among illicit drug users, all older adults with illicit drug use (current or past) should be screened for these conditions. The need for treatment may diminish as in some individuals, addiction wanes with age.

Misuse and inappropriate use of prescription medications (especially benzodiazepines but also opiates) is a substantial issue in this population. Presence of a psychiatric disorder is a risk factor for prescription drug dependence in older adults. Benzodiazepine use increases with age, and older adults tend to be on higher doses. Depression in older individuals often presents with features of anxiety and may be inappropriately treated with benzodiazepines rather than an antidepressant or *referred* for psychotherapy. Signs of prescription drug abuse in older people include loss of motivation, memory loss, family or marital discord, new difficulty with activities of daily living, trouble with sleeping, drug seeking behavior, and doctor shopping. The long-term treatment of older adults who have misused or abused prescription drugs should be individualized. Most misuse can be treated outside of specialized substance abuse treatment programs through education of patients, families, and providers. Self-help groups (e.g. narcotic anonymous) is unlikely to benefit an older adult with prescription opioid abuse. Groups specific for older adults should be sought. Primary care provider involvement is essential, both for counseling and for coordination of a treatment plan. In older adults, safe withdrawal may take weeks to months as compared with days to weeks in younger adults. Implementation of nonpharmacologic methods for treating chronic pain or insomnia can play an essential role in long-term treatment. Specific advice about the dangers of combining alcohol with prescription and over-the-counter (OTC) medications, especially psychoactive agents, should be given and regularly reinforced (Blow and Oslin, 2003). Effective screening and intervention can prevent and reverse morbidity.

ANXIETY DISORDERS

Although anxiety disorders are the most prevalent disorders among older adults, we know far less about the clinical characteristics, course, treatment, and prognosis of these disorders (Mellow *et al.*, 2003). Substantial comorbidity of medical and anxiety disorders with the possibility that physiologic symptoms of anxiety can be a manifestation of a medical condition or adverse effects of a drug further confound and complicate proper detection of anxiety disorders in older adults. Despite these challenges, parsing anxiety symptoms from medical conditions can be accomplished by a thorough clinical assessment, the use of self-report inventories, and laboratory findings.

GAD is one of the most common psychiatric syndrome in older adults. Half of older adults with GAD have had symptoms for most of their lives, whereas the remaining half report developing GAD within the last 5 years. Anxiety symptoms are also common features of late-life depression and dementia. Preliminary evidence indicates that many older patients with onset of panic attacks in early life continue experiencing symptoms in later life, with few receiving adequate treatment over the years. Less common are new onset cases of panic disorder in old age. Phobic disorders are highly prevalent, chronic, and persist into old age.

posttraumatic stress disorder (PTSD) symptoms may recur later in life and recent losses or dementia may trigger a recurrence of symptoms.

Anxiety commonly is associated with medical illness (such as chronic obstructive pulmonary disease, coronary artery disease, Parkinson's disease) in older adults. Anxiety disorders occasionally may be due to an underlying medical condition (such as hyperthyroidism or pheochromocytoma), drug-induced (such as due to theophylline, OTC sympathetomimetics, steroids, thyroid preparations) or drug-withdrawal states (such as caffeine withdrawal, alcohol withdrawal, sedative hypnotic withdrawal).

Treatment of anxiety in elderly persons has typically involved the use of benzodiazepines, which are often effective but problematic because they are associated with increased risk of cognitive impairment, falls, and fractures (Desai, 2003). Pharmacological alternatives such as antidepressants (especially selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors) and buspirone are recommended for the treatment of anxiety disorders in older persons. Because it may take 2 to 4 weeks for the onset of therapeutic action with these compounds, use of an adjunctive short acting benzodiazepine for the first few weeks may be considered in severe cases. Cognitive-behavioral therapy may also be useful for treatment of anxiety disorders in older adults. Collaborative care models that address physician, patient, and health-care service delivery barriers also hold promise for adequately treating anxiety disorders experienced by older adults.

GERIATRIC PSYCHIATRY EMERGENCIES

1. **Suicide:**

Suicide rates are highest in older adults; the majority of older adults who die by suicide have seen a primary care physician in preceding months (Maris, 2002). Older white men are the most at risk. In contrast, older black women have the lowest rate of suicide. Although reasons for this difference are not clear, strong ties to social and religious support networks may be the key protection for older black women. Depression is the strongest risk factor for late-life suicide and for suicide's precursor, suicidal ideation. Chronic medical illness, psychiatric disorders, physical disability, unrelenting pain/discomfort, alcohol abuse, psychosocial stressors, and poor social support are some of the other major risk factors for late-life suicide. Older adults are more likely to be socially isolated and have more physical illnesses than younger adults. They are also more likely to use highly lethal methods of suicide, such as firearms. Health-care providers are less apt to determine that suicidal thinking in an older adult is a serious condition that might respond to treatment. With novel interventions in community-based primary care, suicidal ideation can be reduced regardless of depression severity (Bruce *et al.*, 2004). Such interventions include utilizing depression case managers, education of primary care providers on assessment and management of suicide and incorporation of such education into clinical practice. Psychiatrists must take prominent, central roles in this training and work more integrally with primary care physicians.

2. **Elder abuse:**

Elderly men and women of all socioeconomic and ethnic backgrounds are vulnerable to abuse and neglect, and most often it goes undetected. Physical abuse is most recognizable, yet neglect is most common. Psychological and financial abuse may be more easily missed. Awareness of the risk factors (cognitive impairment, depression, frailty, caregiver stress, institutionalization) and clinical manifestations (bruises, fractures, malnutrition) allows primary care physicians to provide early detection and intervention for elder neglect and abuse (Levine, 2003). Interdisciplinary collaboration between physicians, social workers, and mental health professional is crucial. Health-care providers should have a high index of suspicion for abuse and neglect in older adults at risk. Physical and verbal abuse by older adults with dementia toward their family members and other caregivers (many of whom are elderly themselves) is a growing problem and needs to be inquired into and addressed during the visit to primary health-care provider.

DRUG-INDUCED PSYCHIATRIC DISORDERS

Psychotropic side effects of commonly prescribed medications in the elderly are prevalent and, in most instances, predictable and preventable (Desai, 2004). They are also associated with considerable morbidity and mortality. Delirium, mood changes, and psychotic symptoms are the most serious categories of psychotropic side effects. Anticholinergics, antihistaminics, psychotropics, and many OTC drugs are the usual suspects. Long-acting benzodiazepines are the most common cause of drug-induced cognitive impairment in older adults. Herbal medicine use is prevalent in the older adult population and is associated with high risk of serious herb–drug interactions (Desai and Grossberg, 2003). Psychotropics are one of the most common class of drugs prescribed inappropriately in older adults (Curtis *et al.*, 2004). Avoiding potentially inappropriate medications and performing a routine evaluation of the drug regimen in question (including OTC drugs, herbal, and nonherbal supplements) are some of the key interventions for preventing psychotropic side effects of commonly prescribed medications (Fick *et al.*, 2003).

INSOMNIA

Insomnia is highly prevalent in older adults (Ancoli-Israel, 2000). However, few mention their sleep problems to their primary care providers and most self-medicate with OTC

medications. Many OTC sleep-aides (such as diphenhydramine) have considerable risk of cognitive and behavioral toxicity (Desai, 2004). Those who receive treatment typically receive benzodiazepines, which have known side effects including tolerance, addiction, daytime sedation, cognitive impairment, associated falls, hip fractures, and motor vehicle accidents – especially from preparations with a long half-life – and impaired sleep due to long-term use. Initial assessment of insomnia involves evaluating the cause. Causes of insomnia in older adults include: medical, psychiatric, and drug issues; circadian rhythm changes; sleep disorders; and psychosocial factors. Sleep apnea occurs in 4% of middle-aged men and 2% of middle-aged women. In males over 65, the figure rises to 28%; for women, the number climbs to 24%. Nonpharmacological interventions such as cognitive-behavioral interventions for psychophysiological insomnia, bright light treatments for problems related to timing of sleep, and physiological interventions such as exercise for insomnia may be considered. Pharmacotherapy should be limited to short-term use of agents least likely to cause daytime sedation such as zolpidem, zaleplon, trazodone, and perhaps valerian. A systematic review of the efficacy of acupuncture and acupressure is currently underway.

PERSONALITY DISORDERS

Late-life personality disorders (PDs) have not been well studied. The most commonly identified PDs in late life include obsessive-compulsive, dependent, and mixed. Research indicates gradual improvement of several PDs in middle age, most notably borderline and antisocial PDs. Studies of behavioral traits in late life have consistently found decreased levels of activity, extroversion, impulsivity, aggression, and increased levels of introversion and suspiciousness. All PDs in late life are particularly vulnerable to the reemergence or exacerbation of maladaptive traits, or to the development of secondary psychopathology as a result of acute stress or the accumulation of age-related losses and other stressful experiences. Longitudinal research relative to PD's has not looked beyond middle age. Owing to limited information and lack of awareness, many health-care providers often end up deferring the diagnosis of a PD. But there is a cost to this: patients may consequently be labeled as treatment-resistant when short-term psychotherapy or pharmacotherapy fails to alleviate distressing or disruptive behaviors, which actually reflect long-standing personality characteristics. Treatments of PDs in late life utilize the same basic approaches as with younger patients, but clinicians must incorporate a much broader understanding of the impact of age-related stressors and comorbid conditions. The overall goal of treatment is not to cure the disorder, but to decrease the frequency and intensity of disruptive behaviors. It may be necessary to convey a basic formulation of the patient's behaviors to caregivers and affiliated health-care professionals, such as primary care providers, social workers, and visiting nurses (Agronin and Maletta, 2000).

SEXUAL DISORDERS

Sexual function is a very important life issue for older adults but is often overlooked. Psychosocial factors such as societal attitude and lack of available partners (especially for older women) can negatively impact sexual functioning. Medical conditions such as diabetes, hypothyroidism, neuropathy, cardiovascular disease, adverse drug effects and psychiatric conditions such as depression, dementia, and chronic alcoholism often negatively impact sexual functioning. Many of these conditions are treatable. The critical first step to address sexual disorders for health-care providers is to start talking about sex with their older patients.

SPECIAL POPULATIONS IN GERIATRIC PSYCHIATRY

1. **LTC residents:**

Psychiatric disorders account for at least one-half of the morbidity in LTC and are the prime reason for admission to LTC facilities. The LTC setting is unique relative to patient characteristics and systems issues. Depression and behavioral and other psychiatric symptoms associated with dementia are the most common psychiatric problems in nursing homes. Nursing directors report substantial limitations in the competence of staff at all levels in managing behaviorally disturbed patients and a broad-based need for improvement in skills. Nursing assistants report low confidence in their ability to prevent agitation or aggression in LTC residents and report an even lower confidence in their ability to decrease resident's agitation and aggression once they become agitated or aggressive (Gates *et al.*, 2004). Education and training of mental health professionals working in nursing homes and of nursing home staff in the recognition, assessment, treatment, and monitoring of behavioral symptoms in nursing home residents is thus essential.

Depression screening instruments should be used for the identification and assessment of depressed residents and evaluation of treatment effectiveness. Verbal, nonverbal, and physical behavioral symptoms should be described and quantified as current tools are not adequate in identifying all residents with behavioral symptoms. Violence by residents against other residents and health-care providers is highly prevalent and one of the most serious issues in LTC. There is an immediate need for violence prevention education and for developing violence prevention programs in nursing homes. Major depression in LTC residents can be effectively treated with nonpharmacological or pharmacological interventions and minor depression can be effectively treated with nonpharmacological intervention although data regarding pharmacological intervention for minor depression in LTC residents is limited. Atypical antipsychotics are the first line pharmacological intervention for severe behavioral disturbances with psychotic features in LTC residents and

may even be effective for severe agitation without psychotic symptoms. Neither pharmacological nor nonpharmacological interventions totally eliminate behavioral symptoms, but both types of interventions decrease the severity of symptoms (Snowden *et al.*, 2003).

2. **Older inmates:**

As the prison population grows, so does the number of older inmates. 8.6% of all inmates are aged 50 years or older. The age 50 cutoff is important in understanding prison health care. A 50-year-old inmate may have a physiological age that is 10 to 15 years older, because inmates generally age faster because of such factors as abuse of illicit drugs and alcohol and limited lifetime access to preventive care and health services. Up to 20% of inmates older than 55 have a significant mental illness (Mitka, 2004). Ethnic minorities are overrepresented in prison population. About one-third of the prison population tests positive for hepatitis C. Almost all inmates are released back to their family and community. Treatment inside the institution needs to address this transition. Involving clinical faculty and staff from academic medical centers to provide health care (including mental health care) to the aging prison population can produce significant improvements in access to care and health outcomes (Raimer and Stobo, 2004).

3. **Caregivers:**

Families are now the major caregivers and lifetime support systems to the majority of older adults with dementia or chronic mental disorders. The majority of the caregivers are wives or daughters. Caregiving can take a toll on the mental health of caregivers and has been associated with an increased risk of depression, poor health, and substance abuse in the caregivers. Living with older adults suffering from dementia or chronic mental illness is about learning to "bend without breaking" (Gwyther, 1998). These disorders affect multiple generations within the family and each family responds in its own unique ways. Transition to institutional care is particularly difficult for spouses, almost half of whom visit the patient daily and continue to provide help with physical care during their visits. Symptoms of depression and anxiety do not diminish after institutional placement, use of anxiolytic medications increase, and nearly half the caregivers are at risk for clinical depression following placement of their loved one in long-term facilities (Schulz *et al.*, 2004). Clinical interventions that prepare the caregiver for a placement transition and treat their depression and anxiety following placement are recommended.

Living with older adults with chronic psychiatric disorders implies a permanent imbalance in the normal give-and-take of family relationships. Health-care providers must help families work toward effectively coping with the disease, decreasing the harmful effects on the family, and keeping family conflicts to a minimum (Gwyther, 1998). Interventions such as counseling, support groups, psychoeducational groups, training in contingency planning, respite services, skills training, and family-directed treatments can alleviate caregiver stress, prevent caregiver depression, and improve coping skills.

4. **Ethnic/minority elderly:**

Psychiatric disorders in ethnic/minority elders are underrecognized and undertreated (Charney *et al.*, 2003). Older African-American patients with bipolar disorder are more likely to receive diagnoses of schizophrenia (Kilbourne *et al.*, 2004). Differential response to psychotropic medications by ethnicity (besides age and gender) is an important factor when choosing a potential pharmacotherapy regimen for an older minority adult. Inclusion criteria for clinical dementia trials have been shown to preferentially select subjects who are not ethnic minorities (Schneider *et al.*, 1997). Also, values of many older adults with psychiatric illness are often not reflected in research objectives and methods. There has been a proclivity for western research to reflect assumptions of individualism and personal advancement rather than mutuality and social equity. Health-care providers extrapolating current evidence-based practice recommendations for late-life mental disorders need to be aware of this bias when they treat patients from a different cultural background and must make appropriate intuitive adjustments in treatment recommendations. Clinical practice and research need to tailor their approach to reflect sensitivity to cultural, race, and ethnic issues in older adults with psychiatric disorders.

5. **Oldest old:**

One of the most critical areas of neglect in geriatric psychiatry to date is the neglect of the oldest old. This term refers to the 85 plus age group, which is the fastest growing age group in our society. This group remains difficult to study and is poorly understood by psychiatrists. Though function varies widely among the oldest old, once people reach this age they frequently experience serious medical and/or psychiatric illness along with physical and social impairments, which coalesce and cascade, often resulting in the condition described by geriatricians as frailty. After the age of 85, nearly half of all elders living in the community are frail despite their apparent functional well-being. Geriatric psychiatry might take a lesson from geriatric medicine and recognize that syndromes such as frailty may be critical to formulating appropriate care for all older adults and especially for the oldest old, the most vulnerable of the older adult population.

END-OF-LIFE CARE

80% of deaths in developed countries now occur among persons age 65 and older (Lyness, 2004b). Majority of death in older adults occur in the context of chronic illnesses and are too often accompanied by potentially remediable emotional or physical suffering. Conversations with patients and family about end-of-life care; the evaluation and treatment of suffering, including pain, depression, suicidality,

anxiety, and delirium; providing individual and family therapy to address conflicts; capacity determination; advance care planning; withholding life-sustaining treatments; palliative/hospice care and management of terminal agitation are some of the key areas where geriatric psychiatrists and other health professionals can contribute to a dignified and peaceful final phase of life of older adults.

GERIATRIC PSYCHOPHARMACOLOGY

Older adults are substantial users of psychopharmacologic agents (Desai, 2003). 12 to 15% of older adults living in the community and up to 75% of LTC residents receive psychotropic medications. The decision to prescribe a psychopharmacologic agent in older adults is a serious and complex issue. Randomized controlled studies for many psychopharmacologic agents in the elderly are lacking, especially among the oldest old (patients aged 85 and older), frail medically ill elderly, and ethnic/minority groups. Despite these limitations, appropriate and judicious use of psychopharmacologic agents in the elderly has the potential for dramatically improving the quality of life and functional status of many elderly patients with psychiatric disorders. Although risperidone and olanzapine use has recently been associated with increased risk of adverse cerebrovascular events in older adults with dementia, new data indicate that risperidone and olanzapine are not associated with a statistically significant increased risk of adverse cerebrovascular events compared with typical antipsychotic use in older adults with dementia and that mortality in older adults receiving haloperidol may be higher than those receiving risperidone and olanzapine (Herrmann *et al.*, 2004; Nasrallah *et al.*, 2004). A recent unexpected finding that venlafaxine was less well tolerated than sertraline in frail older adult nursing home population raises concerns about whether other medications that appear safe in mixed-age adults and healthier older adults in the community may be poorly tolerated in the frail older adults (Oslin *et al.*, 2003). Although there may be substantial public health benefits from systematic testing of drugs that are to be used in these populations, the US Food and Drug Administration (FDA) regulations and regulations by its equivalent in other developed countries do not provide requirements or incentives for such research. An alternative may be to develop specific approaches to surveillance for the safety and tolerability of medications in the nursing home population.

ELECTROCONVULSIVE THERAPY

ECT is a safe, useful, and effective treatment for late-life depression and other psychiatric and medical conditions and can be administered safely in elderly patients (Kamat *et al.*, 2003). ECT may be used with older adults regardless of age. The efficacy of ECT does not diminish with advancing age and may be enhanced. Because of comorbid medical conditions, poor tolerance of psychotropic medications, and psychotic features or marked disability associated with depression, ECT is often the treatment of choice in older adults with severe depression. As a result, older adults constitute more than one-half of patients who receive ECT for the treatment of depression (Kamat *et al.*, 2003).

PREVENTION IN GERIATRIC PSYCHIATRY

There needs to be increased focus on preventive services. Crucial targets for prevention in older persons include excess disability associated with mental illness, premature institutionalization, suicide, depression, alcohol or medication misuse, and cognitive decline (Bartels, 2003a). Table 2 highlights some of the evidence-based prevention interventions. Educating the public, the media, and health-care providers about the risk factors for various targets mentioned above, and effective evidence-based interventions and other potential interventions to modify the risk factors are recommended. A prescription for successful aging and maintaining cognitive vitality includes healthy dietary choices, maintaining physical activity, leading a socially active life, and pursuing cognitive challenges.

BEST PRACTICE MODELS FOR GERIATRIC PSYCHIATRY SERVICES

Service needs of older adults with psychiatric disorders are complex. Older adults with psychiatric disorders commonly face, in addition to persistent symptoms, increasing medical morbidity, dwindling financial resources, and social impoverishment. In addition, older adults are victims of a culture that has stigmatized both mental illness and advanced age.

Table 2 Examples of evidence-based prevention in geriatric psychiatry

Interventions	Potential outcomes
Nonpharmacologic multicomponent interventions (Inouye *et al.*, 2003)	Prevent delirium
Telemedicine (Lyketsos *et al.*, 2001)	Prevent psychiatric admissions from a long-term care facility
Family intervention (Mittelman *et al.*, 1996)	Delay institutionalization of patients with dementia.
Exercise plus behavioral management (Teri *et al.*, 2003)	Reduced disability in patients with dementia
Caregiver counseling and support (Mittelman *et al.*, 2004)	Prevention of caregiver depression
Depression care managers in primary care (Bruce *et al.*, 2004)	Prevent suicide
Comprehensive nutritional treatment (Keller *et al.*, 2003)	Prevent weight loss in patients with dementia
Exercise (Christmas and Andersen, 2000)	Prevent depression

Older adults may be more susceptible to the stigmatization of psychiatric disorders compared to younger adults and therefore less likely to seek help. Older adults are less likely than younger persons to self-identify mental health problems or seek specialty mental health services (Mickus *et al.*, 2000). This problem is further compounded by family members and professional providers who share the misperception that mental disorders are a "normal" part of aging (Gallo *et al.*, 1999). Without addressing stigma, systemic reforms designed to improve access are unlikely to be successful.

Current financing and systems of care are oriented toward providing mental health services in hospitals, nursing homes, or specialty mental health outpatient clinics, despite the preferences of older adults for services in community and home-based settings. Most older adults who receive mental health services are treated in primary health-care settings. Approximately one-third of older primary care patients have significant mental health problems. The usual mental health care provided by primary health-care providers is inadequate. Older adults often do not follow through when *referred* to mental health specialists. Care management models that integrate mental health providers into the primary care setting to provide same-day mental health services show promise in enhancing access and quality of care.

The use of community-based, multidisciplinary, geriatric mental health treatment teams is one of the ideal models of psychiatric service delivery in the community (Bartels *et al.*, 2002). Academic detailing, which consists of brief one-to-one educational sessions coupled with provider-specific feedback on treatment practices, is effective in influencing the practice behavior of primary care physicians and can be used to improve the management of psychiatric disorders in primary care. Hospital-based geriatric psychiatry consultation–liason services are also recommended to meet the complex mental health needs of hospitalized older persons. Geriatric psychiatry subspecialty care for older adults needing treatment in an inpatient psychiatric unit appears to be associated with distinct clinically relevant assessment and treatment advantages (such as complete medical workups, structured cognitive assessment, aging sensitive aftercare referral, and monitoring of psychopharmacological side effects and blood levels) over general psychiatry care (Yazgan *et al.*, 2004). Rates of mental illness are also high among home health-care population and LTC residents but most have inadequate access to comprehensive geriatric psychiatry services. Best practice models for mental health care in LTC facilities include routine presence of qualified mental health clinicians in the nursing home, interdisciplinary and multidimensional approaches using innovative techniques in training and education, and consultation and feedback on clinical practices.

Older adults with severe and persistent psychiatric disorders commonly face, in addition to persistent symptoms, increasing medical morbidity, limited financial resources, and social impoverishment. Although older adults represent a small percentage of the homeless population, their numbers are growing (Stergiopoulos and Herrmann, 2003). The available literature suggests a high prevalence of psychiatric disorders and cognitive impairment in this population. Model services to meet the growing needs of all older adults with psychiatric disorders will require a multidisciplinary approach to treatment, encompassing both the traditional modes of psychiatric treatment and treatments that focus on medical, cognitive, and social arenas.

SUCCESSFUL AGING

In 1990, there were 4 million people aged 85 and older (the oldest old) in the United States. There will be 10 times that many in 2040. Over the last century, the number of years an individual spends in active retirement has increased 10-fold. Thus, psychiatry in the twenty-first century must pay attention not only to the ills of the oldest old but also to the determinants of successful biopsychosocial aging (Vaillant and Mukamal, 2001). While usually underemphasized, positive personality changes, such as tolerance, regulation of affect, and ability to appreciate different points of view, occur with aging and can contribute to successful adjustment and high quality of life. Older adults as a whole do not have more psychiatric disorders than younger adults, they do not see themselves as sick even when they take three to eight different medications, their fear of death declines, and their spirituality and serenity increase. Improving education to the extent allowed by each socioeconomic stratum may have a positive impact on quality of life and longevity.

There are many predictors of successful aging (such as absence of alcohol abuse and of cigarette smoking before the age of 50) that are under the individual's own control. Stable marriage and adaptive defenses are also predictive of successful aging, subjective satisfaction, and objective mental health. Among factors outside the individual's control, only depression before the age of 50 years was a significant predictor of mortality, medical morbidity, and sadness during late life (Alexopoulos, 2001). A recent study found that those Mexican Americans with high positive affect were less likely to develop disability in activities of daily living, to develop a slow walking speed, and to die during the 2-year follow-up compared with those with low positive affect (Ostir *et al.*, 2000). Older adults with strong feelings of personal control and self-efficacy (that is, the personal conviction that one can successfully execute behaviors required in novel or stressful situations) are more likely to cope successfully with late-life challenges and, consequently, more likely to maintain a high level of emotional well-being. High levels of personal control and self-efficacy have also been shown to be independent predictors of longevity and high physical functioning (Penninx, 2000). The presence of a spiritual belief system has also been correlated with decreased depression, faster recovery from illness and increased longevity in later life (Penninx, 2000). The poem by an Indian poet Rabindranath Tagore reflects the attitude many older adults who age successfully

have toward life, death, and disease. It is time geriatric psychiatry pays as much attention to health promotion as to disease.

On the Fear of Death

Let me not pray to be sheltered from dangers but to be fearless in facing them.
Let me not beg for the stilling of my pain but for the heart to conquer it.
Let me not look for allies in life's battlefield but to my own strength.
Let me not crave in anxious fear to be saved but hope for the patience to win my freedom.
Grant me that I may not be a coward, feeling your mercy in my success alone; but let me find the grasp of your hand in my failure.

Rabindranath Tagore (in Fruit Gathering)

CONCLUSION

Psychiatric disorders are prevalent in later life and are expected to increase dramatically over the next three decades. These disorders are eminently treatable provided evidence-based interventions are used. Without adequate and effective treatment, psychiatric disorders in older persons are associated with significant disability and increased mortality. Mental health consumers deserve services that extend beyond symptom-reduction to support the development of skills to achieve personal goals and to improve self-efficacy and self-reliance. Health-care professionals involved in caring for older adults need to get involved with public policy, create new public expectations and perceptions, create a context of professionalism, set personal standards of excellence and radiate passion in order to change the current pessimistic world view of mental and physical health care for older adults.

KEY POINTS

- Late-life psychiatric disorders are a global health problem.
- Late-life psychiatric disorders are eminently treatable with evidence-based interventions.
- Initial identification and treatment of these disorders is inextricably linked to primary care.
- Evidence-base is most developed for interventions addressing late-life depression and dementia, although effective treatments and service models have been identified for a variety of psychiatric disorders in older adults.
- Overcoming barriers such as stigma, lack of geriatric expertise, financial constraints, fragmented care, and lack of integration of primary care and mental health services is crucial to preventing the upcoming crisis in geriatric psychiatry services.

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Organization of Services in Geriatric Psychiatry

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INTRODUCTION

Old age psychiatry is a relatively young speciality of psychiatry: the first pioneers of "psychogeriatrics" began to develop specialist services for older people in the United Kingdom in the 1960s and 70s. Early service principles included:

- a comprehensive age-related catchment area service;
- assessment at home before admission by a senior member of the team;
- diagnosis followed by active treatment;
- team working;
- close liaison with GPs, geriatricians, and social services.

The introduction of mixed sex wards was a radically progressive move at the time, and home visits were perhaps the first steps toward assertive outreach. In 1989, old age psychiatry was recognized as a speciality by the Department of Health, and by the millennium the Royal College of Psychiatrists recognized over 350 specialists in the psychiatry of old age. A recent report on progress in older people's health over the past 3 years gives the current number of old age psychiatrists, as of June 2004, as 444 (Department of Health, 2004).

It is useful to revisit the reasons why old age psychiatry first developed. Within an all-age adult psychiatry service, older adults did not receive the dedicated care and attention that a specialist service provides, as they were in competition with younger adults who present high profile risks and are valued more by society, perhaps because they are regarded as potentially economically active. This ignores the enormous contribution that older adults make to society: most voluntary organizations would disappear without the input they provide, many continue to work long after retirement age, many take up or continue roles as carers (to younger people, people with learning disability, to other elders), and others continue to make their wisdom and talents available to the rest of society. In addition to these ageist and attitudinal obstacles, mental illness in late life is complicated by cumulating physical illnesses, the physical and psychological changes associated with aging, and increasingly by the coexistence of cognitive impairment, all of which demand special skills of the mental health professionals who aim to provide appropriate assessment, diagnosis, treatment, rehabilitation, support and care for this group, and a service orientated to the practical needs of many elders.

The National Service Framework for Older People (NSF-OP) in Standard 7 set out a service model for a comprehensive mental health service for older people (Department of Health, 2001a). Components of the model service should include

- mental health promotion;
- early detection and diagnosis;
- assessment and treatment;
- support for carers;
- specialist mental health services, which will include acute admission and rehabilitation beds, day hospitals and memory clinics, domiciliary and outreach care, and outpatient/community clinics.

The NSF-OP was warmly received by many old age psychiatrists as it embeds mental health as integral to the health of older people and its core principles ("rooting out age discrimination" and "person-centered care") are potentially powerful influences for positive change in older people's mental health.

The National Service Framework for Mental Health (NSF-MH) had been less well received (Department of Health, 1999) as it excluded older adults and focused on services to working aged adults. Monies and developments associated with the NSF-MH therefore excluded older adult

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services and have led to expansion of working aged adult mental health services at the expense of services to older adults. The NSF-OP states that older people with severe mental illness will require the packages of care set out in the NSF-MH. The same standards must apply irrespective of age, and care should be provided within the framework of the Care Programme Approach (CPA) (Department of Health, 2002). This requirement seems to have gone largely unnoticed until recently.

The exclusion of older people from the NSF-MH could be regarded as ageist, but it is equally ageist to deny that this group has special needs to which services should be sensitive, and in dealing with which the service organization and response must be competent. What is right for adults of working age will not always be right for older people. Older people need a special service. This should not be one confined to problems of dementia, but should encompass the whole range of mental disorders of late life. Thus, the issue of age discrimination in mental health is a challenge for services, which must be tailored to need and not to rigid age cutoffs. This is an important principle in service planning and delivery.

MENTAL HEALTH PROMOTION FOR OLDER PEOPLE

Mental health promotion is defined as "any action to enhance the mental well-being of individuals, families, organizations and communities, and a set of principles which recognize that how people feel . . .(has) a significant influence on health" (Friedli, 2000). This is a daunting challenge, yet aspects of mental health promotion are already incorporated into good service planning and operation. Extending from this base provides the potential for improved services, and for improving the quality of life for people using those services by treatment of symptoms and reducing the likelihood of relapse.

Mentality's briefing paper on evidence-based mental health promotion (Mentality, 2003a) sets out a range of possibilities: opportunities for social and physical activities, access to information and practical help, volunteering, discussion and self-help groups are all linked with an evidence base showing a positive effect on mental well-being. The links between physical and mental health are also highly relevant to older adults (Mentality, 2003b).

Mental health professionals often encourage people to modify their lifestyle following an episode of mental ill-health, in order to improve their resilience. The challenge is to incorporate routine use of mental health promotion techniques into the design of clinical services.

EARLY DETECTION AND DIAGNOSIS: INTERFACE WITH PRIMARY CARE

The vast majority of people with mental health problems in late life will never be seen by a specialist service. Many will remain unrecognized even when they have contact with primary and social care services. Family doctors are, however, well placed to identify cognitive problems and mood disorders early, to provide people with information and to introduce them, where necessary, to further investigations, treatment, and support. Those working in primary care see many elders with physical problems regularly, and this gives the opportunity to assess and monitor the person's mental health in a familiar setting. An established relationship with their family doctor or practice nurse may also help an older adult accept the need for referral to specialist services for assessment, treatment or support, or to social services or voluntary organizations. The family doctor is an essential and central person in care coordination. A useful opportunity for early detection presents when people are being seen in primary care for other reasons. For example, people at high risk of arteriosclerosis are also at high risk of developing a vascular dementia, and family doctors screen people routinely for cardiovascular disease. Those who are identified as *at high risk* are examined regularly and have renal function and lipid levels checked. Some family doctors add a cognitive test to the cardiovascular assessment, and use this opportunity to detect cognitive problems.

One of the milestones set out in the Older People's NSF (Department of Health, 2001a) was that Primary Care Trusts (PCTs) were required by April 2004 to ensure that every general practice was using a protocol agreed with local specialist services for the diagnosis, treatment, and care of older adults with depression or dementia. Protocols for the treatment of people with Alzheimer's disease may set out physical investigations and cognitive testing which can be carried out in primary care, in order to facilitate early detection and rapid access to antidementia drug treatment if appropriate.

Some services are developing formal links with primary care: nurses identified to link with particular practices offer one possible model; formal meetings between secondary and primary care staff offer another.

CARER SUPPORT

Carers in the United Kingdom have the right to an independent assessment of their needs (but not a right to services) under the Carers (Recognition and Services) Act (Department of Health, 1995), if the person they care for has a right to a community care assessment. Many people who care for elders are themselves older adults (often spouses) and they may themselves be stressed or have mental health problems. The National Institute for Social Work (Levin, 1997) has identified 10 key requirements for carers:

early identification;
comprehensive assessment (including medical and social assessment);
medical treatment of treatable problems;

prompt referral to other sources of help;
information, advice, and counseling;
continuing support and review, preferably from a person known and trusted by the carer;
regular help with domestic tasks and personal care;
regular breaks from caring (respite);
financial support;
access to permanent residential care when needed.

Thus, carer support is a fundamental component of all aspects of service provision. One specialist model, available in some parts of England, is the Admiral nurse service, which aims to support the carers of people with dementia. More commonly available are carer support groups, which may be aimed at particular groups and their needs, for example, early onset services often have active carers groups, and our local service has a thriving support group for Asian carers (paper submitted). The Alzheimer's Society produces an advice sheet for carers (Alzheimer's Society, 2004), which addresses how carers can care for themselves, but the challenge for services is to ensure that they care for the carers as well as the person who is seen as their client or patient. This will often involve sensitive negotiation with carer and service user, who will not uncommonly have differing views. In accommodating disparate views, it is vital that social and health-care staff work with families long term to establish a trusting relationship and also have access to a broad range of flexible services. Respite is a big issue and the Audit Commission (2000) found that the need for more respite was the most common comment made by the carers of people with dementia: over one-third of carers reported difficulty in accessing respite care (Audit Commission, 2002). Respite includes a range of possible provisions, including day care, respite admissions to residential or nursing care, regular or planned respite admissions, and respite within the home, for example, day and night sitting services. The lack of good written information about services was also highlighted by the Audit Commission (2002).

COMMUNITY MENTAL HEALTH TEAMS FOR OLDER PEOPLE

The NSF-OP (Department of Health, 2001a) sets out the disciplines who should be core members of the CMHT-OP: this should include community mental health nurses, consultant old age psychiatrists, clinical psychologists, social workers, and occupational therapists. A range of other disciplines is listed as needing to have agreed working and referral arrangements with the team but not working as full members of it.

One of the big issues for a CMHT-OP is that of "integration". In this context, integration usually refers to the integration of health and social care. Lingard and Milne (2004) have written a scholarly commentary and resource document on the topic which describes the different components of integrated teams. The Durham mapping project pilot in older people's mental health services uses four main criteria for an integrated CMHT-OP:

- The team should include interagency multidisciplinary staff involving health and social services.
- It should provide integrated assessment, care planning and care coordination.
- It should use shared recording systems and IT, supporting both CPA and the Single Assessment Process (SAP).
- There should be a single point of entry to specialist mental health assessment.

How teams work in relation to team members' responsibility is another major issue. This has become increasingly important because of high consultant psychiatrist vacancy levels in the United Kingdom (running at around 12–14%) with associated problems of recruitment and retention. There is evidence that consultants are overburdened, stressed (Benbow and Jolley, 1997) and retiring earlier (Mears *et al.*, 2004a). Factors in this may include large and increasing caseloads, style of working (Mears *et al.*, 2004b) and the increasing pressure to avoid risk. Locum consultants are in short supply and attract high rates of pay. Thus, reliance on them may compromise service development and lead to a perverse incentive, which encourages doctors to continue working as locums rather than accept a reduced salary together with greater responsibility in a substantive post.

- Do doctors have to see and take responsibility for every person known to the CMHT-OP?
- How is responsibility carried or shared by team members?

These questions have been explored by a working party on new ways of working for consultant psychiatrists (Royal College of Psychiatrists Scoping Group on the Roles and Values of Psychiatrists, 2004; National Steering Group, 2004).

The way ahead is seen as requiring

- a single point of entry to the CMHT (for older people);
- the definition of the responsibilities of team members with agreement of when and why people need to see psychiatrists;
- better IT support to the team;
- clarification of issues of team members' responsibility, power, and accountability.

Three options were identified for consultant responsibility as team members:

Option 1 involves *no change* to consultant responsibilities from the present. The characteristics of this model are that the consultant psychiatrist within a team continues to carry responsibility for large numbers of patients and other professionals are less autonomous. This model is anticipated to lead to continuing workload problems for psychiatrists with an increasing demand for doctors and a lag before medical school output increases sufficiently to provide more potential psychiatrists.

Option 2 is characterized by consultant psychiatrists carrying smaller caseloads with responsibility *delegated* to other professionals. In this model, although team consultants carry a smaller personal caseload, they remain responsible for large numbers of patients and all outpatients are required to have a named consultant. The relationship between consultant psychiatrist and other team members is regarded as *supervisory*, although other professionals are more autonomous than in option 1.

Option 3 is characterized by responsibility being *distributed* amongst members of the team. The consultant psychiatrist is therefore directly responsible for fewer patients and is freed up to concentrate on high risk or complex cases (although complexity will need to be defined). The consultant's relationship to other team members is that of a *consultant* and other professionals are more autonomous in this model. Guidance from the General Medical Council on medical responsibility is anticipated in 2005, and is expected to support doctors in moving toward this model, which has been strongly supported by the Faculty of Old Age Psychiatry within the Royal College of Psychiatrists.

COMMUNITY TREATMENT

One of the early principles of old age psychiatry was assessment at home by a senior member of the old age psychiatry team (Arie, 1970). This led on to the concept of a community clinic (Benbow, 1990), and many services carry out the majority of their assessment, treatment, and follow-up by seeing people in their homes, coordinating the activity of different disciplines using IT support and close liaison between team members. Perhaps the recent move to extend the principles of the NSF-MH to older adult services might lead to an expansion in the home treatment element of the CMHT-OP.

Community treatment for older people will involve close working with social services (particularly with day centers for older adults and domiciliary services) and voluntary organizations, and close links between the CMHT-OP and places where older adults are resident, including sheltered and extra care housing, and the residential and care home sector.

HOSPITAL-BASED FACILITIES

Acute Inpatient Beds

Community-orientated services need access to inpatient beds for the assessment and treatment of older people with a range of diagnoses, who cannot be managed in the community, a small proportion of whom will be detained under mental health legislation. The main distinction is between people who have an organic brain disorder and those with so-called functional disorders, the most common of which is depressive illness. Current thinking often supports separate inpatient provision for people with organic brain disorders and those with other mental health problems in later life (Audit Commission, 2000, 2002). The distinction is often neither clear nor absolute in practice, and flexibility and tolerance are needed when accommodating the various and changeable complex needs of very ill/disturbed older people. It is not usually appropriate to care for older adults with complex needs on wards for younger adults (Audit Commission, 2002): this would place them at risk and deprive them of the specialist nursing, medical, and other care which they require.

Day Hospitals

Day hospitals for older people are widely available across the United Kingdom but the literature supporting their role is remarkably sparse. The Faculty of Old Age Psychiatry carried out a survey of old age psychiatric day hospitals, published in a report in June, 2001: (Audini *et al.*, 2001). Three quarters of day hospitals operated a mixed service to people with organic and functional illnesses in late life. The study found that people attend day hospitals for a great many different reasons and for varying periods of time: over a third of people attend for over one year. Carer support is a common feature of a day hospital service, and some units aim to provide a respite service for people with dementia in association with particularly challenging behaviors, which restrict the availability of alternative sources of respite.

Possible aims for an old age psychiatry day hospital include the following:

- Reduction of inpatient bed use by functionally ill older people.
- Prevention of admission: by supporting CMHTs in maintaining ill people in the community during crisis.
- Prevention of readmission through relapse prevention.
- Prevention of readmission through prevention of recurrence.
- Reduction of duration of an episode of inpatient treatment.

Outpatient Clinics

For many services, the majority of activity takes place in the community using a community clinic model. Some older adults may prefer to be seen in a traditional outpatient clinic, and there may also be specialist clinics, for example, clinics carried out jointly with geriatric physicians, and memory clinics (though memory clinics may themselves work primarily in the community or in a day hospital.) Other models involve clinics carried out in GP surgeries, day centers, nursing or residential homes. There are also clinics specializing in family therapy (Benbow and Marriott, 1997).

Memory Clinics

The number of memory clinics in the British Isles has been increasing in recent years. In 1993, Wright and Lindesay (1995) carried out a survey which identified 20 clinics, largely offering a multidisciplinary specialized hospital-based assessment service. When the survey was repeated in 1999–2000 (Lindesay *et al.*, 2002), 58 active memory clinics were identified, and over a quarter were partly or wholly based in the community. The authors concluded that the growth in memory clinics has been stimulated by the licensing of drug treatments for Alzheimer's disease and that they have now moved into mainstream clinical services. They reported that the term "memory clinic" has extended to a wider range of service models, with a less academic, more service orientated focus. They are closely associated with antidementia drug treatments, but also with psychosocial interventions: over half of the clinics surveyed offered memory training and anxiety management. The authors also suggest that memory clinic development has been driven by a need for services for people with early onset dementia syndromes.

Services to the General Hospital

Older people are frequently admitted to hospital because of intercurrent illness. Some will have preexisting psychiatric problems, others may develop them in association with their acute physical illness. All deserve attention to the full range of their needs. Unhappily, the environment of large general hospitals is often less than helpful to frightened, confused old people. The pressure to move on from assessment ward to treatment ward and out may compound their difficulties. Formal Liaison Psychiatric services have not, traditionally, taken a major interest in older people, and Old Age Psychiatry services have often given greater priority to patients in the community. This failing is being addressed in some centers and there is progress toward generalizing good practice (Holmes *et al.*, 2002). Admission to hospital for physical illness may provide an opportunity to recognize a memory problem and initiate referral to the old age psychiatry service. Figure 1 sets out the referral pathway for people with a suspected dementia and illustrates the overlap between physical and mental health services in late life (Figure 1).

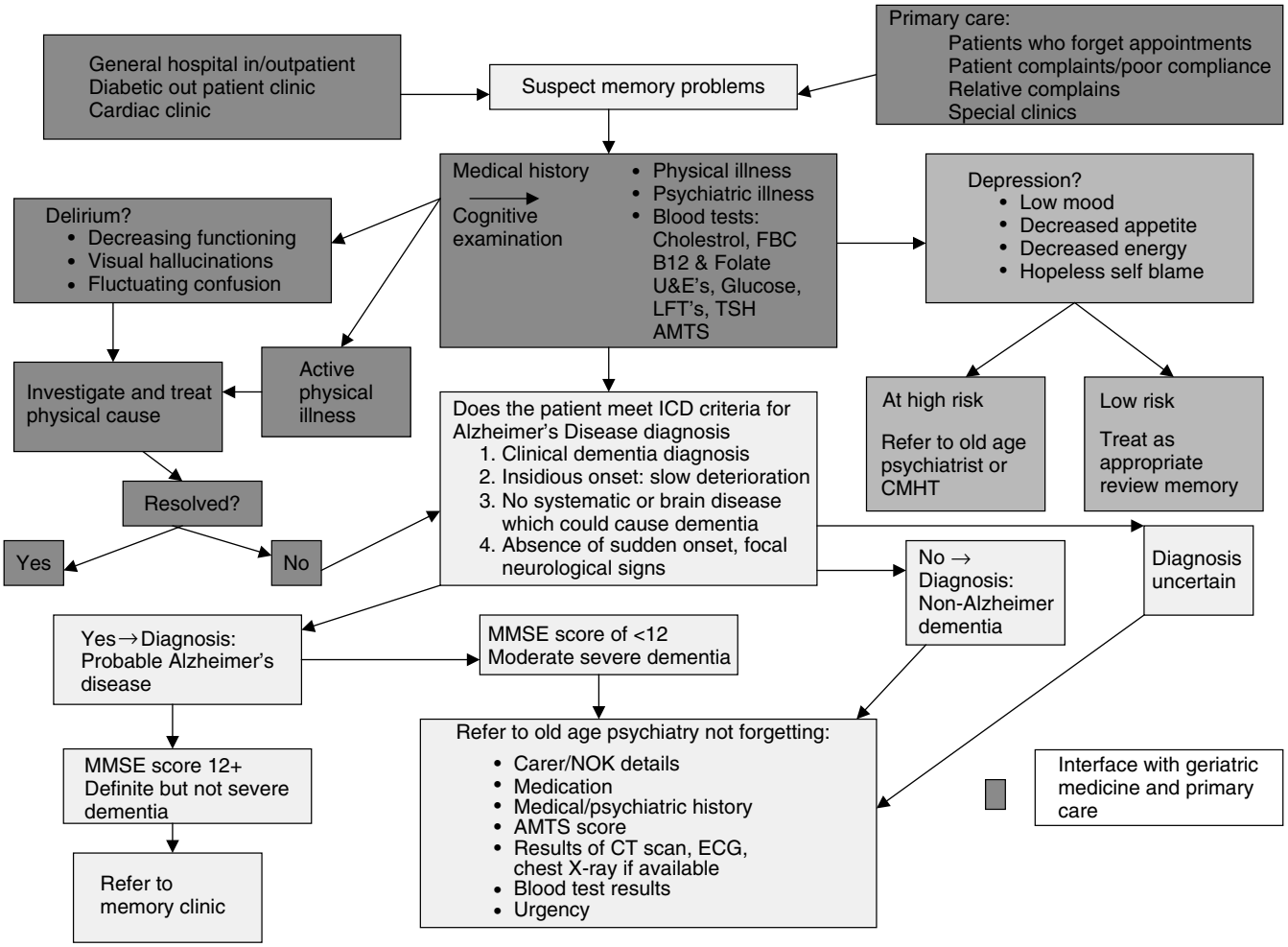

Figure 1 Dementia referral pathway

SPECIAL GROUPS

Elders with Learning Disability

People with a Learning Disability are much more likely to survive into their 60s and beyond now, than was the case in the past (Collacott, 1997). People with Learning Disability may develop problems characteristic of late life earlier than the general population. People with Down's Syndrome are particularly at risk of Alzheimer's Disease (Holland and Oliver, 1995), which requires skillful care in its terminal phases.

Thus, older people with Learning Disability may have complex needs which cross the interface between old age psychiatry, geriatric medicine, and learning disability services. Good practice will often require that services work together to best meet an individual's needs (Department of Health, 2001b). Flexibility and trust are vital. Users and their families need to be clear about care plans: who is taking responsibility for what, and how they might be contacted. Commissioners need to ensure that this group is not neglected in service planning.

Early Onset Dementia Services

In 2000, the Royal College of Psychiatrists (2000) published a Council Report which recommended that each district should have a named consultant responsible for the service for younger people with dementia and that old age psychiatrists should take the lead. Subsequently, the Alzheimer's Society carried out a postal survey of all members of the Faculty of Old Age Psychiatry, to assess members' awareness of the report and determine what developments in service provision had occurred since its publication. Awareness of the report was comparatively high, but no area met all the report's recommendations. There was evidence of improvement in service provision, and many respondents outlined plans for future development. Currently, the Council Report is being revised and the revised document is likely to recommend that commissioners should have

- a named individual who takes responsibility for commissioning services for younger adults with dementia and
- specific contractual arrangements for a specialized service for younger people with Alzheimer's disease and other dementias, including programed time from a named consultant (usually an old age psychiatrist).

The Alzheimer's Society (1996) has a charter for younger people with dementia and their carers, which supports early diagnosis, assessment and referral, and access to specialist services.

People with Enduring or Relapsing Mental Illness

Those individuals who lived out their lives with chronic schizophrenia, manic-depressive psychosis, brain damage or personality disorders in large mental hospitals, were overlooked by the psychogeriatric services of the 1970s and 1980s. Closure of the hospitals and changing expectations have meant that the new generations of "graduates" with a psychosis live within the community, often in hostels or nursing homes. There they may have remained in touch with mental health services, or drifted out of touch. They are at risk of neglect or misunderstanding or of falling into a gap between different services (Jolley *et al.*, 2004). Their plight has been recognized, and existing guidance encourages all authorities to recognize them, discover their needs, and agree the best arrangements for their care within the range of available local resources (Royal College of Psychiatrists, 2002).

People in Residential and Nursing Care

Despite the emphasis on supporting people in their own homes and providing alternative and innovative housing solutions for older, frailer people, large numbers spend their last months or years in residential homes or nursing homes. In many residential homes, 40% or more of the residents have dementia, and up to 20% are depressed or demonstrate other psychiatric morbidity (Mann, 1991). Roughly, half of the population with a diagnosis of dementia in the United Kingdom is in care at any one time. For most, this is terminal care. The transfer of care from large, ill-sited, ill-equipped, and poorly staffed mental hospitals to community-based homes nearer their families represents progress for many people, but there are continuing concerns over the quality of life available to residents, particularly those with mental illness or dementia. Early progress in service improvement followed scandals relating to hospital care (Arie and Isaacs, 1978). A recent driver for improved standards in inpatient care has been the Rowan Report (Commission for Health Improvement (CHI), 2003). Rowan ward was an "isolated facility": it was a ward that was left behind when the rest of a large hospital closed and became a building site. Allegations of physical and emotional abuse led to an investigation by the then Commission for Health Improvement (CHI), who produced a report in September 2003. This revealed a poor and institutionalized ward environment with low staffing levels, high use of bank/agency staff, little staff development and poor supervision. The culture was described as closed and inward looking with weak management at ward and locality level. Although the history of inpatient older people's mental health (OPMH) care reveals a progression of similar reports, this report attracted a lot of publicity, attention to current inpatient standards, and reflection on acceptable standards of care. It was followed by an audit of inpatient care carried out by Strategic Health Authorities across England, which moved OPMH up the agenda nationally.

It is essential that specialist services, both medical and mental health, take responsibility for the care of older people in the time of their greatest need, be this in residential or nursing homes, or the much diminished National Health Service (NHS) continuing care sector.

Black and Minority Ethnic (BME) Elders

The Royal College of Psychiatrists (2001) published a report on psychiatric services for BME elders in 2001. This made five main recommendations:

- assessment and treatment should remain within mainstream psychiatric services;
- continuing care services should be targeted at particular user groups;
- services should endeavor to recruit a mix of staff reflecting the ethic mix of the local population;
- good practice should be established and shared, perhaps using a website;
- staff should be trained in culturally sensitive issues.

There are already examples of good practice developing around the country. In Wolverhampton alone, there are several initiatives:

- social services and health staff have jointly undertaken a course in basic Punjabi;
- staff at a local day center for Asian elders undertake exchanges with staff at the Resource Center for older adults with mental health problems;
- a specialist community psychiatric nurse (CPN) is employed to work with Asian elders presenting to old age psychiatry;
- a support group for Asian carers of older adults with mental health problems has been established.

This experience must be multiplied many times around the country, as services increasingly address the needs of ethnic elders within their localities.

SPECIAL ISSUES

Access to Psychological Therapies

The NSF-OP states that a full range of psychological treatments should be available for older people with mental health problems. This is probably not the case at present: Evans (2004) found that provision varies widely across the United Kingdom and is of unknown quality. Hepple (2004) recently reviewed psychological therapies for older adults and states that their slow development is due to agism. It is likely that upcoming cohorts of older adults will be more likely to expect access to psychological therapies and that this aspect of service provision will need to respond to their demands in future.

Intermediate Care for Older People with Mental Health Problems

Intermediate care is an emerging concept in health care, which may offer alternatives to hospital care. It was conceived originally in response to the increasing demand for acute hospital services, and the fact that a high proportion of acute hospital beds is occupied by older people. The British Geriatrics Society (2001) quotes several definitions of intermediate care: one simply describes intermediate care as delivered by those health services that do not require the resources of a general hospital but are beyond the scope of the traditional primary care team. The NSF-OP sets out the following aims for intermediate care in Standard 3: to provide integrated services to promote faster recovery from illness, prevent unnecessary acute hospital admissions, support timely discharge, and maximize independent living. Its two main thrusts are prevention of admission and facilitation of early discharge. Ways of preventing acute admissions amongst people with mental health problems include the provision of specialist home care/community support, access to specialist community nursing, home-based respite services, assertive in-reach/outreach projects, flexible, and rapid access to intensive home care. Ways of facilitating early discharge of people with mental health problems from hospital beds include liaison services which work across the interfaces of care, and rapid easy access to short periods of postdischarge intensive home support. Intermediate care is as relevant to older people's mental health services as it is to everyone who has access to acute hospital services (Read, 2004). People with dementia, depression, and other mental health diagnoses should have access to intermediate care services, whether or not they have a physical illness. In the past, intermediate care services have, not uncommonly, excluded people who they identify as having mental health problems, but there has been growing recognition that this is unacceptable and that older people with dementia and other mental disorders must have appropriate access to intermediate care. There are a range of ways in which this can be done, for example, by setting up specialist provision, by ensuring close links between specialist OPMH service and generic intermediate care services, and by placing mental health staff within generic intermediate care services. The development of intermediate care offers an opportunity to investigate a range of options for flexible community treatment and support.

AN INTERNATIONAL PERSPECTIVE

This chapter is written from the vantage of developments and current considerations in the United Kingdom. The speciality of old age psychiatry is one of the gifts of British medicine to advances in the twentieth century (Arie and Jolley, 1999). Yet the importance of mental health problems in late life is a global phenomenon, as developing countries join developed countries in seeing life-expectation rise beyond 60 years from birth (Kalche, 1996).

From the mid-1970s British pioneers encouraged colleagues in Europe, America, Canada, and Australia to follow their designs for community-based services through the medium of personal lecture tours (Pitt, 1974). Professor Arie's Nottingham courses, sponsored by the British

Council, shared principles and practicalities with a wider audience and were followed by the establishment of the European Association of Geriatric Psychiatry (EAGP) and the International Psychogeriatric Association (IPA). Professional advice has been supported by the interest of voluntary organizations. Alzheimer's International, for instance, currently lists 72 active national centers. Thus, the countries of the world are responding to the needs of older people with mental health problems in different ways according to their economies, philosophies, and health-care configurations. But they are in touch with approaches used elsewhere and most use elements of the comprehensive services outlined here within the British model.

These principles were affirmed in the Lausanne Technical Consensus statements on the psychiatry of the elderly by the World Psychiatric Association in 1999. Many examples of friendly, supportive international collaboration exist, as experienced practitioners and researchers add to their own breadth of understanding by working in new situations for the benefit of others. One notable example is that of the Alzheimer's International 10/66 Dementia Research group (Prince *et al.*, 2004).

CONCLUSIONS

Older people's mental health services in the United Kingdom have developed rapidly over the last 30 years, despite a series of threats and uncertainties. Good has come from the Rowan Report (Commission for Health Improvement (CHI), 2003), which has moved OPMH up the national agenda. Other powerful forces for good include the Alzheimer's Society, Age Concern, and Rethink. The Dementia Services Development Centers continue working to improve standards in care, and recently the National Institute for Mental Health in England has launched a work program in OPMH. All of these are reasons for optimism. Generations of older adults in future (which include those of us writing and reading this chapter) are going to be increasingly demanding of services: we must design and operate services that we ourselves would be happy to use.

KEY POINTS

- Specialist older people's mental health services should address the needs of people with a range of mental disorders in late life.
- Early detection, diagnosis, and treatment are important principles of OPMH services.
- Active community assessment, treatment and support needs to be complemented by hospital-based services, including inpatient provision.
- A number of special groups will need be addressed in service planning, including elders with learning disability, people with an early onset dementia, and those from minority ethnic groups.
- Liaison is needed across a broad range of voluntary and statutory agencies to provide flexible person-centered services.

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Depression in Late Life: Etiology, Diagnosis and Treatment

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INTRODUCTION

Depression, the most frequent cause of emotional suffering in later life, is associated with significant losses in health-related quality of life (Blazer, 2003). Depression adversely influences the outcome of comorbid health disorders (Unützer *et al.*, 2000; Cole and Dendukuri, 2003) and is associated with increased risk of mortality (Frasure-Smith *et al.*, 1993).

VARIETIES OF LATE-LIFE DEPRESSION

Formal diagnostic criteria for depression are derived from the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (APA, 1994). *Major depression*, the most common of the mood disorders, is diagnosed when the individual exhibits, for at least two weeks, one or both of two core symptoms (depressed mood and lack of interest in most activities) along with four or more of the following symptoms: feelings of worthlessness or guilt; diminished ability to concentrate or make decisions; fatigue; psychomotor agitation or retardation; insomnia or hypersomnia; significant decrease or increase in weight or appetite; and recurrent thoughts of death or suicidal ideation (APA, 1994). Depression is similar for older adults if there are no comorbid conditions (Blazer *et al.*, 1987); however, subtle differences with aging may emerge. For example, depression with melancholia (symptoms of anhedonia, noninteractiveness and psychomotor retardation or agitation) appears to have a later age of onset than nonmelancholic depression in clinical populations (Parker *et al.*, 2001). Older adults often experience depressive symptoms associated with *bereavement* after the loss of a loved one, symptoms consistent with that of a major depressive episode. Major depression may be diagnosed if the depressive symptoms are present at least two months or longer after the loss.

Minor, subsyndromal, or subthreshold depression is diagnosed according to the Appendix of DSM-IV when one of the core symptoms is present (sad mood or loss of interest in most activities) along with one to three additional symptoms (APA, 1994). Other operational definitions of these less severe variants of depression include a score of 16 or more on the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977; Beekman *et al.*, 1995), a primarily biogenic depression not meeting criteria for major depression, yet responding to antidepressant medication (Snaith, 1987), or a score of 11–15 on the CES-D (Hybels *et al.*, 2001).

Dysthymic disorder is a long-lasting chronic disturbance of mood, less severe than major depression that lasts for two years or longer (APA, 1994). It rarely begins in late life but may persist from midlife into late life (Blazer, 1994; 2003). Finally, other investigators have suggested a syndrome of *depression without sadness*, thought to be more common in older adults (Gallo *et al.*, 1999) or a depletion syndrome manifested by withdrawal, apathy, and lack of vigor (Adams, 2001; Blazer, 2003).

Depression among individuals with dementia is also quite common (Sachs-Ericsson and Blazer, In Press), so much so that recently a group of investigators proposed a *depression of Alzheimer's disease*. Three of a series of symptoms that includes depressed mood, anhedonia, social isolation, poor appetite, poor sleep, psychomotor changes, irritability, fatigue or loss of energy, feelings of worthlessness, and suicidal thoughts must be present for the diagnosis to be made (Olin *et al.*, 2002; Blazer, 2003). Finally, depression in late life is frequently comorbid with physical conditions. When the depression derives from the physiological consequence of the medical condition, the disorder is diagnosed as *mood*

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Table 1 Depressive disorders and subtypes: core and additional symptoms

Diagnosis	Core symptoms	Additional symptoms
Major depression (symptoms for at least 2 weeks)	Depressed mood and/or lack of interest or pleasure in most activities	Feeling of worthless or guilt Poor concentration Psychomotor agitation or retardation Fatigue, insomnia or hypersomnia Appetite or weight changes Thoughts of death or suicide
Major depression with melancholic features	Lack of interest or pleasure in most activities Lack of reactivity to usually pleasurable stimuli Cannot feel better, even temporarily	Depression worse in morning Early morning awakening Psychomotor retardation or agitation Anorexia/weight loss Excessive inappropriate guilt.
Depressive symptoms with bereavement	Depression occurring after death of a loved one	Major depression diagnosed if symptoms persist after 2 months
Minor or subthreshold depression	Depressed mood or lack of interest or pleasure in most activities	One to three additional symptoms of major depression (not meeting criteria for Major depression)
Dysthymic disorder (does not met criteria for major depression)	Depressed mood (2+ years)	(see additional symptoms Major depression)
Depression of Alzheimer's disease	Clinically significant depressed mood Decreased positive effect in association with activities or social interactions	Social isolation, appetite disturbance, disruption in sleep, psychomotor retardation or agitation, fatigue, irritability, feelings of worthlessness, hopelessness, guilt, suicidal
Mood disorder due to general medical condition	Prominent and persistent disturbance in mood	Depression derives from the *Physiological consequence* of the medical condition

disorder due to general medical condition (APA, 1994) (see Table 1).

THE EPIDEMIOLOGY OF LATE-LIFE DEPRESSION

Depressive symptoms are no more frequent in late life than in midlife (Blazer *et al.*, 1991; Charles *et al.*, 2001). Several large epidemiological studies have been conducted to assess prevalence of affective disorders in older populations. Generally, among the elderly, the prevalence of major depression is approximately 1 to 3% (Cole and Yaffe, 1996; Blazer, 2003) and clinically significant depressive symptoms in community-dwelling elderly are approximately 8 to 16% (Berkman *et al.*, 1986; Blazer *et al.*, 1988; Blazer, 2003). Further, the incidence of major depression appears to increase among the oldest of old, reaching approximately 13% among those aged 85 years or older (Meller *et al.*, 1996). However, this increased rate is explained by factors associated with aging, such as a higher proportion of women, more physical disability, more cognitive impairment, and lower socioeconomic status (White and Blazer, 1990).

Higher rates of depression have been consistently found for women compared to men in the general population and for the elderly (Steffens *et al.*, 2000). Whereas, some studies of the elderly have found few racial differences in the frequency of depressive symptoms (Blazer *et al.*, 1998; Cummings *et al.*, 2003), or in the frequency of depressive diagnoses (Weissman *et al.*, 1991; Gallo *et al.*, 1998), others have found African-American elders to have a higher frequency of depressive symptoms than Caucasians (Fabrega *et al.*, 1994; Cochran *et al.*, 1999). Nevertheless, African-Americans are generally thought by psychiatrists to have fewer depressive symptoms and are much less likely to be treated with antidepressant medications (Blazer *et al.*, 2000; Teresi *et al.*, 2002).

Comorbidity of Depression with Medical Illness and Dementia

Depression, late in life, often occurs in the context of physical impairment (Hays *et al.*, 1997), especially in the oldest old (Blazer, 2000). For example, in one study the degree of association between clinical depression and medical comorbidity increased linearly with medical comorbidity (Watkins *et al.*, 2003). Depression adversely influences the outcome of comorbid health disorders in the elderly as well (Alexopoulos, 2003; Cole and Dendukuri, 2003).

Depression is associated with both mild cognitive impairment (Lopez *et al.*, 2003) and dementia (Sachs-Ericsson and Blazer, In Press). The prevalence of depression among the cognitively impaired has been found to range from 20 to 50% (Olin *et al.*, 2002; Zubenko *et al.*, 2003). Depression among individuals with dementia may be more frequent in those with vascular diseases compared to those with Alzheimer's disease (AD) (Ballard *et al.*, 1996; Kim *et al.*, 2003). Elevated rates of depression have also been found among individuals with dementia secondary to Parkinson's disease (Aarsland *et al.*, 1996). Depression may signal the onset of AD and may represent prodromal signs of dementia (Ritchie *et al.*, 1999; Geerlings *et al.*, 2000).

COURSE OF LATE-LIFE DEPRESSION

Depression is a chronic and recurring illness (Reynolds *et al.*, 1992; Alexopoulos *et al.*, 1996). In a meta-analysis

(Cole and Bellavance, 1997) of the prognosis of elderly medical inpatients with depression, researchers found that at three months, 18% of patients were well, 43% were depressed, and 22% were dead. At 12 months or more, 19% were well, 29% were depressed, and 53% were dead. Factors associated with worse outcomes included more severe depression and more serious physical illness. Among those older depressed adults without significant comorbid medical illness or dementia and who were treated optimally, the outcome was much better, with over 80% recovering and remaining well throughout follow-up (Reynolds *et al.*, 1992).

Medical comorbidity, functional impairment, and comorbid dementing disorders all adversely influence outcome of depression (Blazer, 2003). Depression also adversely affects the outcome of the comorbid problems such as cardiovascular disease (Frasure-Smith *et al.*, 1993) in which, depressive disorder is associated with an increase in mortality (Romanelli *et al.*, 2002), particularly for women but less so for men (McGuire *et al.*, 2002; Williams *et al.*, 2002a).

NONSUICIDE MORTALITY

Psychiatric disorders in general and severe depressive disorders increase the risk of nonsuicide related mortality (Bruce *et al.*, 1994; Blazer, 2003). For example, in a review of 61 reports of this relationship from 1997 to 2001, 72% demonstrated a positive association between depression and mortality in elderly people (Schulz *et al.*, 2002). Both the severity and duration of depressive symptoms predict mortality in the elderly population in these studies (Geerlings *et al.*, 2002). Other studies, however, have suggested that the association between depression and mortality is related to the high correlation between depression and other medical problems. That is, depression impacts nonsuicide mortality through intermediate risk factors.

SUICIDE

The association of depression and suicide across the life cycle has been well established (Goldstein *et al.*, 1991; Conwell *et al.*, 2002; Turvey *et al.*, 2002). Older adults are at a higher risk for suicide than any other age-groups. While older Americans comprise about 13% of the US population, they account for 18% of all suicide deaths (Arias *et al.*, 2001). Increased risk for suicide attempts in late life is associated with being a widow or a widower, living alone, perception of poor health status, poor sleep quality, lack of a confidant, and experience of stressful life events, such as financial and interpersonal discord (Conwell *et al.*, 2002; Turvey *et al.*, 2002) (see Table 2).

The most common means of committing suicide in the elderly are use of a firearm (Goldstein *et al.*, 1991) and drug ingestion (Blazer, 2003). Women attempt suicide more than men do; however, men completed suicide more often than women (Sachs-Ericsson, 2000). Though completed suicides increase with age, suicidal behaviors do not increase (De Leo *et al.*, 2001). This is consistent with the contention that older adults are more intent in their efforts to commit suicide (Conwell *et al.*, 1998).

Table 2 Demographic characteristics, symptoms, and behaviors associated with increased risk factors for suicide

Demographic characteristics	Symptoms and behaviors	Suicidal thoughts or behaviors
Widow(er)	Depressive symptoms	History of suicide attempts
Living alone	Pervasive hopelessness	Resolved plans regarding suicide
Male	Feelings of being a burden	Courage and/or competence regarding suicide
Caucasian	Self-harming behaviors	Access to means of suicide (e.g. gun or pills)
Over age 65	Social isolation	
	Poor social support	
	Marked impulsivity	Acute desire for death
	Substance abuse	
	Personality disorder	

There are many risk factors for suicide. Depression is the strongest risk factor (Bruce *et al.*, 2004). Perhaps the most well studied factor is pervasive feelings of hopelessness (Rifai *et al.*, 1994). Other psychological constructs include emotional pain (Shneidman, 1992), feelings of being a burden, and social isolation (Alexopoulos *et al.*, 1999). The lack of social networks and their disruption are significantly associated with risk for suicide in later life (Conwell *et al.*, 2002).

Older persons with mental disorders rarely seek help from mental health professionals, preferring to visit their primary care physician instead (Goldstrom *et al.*, 1987). The majority of older adults who die by suicide have seen a primary care physician in preceding months, underscoring the physicians potential role in intervention. Suicide prevention strategies rely on the identification of specific, observable risk factors. Depression, hopelessness, and self-harming behaviors (such as food refusal) are possible indicators of suicide risk (Pearson and Brown, 2000; Conwell *et al.*, 2002).

Individuals with a previous history of suicide are more likely to attempt suicide again (Goldstein *et al.*, 1991). Increased risk is also associated with resolved plans, a sense of courage and/or competence regarding suicide, and access to means of suicide (e.g. pills or gun) (Joiner *et al.*, 1999). Other variables that increase suicide risk include substance abuse (Conwell and Brent, 1995), marked impulsivity, and personality disorder (Duberstein, 1995).

ETIOLOGY

Biological

As noted above, increased rates of depression are associated with many medical conditions including dementing disorders

(Sachs-Ericsson and Blazer, In Press), cardiovascular disease (Schulz *et al.*, 2000), hip fractures (Whooley *et al.*, 1999), and Parkinson's disease (Starkstein *et al.*, 1990). Depression has been associated with pain in institutionalized elderly people (Parmelee *et al.*, 1991) and is also common among homebound elders with urinary incontinence (Endberg *et al.*, 2001). Therefore, any exploration of the etiology of late-life depression must begin with the possibility that the depression is caused in part, or perhaps in whole, by physical illness.

The role of heredity, that is, genetic susceptibility, has been of great interest in exploring the origins of depression across the life cycle (Barondes, 1998). Among elderly twins, genetic influences accounted for 16% of the variance in total depression scores on the CES-D and 19% of psychosomatic and somatic complaints. In contrast, genetics contributed a minimal amount to the variance of depressed mood and psychological well-being (Gatz *et al.*, 1992). Attention has been directed to specific genetic markers for late-life depression. For example, a number of studies have focused on the susceptibility gene apolipoprotein E (APOE; the e4 allele) for Alzheimer's disease. No association was found in a community sample between e4 and depression (Blazer *et al.*, 2002). In another study, hyperintensities in deep white matter but not in the periventricular white matter were associated with depressive symptoms, especially in elders carrying the e4 allele (Nebes *et al.*, 2001).

Much attention has been directed to vascular risk for late-life depression, dating back at least 40 years, although the advent of MRI increased interest considerably (Kumar *et al.*, 2002a,b). Vascular lesions in some regions of the brain may contribute to a unique variety of late-life depression. MRI of depressed patients has revealed structural abnormalities in areas related to the cortical–striatal–pallidal–thalamus–cortical pathway (George *et al.*, 1994), including the frontal lobes (Krishnan *et al.*, 1993), caudate (Krishnan *et al.*, 1992), and putamen (Husain *et al.*, 1991). These circuits are known to be associated with the development of spontaneous performance strategies demanded by executive tasks. Recent serotonin activity, specifically 5 HT2A receptor binding, decreases dramatically in a variety of brain regions from adolescence through midlife, but the decline slows from midlife to late life. Receptor loss occurred across widely scattered regions of the brain (anterior cingulated, occipital cortex, and hippocampus). Serotonin depletion can also be studied indirectly by the study of radioisotope-labeled or tritiated imipramine binding (TIB) sites. There is a significant decrease in the number of platelet-TIB sites in elderly depressed patients, compared with elderly controls and individuals.

Late-life depression is also associated with endocrine changes. Although the dexamethasone suppression test was long ago ruled out as a diagnostic test for depression, nonsuppression of cortisol is associated with late-life depression compared with age-matched controls (Davis *et al.*, 1984). Depression is also associated with increase of corticotrophin releasing factor (CRF), which mediates sleep and appetite disturbances, reduced libido, and psychomotor changes (Arborelius *et al.*, 1999). Aging is associated with an increased responsiveness of adrenocorticotropic hormone (ACTH), cortisol, and dehydroepiandrosterone sulfate (DHEA-S) to CRF (Luisi *et al.*, 1998). Low levels of DHEA have been associated with higher rates of depression and a greater number of depressive symptoms in community-dwelling older women (Yaffe *et al.*, 1998). Total testosterone levels have been found to be lower in elderly men with dysthymic disorder than in men without depressive symptoms (Seidman *et al.*, 2002). However, the efficacy of testosterone in treating depression has not been established (Seidman *et al.*, 2001).

Psychological and Social

A variety of different psychological origins have been theorized for depression in later life including behavioral, cognitive, developmental, and psychodynamic theories. Among the behavioral explanations, learned helplessness (Seligman and Maier, 1967) was originally used to describe the increasingly passive behavior of dogs who were exposed to inescapable shock. The theory has been expanded, suggesting that one cause of depression is learning that initiating action in an environment that cannot be changed is futile (Seligman, 1972; Blazer, 2002). As individuals face new challenges associated with aging, coping strategies that were once useful may become less effective. Within this context, behavioral interventions (described below) encourage the individual to find new ways to successfully cope with environmental stress.

The most dominant current psychological model of depression is that of cognitive distortions (Beck, 1987). Several researchers have found consistent differences in the cognitive styles of depressed individuals compared to nondepressed individuals. Beck and others have described the cognitive schema of depressed persons as having logical errors that promote depression (Beck, 1963; Kovacs and Beck, 1978; Beck, 1987). Cognitions may be distorted such that the elder has expectations that are not realistic, overgeneralizes or overreacts to adverse events, and personalizes events. Thus, in reaction to a negative life event (loss of a loved one, move into a nursing home), an individual's cognitive style may increase the likelihood of an episode of depression.

A developmental theory of aging, the *disengagement theory* of aging (Adams, 2001) contends that there is a mutual social and affective withdrawal between older adults and their social environment. Similarly, *Gerotranscendence* (Tornstam, 1989) is a concept in which the older individuals are thought to narrow their personal social world and to have a decreased investment in activities that were once important. Others have conceptualized this withdrawal as a subtype of geriatric depression that has been termed *depletion* (Johnson and Barer, 1992). A more recent, yet controversial theory complements the depletion theory, suggesting that successful aging is associated with *selective optimization with compensation* (Baltes and Baltes, 1990). This model is based on the

recognition by the elder of the realities of aging, especially the losses. Such recognition leads to selection of realistic activities, optimization of those activities, and compensation for lost activities, which in turn leads to a reduced and transformed life. More recently, *socioemotional selectivity theory* (Frederickson and Carstensen, 1990; Carstensen, 1992) posits that decreasing rates of social contact reflect a greater selectivity in social partners. Other factors being equal, it is probable that elders who are less socially engaged are more depressed. For example, elders who stopped driving had a greater risk of worsening depressive symptoms (Fonda *et al.*, 2001).

The association between late-life depression and impaired social support has been established for many years. Poor social support is strongly associated with depression in the elderly (Goldberg *et al.*, 1985; DuPertuis *et al.*, 2001). The quality of social support networks has been identified as an important factor in predicting relapse in depressive episodes and future levels of depressive symptoms (Holahan *et al.*, 1999; Joiner and Coyne, 1999). Further, among the elderly, social support may serve as a buffer against disability (Mendes de Leon *et al.*, 2003) while social disengagement may be a risk factor for cognitive impairment (Bassuk *et al.*, 1999).

Perceived negative interpersonal events are also associated with depression among individuals in general, as well as among elders, particularly in those who demonstrate a high need for approval and reassurance in the context of interpersonal relationships. Ironically, the interpersonal behaviors (e.g. excessive reassurance seeking) of individuals who become depressed are often associated with the withdrawal of social support from friends and family (Joiner and Metalsky, 1995).

DIAGNOSIS

The diagnostic workup of late-life depression derives predominantly from what we know about symptom presentation and etiology. The diagnosis is made on the basis of a history augmented with a physical examination and supplemented with laboratory studies. Importantly, there is no biological marker or test that makes the diagnosis of depression. However, for some subtypes of depression, such as vascular depression, the presence of subcortical white matter hyperintensities on MRI scanning are critical to confirming the diagnosis (Kraaij and de Wilde, 2001; Blazer, 2002).

There are several standardized screening measures for depression often used by primary care physicians (Williams *et al.*, 2002b). Examples of such instruments includes the Geriatric Depression Scale (GDS) or the CES-D (Yesavage *et al.*, 1983; Koenig *et al.*, 1995). Screening in primary care is critical. Not only is the frequency of depression high, but suicidal ideation can be detected by screening as well.

Despite the centrality of the clinical interview, other diagnostic tools must be employed to assess the depressed elder. Cognitive status should be assessed with the Mini-Mental State Examination (MMSE) or a similar instrument, given the high likelihood of comorbid depression and cognitive dysfunction (Sachs-Ericsson and Blazer, In Press). Height, weight, history of recent weight loss, lab tests for hypoalbuminemia, and cholesterol are markers of nutritional status and are critical to assess, given the risk for frailty and failure to thrive in depressed elders, especially the very old (Fried, 1994; Blazer, 2000). General health perceptions as well as functional status (activities of daily living) should be assessed for all depressed elderly patients (Fillenbaum, 1988). Assessment of social functioning (Blazer, 1982), medications (many prescribed drugs can precipitate symptoms of depression), mobility and balance, sitting and standing blood pressure, blood screen, urinalysis, chemical screen (e.g. electrolytes, which may signal dehydration), and an electrocardiogram if cardiac disease is present (especially if antidepressant medications are indicated) round out the diagnostic workup.

Dementia and depression have considerable overlap in symptoms (Aarsland *et al.*, 1999). Thus, distinguishing between late-life depression and neurological disorders is one of the more challenging problems facing health-care professionals treating the elderly (Karlawish and Clark, 2003) (see Table 3). There are a cluster of cognitive deficits that are common to both dementia and depression. Memory impairment is the most frequent symptom that is common to both (Knott and Fleminger, 1975; Blazer, 2002). Apathy is also a common symptom among individuals with dementia including those with and without comorbid depression, as well as among nondemented elderly individuals with depression (Starkstein *et al.*, 2001).

Clinicians often have difficulty in their attempt to distinguish a primary mood disorder from other problems associated with depressed mood, in particular, what some have referred to as *pseudodementia* (Blazer, 2002, p 349–372). Pseudodementia is a syndrome in which dementia is mimicked; however, the underlying cause is a psychiatric disorder, which is typically but not always depression (Wells, 1979).

Table 3 Characteristics distinguishing depression from dementia (adapted from Wells, 1979)

Clinical characteristics	Dementia	Depression
Onset	Indeterminate	Rapid
Duration of symptoms	Long	Short
Mood	Consistently depressed	Fluctuating course
Mental status exam	Tries to answer, but typically incorrect	"Don't know" answers
Presentation	Tries to conceal disabilities	Highlights disabilities
Cognitive impairment	Stable	Fluctuates

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TREATMENT

Biological

There is clear and mounting evidence for the efficacy of antidepressant medications (both alone and in combination with psychotherapy) in the treatment of older adults with major depression as well as for the treatment of dysthymia (Unützer *et al.*, 2003) Antidepressant medications have become the foundation for the treatment of moderate to severe depression in older adults (Blazer, 2003). While antidepressant medications are equally effective for treating serious major depression across the life cycle (Forlenza *et al.*, 2000; Salzman *et al.*, 2002), differences in side effects make some antidepressants more desirable. That is, while studies that compare tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) usually find equal efficacy, there are fewer side effects with SSRIs (Mulsant *et al.*, 2001) which make them the first choice for treatment of older adults. Therefore, SSRIs are the treatment of choice (Callahan *et al.*, 1996). The antidepressants even appear to be efficacious in subjects with AD and vascular depression (Reifler *et al.*, 1989; Lyketsos *et al.*, 2000) (see Table 4).

Interestingly, antidepressants appear less efficacious in treating less severe depression in older adults (Ackerman *et al.*, 2000). The overall evidence suggests that antidepressants and counseling have relatively small benefits in these less severe conditions (Oxman and Sungupta, 2002). However, in a study conducted in a primary care setting, paroxetine (compared with problem-solving therapy) was found to have moderate benefits for depressive symptoms in elderly patients with dysthymia and more severely impaired elderly patients with minor depression (Williams *et al.*, 2000). Most of the currently available SSRIs have been demonstrated to be efficacious in elderly people, including fluoxetine (Feighner and Cohn, 1985), sertraline (Cohn *et al.*, 1990), paroxetine (Mulsant *et al.*, 2001), citalopram (Nyth *et al.*, 1992), and fluvoxamine (Rahman *et al.*, 1991). Escitalopram, recently entering the antidepressant market, has not been shown to be specifically efficacious in the elderly population. Other new-generation antidepressants that have been shown to be efficacious include venlafaxine (Mahapatra and Hackett, 1997), mirtazapine (Schatzberg *et al.*, 2002), and buproprion (Weihs *et al.*, 2001). To date there has been no study of the drug in the elderly population of nefazodone (Baldwin *et al.*, 2001).

In a recent consensus of practicing geriatric psychiatrists, the SSRIs along with psychotherapy were identified as the treatments of choice for late-life depression, along with venlafaxine. Buproprion and mirtazapine are alternatives, as was electroconvulsive therapy (ECT) in severe depression. Medication (SSRI plus an antipsychotic, with risperidone and olanzapine being the antipsychotics most commonly recommended) and/or ECT are the preferred treatments for major depression with psychotic features. Psychotherapy in combination with medications is recommended for dysthymic disorder. Education plus watchful waiting are recommended for minor depression that lasts for less than two weeks (antidepressant medication plus psychotherapy are recommended for minor depression if symptoms persist).

The preferred antidepressant for treating both major and minor depression, according to the consensus report, is citalopram (20–30 mg) followed by sertraline (50–100 mg) and paroxetine (20–30 mg), with fluoxetine (20 mg) as an alternative (escitalopram was not in the market when this survey was conducted). Nortriptyline (40–100 mg) is the preferred tricyclic agent, with desipramine (50–100 mg) as the alternative. The consensus group recommended continuing the antidepressant for three to six weeks before a change in medications is made because of the first choice medication not being effective. If little or no response is observed, the consensus is to switch to venlafaxine (75–200 mg) (Blazer, 2003). For a first episode of depression with recovery following antidepressant therapy, one year of continual therapy is recommended. For two episodes, two years of continual therapy and for three or more episodes, three years of continual therapy are recommended (Alexopoulos *et al.*, 2001).

The new-generation antidepressants inhibit a number of the cytochrome P450 enzymes that metabolize most medications, such as CYP3A, CYP2D6, DYP2C, CYP1A2, and CYP2E1. The CYP3A enzymes metabolize 60% of the medications used today. Fluoxetine is a moderate inhibitor of CYP3A4. Approximately 8–10% of adults lack the CYP2dD6 enzyme, and paroxetine is a potent inhibitor of this enzyme (which

Table 4 Treatment choices and alternatives associated with depressive disorders

Diagnoses	First choice	Alternative
Late-life depression	SSRIs plus psychotherapy Citalopram (20–30 mg) Sertraline (50–100 mg) Paroxetine (20–30 mg) Fluoxetine (20 mg)	Tricyclic agents: Nortriptyline (40–100 mg) Desipramine (50–100 mg)
More severe depression	Venlafaxine. Buproprion Mirtazapine	Electroconvulsive therapy
Depression with psychotic features	SSRI plus an antipsychotic (risperidone or olanzapine)	Electroconvulsive therapy
Dysthymic disorder	Psychotherapy in combination with medications	
Minor depression (less than 2 weeks)	Education plus watchful waiting	
Minor depression (that persists)	Antidepressant medication plus psychotherapy	

may explain, among some patients treated with paroxetine, the lack of efficacy of analgesics such as codeine that are metabolized by this enzyme). Citalopram and venlafaxine are the "cleanest" of the medications in terms of inhibition of the cytochrome P450 enzymes (Greenblatt *et al.*, 1998; Pollock, 2000).

Hyponatremia (39% in one study) is a clear risk for the elderly on SSRIs or venlafaxine. Frail older adults and those with medical illness should have sodium levels checked before and after commencement of antidepressant medications (Kirby *et al.*, 2002). The safest practice is to monitor all elders for sodium levels who are on these medications. This hyponatremia is due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Other serious side effects reported with the SSRIs include the risk of falls (no less risk than with the tricyclics in one study) (Thapa *et al.*, 1998), the serotonin syndrome (lethargy, restlessness, hypertonicity, rhabdomyolysis, renal failure, and possible death) (Gillman, 1999), and gastrointestinal bleeding (de Abajo *et al.*, 1999). Less serious side effects include weight loss, sexual dysfunction, anticholinergic effects (most pronounced with paroxetine), agitation, and difficulty in sleeping.

Psychotic depression in late life responds poorly to antidepressants but well to ECT (Godber *et al.*, 1987; Flint and Rifat, 1998). In one study using bilateral ECT versus pharmacotherapy, the older age-group had a better response to ECT than younger age-groups (O'Conner *et al.*, 2001). Memory problems remain the major adverse effect of ECT that affects quality of life. Memory problems are usually transient and clear within weeks following treatment.

A repetitive transcranial magnetic stimulation (rTMS) could replace ECT in some situations (McNamara *et al.*, 2001). rTMS does not require anesthesia and seizure induction is avoided. Though not studied specifically in elderly people, in one outcome study, patients treated with rTMS, compared with those treated with ECT, responded equally well and their clinical gains lasted just as long (Dannon *et al.*, 2002). In another study, executive function improved in both middle-aged and elderly depressed subjects with rTMS compared with sham treatments (Moser *et al.*, 2002).

A variety of adjunct physical therapies may alleviate depression. In a community-based study, among subjects who were not depressed at baseline, those who reported a low activity level were at significantly greater risk for depression at follow-up (Camacho *et al.*, 1991). Aerobic exercise training programs may be considered an alternative to antidepressants for treatment of depression in older persons with mild to moderate symptoms. (Blumenthal *et al.*, 1999). However, the advantages of exercise are not limited to aerobic activities. Unsupervised weight lifting has been found to decrease depressive symptoms up to 20 weeks after induction (Singh *et al.*, 2001). Light therapy may also be beneficial, especially if the depression follows a seasonal pattern. Thirty minutes of bright light a day improved depression among institutionalized elders in one controlled study (Sumaya *et al.*, 2001).

Psychological

Cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) have been shown to be efficacious in the treatment of depression for the elderly, especially in combination with medications. Given that these therapies are short-term (12–20 sessions), they are attractive to third-party payers. In addition, the educational (as opposed to a reflective) posture of the therapist employing such therapies is attractive to elders (Blazer, 2003).

Cognitive behavioral therapies focus on the patient's cognitions surrounding a given negative life event and assist the person to cognitively restructure their thought processes in a more realistic manner. The evidence is clear that treatments aimed at changing cognitive distortions can be quite effective in decreasing depressive symptoms and even in preventing future relapse. Treatments that focus on problem solving and behavioral activation have also been found to be effective in the treatment of depression. For example, in a study to determine the effectiveness of a home-based program for treating minor depression or dysthymia among older adults, patients were randomly assigned to a in-home based treatment (Program to Encourage Active, Rewarding Lives for Seniors, PEARLS) or usual care (Frasure-Smith *et al.*, 1993). The PEARLS intervention consisted of problem-solving treatment, social and physical activation, and recommendations to patients' physicians regarding antidepressant medications. The intervention was found to significantly reduce depressive symptoms and improved health status in chronically ill older adults with minor depression and dysthymia.

Another frequently used treatment for depression is IPT (Klerman *et al.*, 1984; Frank *et al.*, 1993) and it has been adapted for older adults (Frank and Spanier, 1995). IPT focuses on four components hypothesized to lead to or maintain depression: grief (e.g. death of a loved one); interpersonal disputes (e.g. conflict with adult children); role transitions (e.g. retirement); and interpersonal deficits (e.g. lack of assertiveness skills). In a study of IPT and elderly depressed patients, clinicians determined that the most common problem areas in therapy were role transition (41%), interpersonal disputes (34.5%), and grief (23%) (Miller *et al.*, 1998). Miller and colleagues (Miller *et al.*, 2001) found that IPT was an effective treatment not only with elderly patients with depression but also including those with moderate cognitive impairment.

It is important to note that most studies of depression have found a combination of psychotherapy and pharmacotherapy to have a better outcome than with either treatment taken alone (Reynolds *et al.*, 1999; Thompson *et al.*, 2001).

SUMMARY

Depression has a profound negative impact on older adults, significantly decreasing quality of life, functioning, and increasing both medical morbidity and mortality. While rates of depressive disorders are no greater among the elderly

than in the general population, significant rates of depressive symptoms have been identified in elderly populations. Older persons with mental disorders rarely seek help from mental health professionals, preferring to visit their primary care physician instead. Nonetheless, depression among the elderly often goes unrecognized and untreated. However, when identified and addressed, depression, regardless of age, is a highly treatable illness. There are several psychotherapies that have been specifically developed for the treatment of depression, the most effective being CBT and IPT. There are antidepressant medications that are efficacious in treating the depressed elderly patient; moreover, a combination of medication and psychotherapy has been shown to produce the most positive outcomes.

KEY POINTS

- Depression, the most frequent cause of emotional suffering in later life is associated with significant losses in health-related quality of life.
- Depression is often comorbid with other disorders including dementia and medical problems.
- Etiological determinants of depression include psychological, biological, and developmental life-span theories.
- There is an association of suicide with depression.
- Depression often goes undetected and untreated; however, when identified, it is a highly treatable illness.

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The Older Patient with Down's Syndrome

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INTRODUCTION

The association between trisomy 21 and Down's syndrome was first recognized in 1959 by Lejeune, Gautier, and Tarpin. In recent times, the number of fetuses conceived with Down's syndrome has increased, but prenatal screening has resulted in a decline in the number of children conceived with this condition. Thus, the occurrence of Down's syndrome has decreased from 1 in 700 to 1 in 1000 live births (Roizen and Patterson, 2003).

In modern times, it is not unusual to see persons with Down's syndrome in their 60s. From 1983 to 1997, the median age of death of persons with Down's syndrome increased from 25 years of age to 49 years (Yang *et al.*, 2002). Another study suggested that the average life expectancy for Down's syndrome was in the mid-50s. The oldest reported person with Down's syndrome lived until 83 years of age. Three factors make the persons with Down's syndrome of interest to the geriatrician viz (1) the increasing life span; (2) the fact that these persons tend to develop early frailty and functional decline in their 40s; and (3) the early onset of Alzheimer's disease.

GENES AND DOWN'S SYNDROME

Three hundred and twenty-nine genes are predicted to be on chromosome 21. Sixteen of these genes play a role in mitochondrial energy metabolism or the generation of free radicals. Abnormalities in these genes are thought to lead to increased free radical production leading to premature aging.

At least ten genes on chromosome 21 play a role in brain development and neuronal loss. Two of these are associated with Alzheimer's disease, namely, the amyloid precursor protein and the S100 calcium binding protein. Overproduction of amyloid precursor protein and, thus, beta amyloid, is thought to play a key role in the early onset of Alzheimer's disease in persons with Down's syndrome. In addition, excess production of beta amyloid has been shown to lead to problems with learning and memory, which may contribute to the cognitive problems seen in persons with Down's syndrome.

There are six genes that are involved in folate and methyl group metabolism on chromosome 21. Elevated levels of homocysteine, which are seen in folate deficiency, are associated with Alzheimer's disease. In our clinical experience, elevated homocysteine levels are not rare in younger adults with Down's syndrome.

THE PHYSICIAN, AND THE PATIENT WITH DOWN'S SYNDROME

Older persons with Down's syndrome are usually easily recognized when they present to the physician, because of the classical facial features (brachycephaly, epicanthal folds, and flat nasal bridge) and short stature. These persons also often have broad hands, lax ligaments, and wide gap between the first and second toes, brachydactyly, and mental retardation. The majority of persons with Down's syndrome live in the community. They may live in group housing and work in sheltered workshops. Physicians need to identify the person who accompanies the individual with Down's to the office. This person often provides supervisory care for the individual with Down's and can provide useful historical information on behavioral and other changes that may be occurring. We recommend office visits every 6 months for healthy persons with Down's and every 3 to 4 months when functional or mental decline is present. This allows the patient to become comfortable with the health-care provider. Many patients enjoy hugging and this can further increase trust in the physician. However, the physician must remember to ask the patient first if they wish to hug. The physician should always discuss the patient's work and how it is progressing. Also, note should be made of their recreational activities, and how they are interacting with other persons within a group home.

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Always address the person with Down's directly, before hearing the caregiver's story. This gains their confidence and allows observation of their language ability. Finally, never assume that changes in persons with Down's syndrome are due to Down's itself before excluding other common medical causes.

For some medical examinations, for example, pap smears, and special tests, for example, MRI or CT scan, or procedures such as dental care, persons with Down's may require sedation. We have found that 0.5–1 mg of lorazepam orally is usually sufficient for this purpose and produces no adverse effects. Low dose intravenous lorazepam can also be used in more difficult situations. Others have recommended oral ketamine and midazolam, given under the supervision of an anesthetist (Smith, 2001). Before undergoing a procedure requiring sedation, a risk benefit evaluation should always be undertaken. Informed consent needs to be obtained from the patient or, where applicable, the court appointed guardian.

Preventive measures should be similar for Down's syndrome patients as for the general adult population. This includes screening for hypertension and heart disease. Because obesity is a common problem in this population, regular counseling on the need for exercise is mandatory. While, in our experience, most of the Down's patients do not smoke or drink alcohol, this should be confirmed both from the patient and the caregiver.

Down's adults tend to complain of pain, even when present, less often than other persons. Therefore, it is important to utilize facial expressions during the examination to obtain input concerning presence of pain. Also, such patients may stop using a limb when it is painful. Rocking and "head banging" behaviors occur as visceral pain proxies. As is the case with older adults, middle-aged adults with Down's often manifest medical problems as a delirium or other behavioral problem.

Persons with Down's are a vulnerable population, and thus, like children and older people, are at increased risk for abuse. When adults with Down's become withdrawn, this may suggest abuse or an unrecognized pain syndrome or depression. Presence of unexplained bruises, skin tears or fractures must increase the physician's suspicion of abuse. New onset falls can suggest delirium, functional deterioration or abuse.

Health counseling includes decisions on advanced directives and guardianship. Financial support questions need to be addressed, and relatives need to be aware of local resources. Estate planning, for example trusts, need to be created where appropriate, as Down's syndrome persons are now regularly outliving their parents and other close relatives. Parent (caregiver) support groups can be invaluable as caregiver stress is common, particularly as the parent ages. Local and national societies for Down's syndrome or for persons with developmental disabilities are an important resource. The physician needs to look for excess stress and/or depression in caregivers, and advise treatment where appropriate.

Functional ability using at least basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs) should be assessed yearly. Where possible, mental status screening using the Mini-Mental Status Examination (MMSE) or the Saint Louis University Mental Status Examination and the Geriatric Depression Scale or the Cornell Depression Inventory should be done yearly.

Table 1 Conditions that occur commonly in adults with Down's syndrome

Obesity
Periodontal disease
Hearing loss
Visual problems including early cataracts
Aortic valvular disease
– Mitral valve prolapse
– Aortic regurgitation
Arthritis
Hypogonadism (male)
Hypothyroidism
Hyperthyroidism
Diabetes mellitus
Early menopause
Osteoporosis
Celiac disease
Sleep apnea
Atlantoaxial subluxation
Testicular cancer
Seizures
Dermatological abnormalities
Depression
Alzheimer's disease
Delirium
Agitated behavior
Foot problems
Seizures

There are a number of disease conditions that occur more commonly in adults with Down's syndrome than in the general population (Table 1). "Health-Care Guidelines for Individuals with Down Syndrome" were developed by a consensus panel of the Down Syndrome Medical Interest Group (Smith, 2001). There is a lack of evidence in this area and so physician-substituted judgment is important in deciding which health-care screening approaches are most efficacious in this population.

DISORDERS ASSOCIATED WITH DOWN'S SYNDROME

Endocrinological

Congenital hypothyroidism occurs in 1 in 141 neonates with Down's and the prevalence increases with age. In adults with Down's between 15 and 40% of persons have hypothyroidism (Karlsson *et al.*, 1998). Its presentation is often insidious, and many of the early signs and symptoms are difficult to detect in patients with Down's. All patients with a recent decline in mental function need to be screened for hypothyroidism. Because of the frequency of hypothyroidism in this population, it is recommended that adult patients are screened by having a TSH measured every year. All patients with a TSH greater than $10\,\mathrm{mU\,l^{-1}}$ should be

treated, regardless of whether or not the thyroxine level is normal. Goiter and thyroiditis also occur commonly in this population. No studies have determined the utility of examining thyroid antibodies to determine which patients will progress to hypothyroidism. Thyroid cancer is extremely rare in this population.

Type 1 diabetes mellitus occurs in over 1% of young persons with Down's syndrome. No studies have examined the prevalence of type 2 diabetes mellitus in adults with Down's syndrome. However, in view of the high prevalence of obesity, it is generally believed that there is a higher prevalence. Similarly, the metabolic syndrome (insulin resistance, hypertension, hypertriglyceridemia, and hyperuricemia) is not rare in this group of patients. Uric acid levels are increased in the serum of most patients with Down's.

Male hypogonadism occurs fairly commonly in males in their 40s with Down's syndrome. It is predominantly of the secondary hypogonadism type, with low lueinizing hormone as well as low testosterone and bioavailable testosterone. Treatment with testosterone can stabilize mood and prevent loss of muscle and bone. Males with trisomy 21 have reduced fertility. Females have a premature menopause of 47.1 years compared to 51 years for the woman without developmental disabilities. At present, based on the findings of the Women's Health Initiative, we are not utilizing estrogen replacement in postmenopausal women with Down's.

Persons with Down's syndrome have lower peak bone mass and, therefore, are more likely to develop osteopenia and osteoporosis (Angelopoulou *et al.*, 1999). This is aggravated by the high use of anticonvulsant medicines in this age-group. Bone mineral density should be measured in all patients with Down's at the age of 50. Calcium and vitamin D administration should be initiated at age 40 for women. The use of hip pads should be considered in Down's patients who have frequent falls.

Otolaryngolic Conditions

Hearing loss occurs in up to two-thirds of persons with Down's syndrome (Venail *et al.*, 2004; Van Buggenhout *et al.*, 1999). This can worsen with aging. In addition, many middle-aged patients have further hearing deterioration because of common impaction. Hearing loss can aggravate speech problems and make the person appear more cognitively impaired than they are or to appear unresponsive to simple requests.

As many as half of the adults with Down's syndrome can have sleep apnea (Dahlqvist *et al.*, 2003). It is related, in part, to mid-facial hypoplasia and also to their short neck and obesity. While in patients it is of the obstructive type, central sleep apnea can also occur. Sleep apnea presents with daytime fatigue and somnolence and nighttime snoring with apneic periods. Behavioral changes such as irritability or withdrawal can result from sleep apnea. Diagnosis is made with a sleep study. Some patients will tolerate continuous positive airways pressure, but this is often rejected. Surgical approaches can help, but the failure rate is relatively high.

Table 2 Presentation of spinal cord compression in persons with Down's syndrome who have atlantoaxial subluxation

Neck pain
Gait disturbance
Clumsiness of hands
Torticollis
Incontinence
Hyperreflexia
Clonus
Quadriplegia/paresis
Positive Hoffman's and Babinski reflexes

Joint Problems

Children with Down's syndrome can develop a condition similar to juvenile rheumatoid arthritis. It is associated with subluxation of joints. The diagnosis is often delayed. Similarly, arthritis is often only diagnosed late in adults with Down's syndrome.

Atlantoaxial instability occurs in Down's syndrome, where there is excessive movement of the first cervical vertebra (atlas) on the second one (axis) (Ferguson *et al.*, 1997). The diagnosis is made when there is increased space between the posterior segment of the anterior arch of C1 and the anterior segment of the odontoid process. This occurs in 15% of patients with Down's syndrome. About 1–2% will have subluxation with neurological signs and symptoms consistent with spinal cord compression (Table 2). When this occurs, it is a neurosurgical emergency. However, outcomes of surgery are often poor.

Severe cervical and lumbar-sacral osteoarthritis are fairly common. This is associated with pain, gait disturbance, sometimes hand clumsiness, difficulty in moving and associated behavioral disturbances.

Celiac Disease

Celiac disease is a malabsorption syndrome that occurs in response to the ingestion of gluten products. It occurs in as many as 7% of Down's syndrome patients (Carnicer *et al.*, 2001). It is screened for at 24 months of age. Symptoms include diarrhea and weight loss. Diagnosis is made by serum antibodies and intestinal biopsy. Celiac disease can present for the first time later in life, and should be considered as the diagnosis in any Down's patients with unexplained weight loss or diarrhea.

Dermatological Conditions

Vitiligo and alopecia are seen in adults with Down's syndrome. Dry skin is extremely common and often associated with pruritus. Fungal infections are common and often

difficult to eradicate. Seborrheic and atopic dermatitis also occur frequently. A fissured or geographic tongue is present in almost a third of patients with Down's syndrome.

Cardiovascular Disorders

Congenital heart disease occurs in about half the children born with Down's syndrome (Howells, 1989). Some of these, such as isolated secundum atrial septal defects, may have been missed in childhood and present for the first time in adults. Mitral valve prolapse occurs in about half of patients and aortic regurgitation in 17%. In the presence of signs or symptoms, an echocardiogram should be carried out. Alterations in cardiac conduction are not rare and should be considered in those with new onset falls with or without syncope. In those with valvular defects, antibiotic prophylaxis needs to be given before dental care or other instrumentation.

In view of the high prevalence of insulin resistance in this population, atherosclerotic heart disease is not rare and occurs at a younger age. Angina often goes unreported in this population.

Dental Problems

Gingivitis and periodontal disease are common and lead to tooth loss. Orthodontic problems are common and may not have been able to be corrected during childhood. Bruxism is not rare.

Cancer

In children, both acute lympoblastic and myeloid leukemia occur with increased frequency (Roizen and Patterson, 2003). While most cancers occur with a decreased frequency in persons with Down's syndrome (Roberge *et al.*, 2001; Goldacre *et al.*, 2004), testicular cancers appear to be more common.

Foot Problems

These include hallux valgus, hammer toe deformities, plantar fasciitis, and early onset of foot arthritis. All of these can result in unstable gait and increased falls. Feet should be examined regularly and the services of a podiatrist utilized when necessary.

Gynecological Problems

Where possible, as in any other adult, papanicolau smear and pelvic examination should be carried out. This is often extremely difficult and may need to be deferred. Similarly, mammography should be carried out when feasible. Breast examinations should be done yearly.

Table 3 Approximate prevalence of Alzheimer's disease in persons with Down's syndrome

Age (years)	% Alzheimer's
31–40	10
41–50	20
51–60	40
61–70	75

Eye Disorders

Refractive errors are present in 40% of adults. Cataracts occur in 3% of patients and keratoconus is present in 15% of patients.

Alzheimer's Disease

Alzheimer's disease occurs commonly in Down's syndrome patients, starting at the age of 30 (Table 3) (Lott and Head, 2001; Schweber, 1989). Over three-quarters of patients, by the time they reach 70 years of age, will have some symptoms of Alzheimer's disease. The diagnosis of Alzheimer's disease is very difficult to make in persons with Down's syndrome. Common early changes are memory loss, loss of conversational skills, withdrawal and functional decline. The diagnosis requires the careful exclusion of other causes of dementia such as drugs, depression, hypothyroidism, vitamin B_{12} deficiency, visual and auditory problems, space occupying lesions, for example, bilatent subdural hematomas following a fall, or infections. Late presentations associated with Alzheimer's disease include seizures, apathy, focal neurological signs and personality changes.

Epilepsy

Seizures occur in about 8% with half occurring with the first year of life and half in the third decade or later (Stafstrom, 1993). We are particularly impressed with the ease of use of kepra, compared to dilantin, in these patients.

Behavior Disorders

Depression occurs commonly. Loss of a parent or caregiver can precipitate depression, as can change in a familiar environment. Problems within the social environment of a group house can also precipitate depression. Most of those who are depressed are treated with selective serotonin reuptake inhibitors. These agents can cause hyponatremia, leading to delirium.

Aggressive behavior occurs in about 6% of adults with Down's syndrome. Management is difficult. Valproic acid, trazadone, lorazepam, and antipsychotics have all been tried with limited success. Oversedation is often a complication of these treatments.

CONCLUSION

Middle-aged persons with Down's syndrome often present with all the special needs of frail-older adults. For this reason, geriatricians are the ideal physicians for this group. In addition, some of the special needs of this population make it preferable for them to utilize a physician who cares for a number of patients with Down's syndrome. The physician needs to work closely with the interdisciplinary team that provides day-to-day care for these individuals.

KEY POINTS

- Down's syndrome (trisomy 21) is associated with early onset of frailty and Alzheimer's disease.
- Sleep apnea occurs commonly in Down's syndrome.
- Hypothyroidism, diabetes mellitus, osteoporosis and celiac disease occur more commonly in Down's syndrome.
- Subluxation of the cervical spine can lead to spinal cord damage in Down's syndrome and is a neurosurgical emergency.

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Drug Misuse and the Older Person: A Contradiction in Terms?

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INTRODUCTION

This chapter will provide a description of the terminology and classificatory systems for drug problems. The epidemiology of drug misuse will then be outlined. There will be a summary of associated psychological and physical complications. Most importantly, attention will be drawn to the effectiveness of treatment interventions in both the pharmacological and psychosocial domains. Some suggested options for ways forward in service delivery and policy are presented.

WHY IS THIS IMPORTANT TO THE CLINICIAN?

No major specialty or subspecialty in medical practice can *avoid* drug misusers. Accident and emergency units, and departments of cardiology, dermatology, gastroenterology, neurology, infectious diseases, and general surgery, as well as those of trauma and orthopedic surgery, will generate their share of older patients with drug-related problems, as will psychiatric specialities such as liaison psychiatry (Fingerhood, 2000). It is well worth noting that even if the patient presents with a drug problem, this may not be his or her major problem. This is because older people may present with abstinence syndromes, convulsions, acute disturbance (psychosis, panic, confusion, perceptual dysfunction), trauma, cancer, or cardiovascular conditions.

Brennan *et al.* (2000) have conducted a study of the characteristics and predictors of hospital readmissions over a 4-year period in elderly medicare inpatients with substance-use disorders. This group found that elderly substance misusers make costly, relatively heavy use of inpatient health services. Elderly women and blacks more often have prior substance-related hospitalizations, psychiatric comorbidities, and accidents (falls, adverse drug reactions, poisoning). Diagnosis at baseline discharge can identify high-risk patients, and plans can be made accordingly.

WHAT IS A DRUG?

In the context of this chapter, the term "drug" will be used to cover illicit substances, central nervous system depressants such as opiates and opioids (for example, heroin and methadone) stimulants such as cocaine, crack, amphetamine and ecstasy, and LSD, khat and magic mushrooms. It will also be used to describe street-use and noncompliant use of prescription drugs such as benzodiazepines, and noncompliance in the use of over-the-counter preparations such as codeine-based products, for example, cough medicines, decongestants.

Although tobacco and alcohol are beyond the scope of this chapter, it should be noted that clinical experience and a growing literature base indicate that people may use a combination of licit and illicit substances, as well as prescribed and over-the-counter medications (used compliantly and noncompliantly). This so-called *polypharmacy* or *polydrug misuse* is a particular issue in older people who have physical or psychological comorbidity. This is what makes this work challenging and stimulating! Patients may borrow, share, not report all medications, use out-of-date drugs, take foods and drugs that interact, and store drugs inappropriately.

Of course, "misuse" may be the result of lack of judgment, misconceptions about the drug(s), inability to purchase medications, inability to manage the combination of medications (due to memory problems, for instance), or they may be intentionally using medications for purposes other than they should.

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EPIDEMIOLOGY – DRUG MISUSERS DO SURVIVE INTO OLD AGE

It has been reported that one in ten older people are receiving a drug that is potentially inappropriate (Gottlieb, 2004). Older people not only receive most of the prescriptions in the United Kingdom but are also being dispensed multiple medications. Multiple analgesic drug use is a particular problem (Chrischilles *et al.*, 1990). The prevalence of psychotropic drug misuse is four times greater in women than in men, and the risk of dependence is enhanced if the woman happens to be widowed, less educated, of lower income, in poor health and with reduced social support (Kelly *et al.*, 2003).

Opiate-dependent people do survive into old age (Lynskey *et al.*, 2003). In the United States the lifetime prevalence rates for illicit drug dependence are 17% for 18–29 years old, 4% for 30–59 years old and less than 1% for the over-60 age-group (Hinkin *et al.*, 2002). Older women drink less, smoke less, and use less illicit drugs than other age–gender groups (Graham *et al.*, 1995).

The Office for National Statistics study of psychiatric morbidity (Coulthard *et al.*, 2002) utilized a number of questions to measure drug use (frequency, started dependence, inability to cut down, need for larger amounts, withdrawal symptoms). Dependence on cannabis only, on another drug, and nondependence were gauged. Age of first use, overdose, injecting, and treatment sought were additional. Data on ages 16–74 were reported. This report indicated that lifetime experience of any illicit drug was 84/1000 in the 55–59 age-group, 65/1000 in the 60–64 age-group, 24/1000 in the 65–69 age-group, and 34/1000 in the 70–74 age-group. Comparable figures for illicit drug use over the last year are 19, 10, 6, and 11 per thousand, and for the last month 7, 7, 2, and 2 per thousand respectively. Over the previous month and year, older people tended to use cannabis and tranquilizers, with some lifetime use of stimulants, magic mushrooms and heroin (Figure 1). In addition, 9% of those in the 55–59 age-group who had ever taken drugs had experienced an overdose, as had 5% of those over 60 who had ever taken drugs. Thus, drug misuse is a problem in older people, which is captured by national datasets.

It has also been established that around half of all elderly people have seen their GP in the last three months, with one-quarter seeing a hospital doctor. Many older people have contact with primary care as well as many other health service providers, who are in a position to assess their substance use. Furthermore, in an epidemiological study of psychiatric illness and substance misuse in primary care, a 27% increase in comorbidity occurred in those aged 75–84. This was due to dependence on licit substances, that is, benzodiazepines, and resulted in confusional states (Frischer *et al.*, 2003). These recent studies demonstrate that there may be some differences in rates of different types of comorbid conditions in older people compared to younger people (Speer and Bater, 1992), and further underline the cumulative effects of benzodiazepines reported earlier (Morgan *et al.*, 1988).

DRUG USE AND MENTAL HEALTH

Psychiatric Comorbidity

In this section the term comorbidity is used to describe the co-occurrence of psychiatric disorder and substance misuse

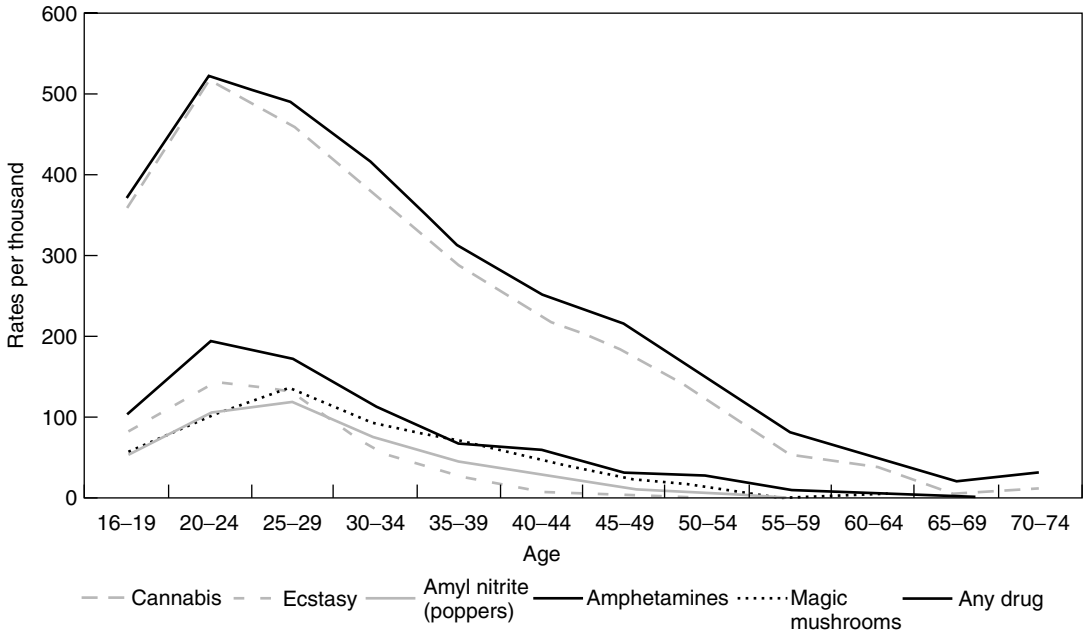

Figure 1 Proportion in each age-group reporting ever using each of the five most commonly used drugs by age (From Coulthard *et al.*, (2002) *Tobacco, Alcohol, and Drug Use, and Mental Health*. London: The Stationery Office.)

(Day and Crome, 2002; Crome and Day, 2002; Banerjee *et al.*, 2002; Waller and Rumball, 2004). Psychoactive substances have differing psychological effects, including those caused by intoxication and withdrawal. Chronic use, intoxication with depressant drugs, and withdrawal from stimulants produce symptoms similar to depressant drugs, while acute intoxication from stimulants and cannabis may mimic a schizophrenic illness. Withdrawal from depressant drugs may result in symptoms of anxiety, panic, and even confusional states. These complex interactions have implications in that not only does drug use interfere with emotional, cognitive, and social behavior but the combination of disorders also results in poorer treatment compliance and both short- and longer-term outcomes.

An association between drug use and psychiatric conditions has been consistently documented in substance-misusing clinical populations, psychiatric populations, the general population, prisons, and the homeless. Indeed, in the well-known Epidemiological Catchment Area (ECA) study, drug addiction was associated with a 53.1% lifetime rate of an additional mental disorder (Regier *et al.*, 1990).

Furthermore, the interrelationships between physical health, mental health, and drug misuse are well documented. Apart from the direct effects of drugs on general health (see later), there are indirect effects such as dietary neglect, impoverishment, trauma, bereavement, and loss. Malnutrition, for instance, may emanate from drug-induced anorexia, malabsorption, and economic deprivation. Liver dysfunction, for example, HIV, Hepatitis B and C, produces psychological as well as physical problems.

Psychiatric conditions such as anxiety, depression, posttraumatic stress disorder, drug-induced psychosis, schizophrenia, delirium, and dementia may lead to, be a consequence of, or coincide with drug misuse. Withdrawal from barbiturates and benzodiazepines leads to delirium, whereas head injuries and serious infections are associated with dementia. The differing mechanisms and types of relationship demand careful history-taking and judicious interpretation. Depression, dementia, delirium, and a heightened risk of suicide are probably the problems most commonly faced by clinicians. Of course, some of these conditions are associated with chronic pain and sleep disorders, which may make patients vulnerable and lead to them seeking relief from prescription and nonprescription medications in a noncompliant fashion.

Because there are effective medications and psychosocial interventions available for many psychiatric conditions, correct diagnosis, and treatment or referral have tangible benefits.

Physical Comorbidity

The health risks which drug use poses include the pharmacological action, for example, toxicity of the drug itself, the route of use, blood-borne pathogens, contaminants, unknown purity, and quantity. The adverse effects are summarized in the following section (Banerjee *et al.*, 2002).

Benzodiazepines

In the short term, users may experience tiredness, depressed respiration, dizziness, and unsteadiness. With other depressants, for example, alcohol and opiates, overdose can be fatal. Dependence can develop on low doses, and convulsions occur with withdrawal. Rebound symptoms such as insomnia, anxiety, and tension can occur.

Opiates and Opioids

Diverted pharmaceutical opiates and opioids may be formulated for injection or oral use, or as suppositories. Tablets may be crushed and injected.

Heroin may be inhaled, snorted, smoked, or injected intravenously, intramuscularly, or subcutaneously. Dependence can develop rapidly, that is, within weeks. Since tolerance also develops rapidly, but diminishes quickly after abstinence, relapse can lead to overdose and death. This is also the case for methadone.

Opiates and opioids depress coughing, breathing, and heart rate, dilate blood vessels, reduce bowel activity, and produce constipation. Overdose usually occurs in combination with other drugs. Injecting carries the risk of HIV and Hepatitis B and C, as well as septicemia and infective endocarditis, which can lead to heart failure.

Cannabis

Cannabis use can lead to depression, anxiety, and paranoia. Panic attacks are a feature, and there is controversy as to whether cannabis "causes" an enduring schizophrenia-like psychosis or simply exacerbates it. Memory and learning are affected. Cannabis is smoked, and evidence is accumulating of the risk of lung cancer, and cancers of the head and neck.

Amphetamines and Cocaine

Use of stimulants may lead to anxiety, exhaustion, depression, and weight loss. A paranoid and/or confusional state may also occur. Hypertension, cardiac arrhythmias, stroke, hepatic and renal damage, and abscesses are the result of heavy use, especially if injecting. Violent and aggressive behavior may ensue. Snorting of cocaine leads to nasal septal perforation and damage to the nasal passages.

Despite all these complications, an early study by McInnes and Powell (1994) demonstrated that most patients assessed by medical staff were not being accurately diagnosed with problematic substance misuse. The main implication was that treatment would, therefore, be denied.

THE IMPORTANCE OF A THOROUGH ASSESSMENT

A Very High Index of Suspicion is Necessary

In order to get to grips with the way in which older people may be affected by substances, the two most important

elements are a very high index of suspicion that older people are using and/or misusing several different substances *and* a thorough history (King *et al.*, 1994).

A Comprehensive History is Fundamental

Although several instruments specifically developed for the assessment of older people have evolved in the clinical situation, there is no substitute for a comprehensive history. A detailed protocol is included in this chapter, but a highly personal style may develop on this foundation. As long as key components are incorporated, potentially related to the patient's clinical condition, any permutation is up to the individual clinician. There are some complaints or symptoms that might alert the physician, especially if the patient is undergoing some life transitions, for example, retirement, bereavement, or new carer responsibilities.

Diagnosis is Based on a Set of Established Criteria

In order to reach a "diagnosis", the two systems that have emerged are the International Classification of Diseases (ICD-10) (World Health Organisation, 1992) and the American Psychiatric Association's Diagnostic and Statistical Manual (DSM IV) (American Psychiatric Association, 1994). The criteria required to reach a diagnosis of either harmful use or dependent use are to be found in Tables 1 and 2. These systems have similarities, but they are not identical.

Table 1 Criteria for substance abuse (DSM IV) and harmful use (ICD10)

DSM IV (APA, 1994)	ICD10 (WHO, 1992)
(A) A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following occurring within a 12-month period 1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home 2. Recurrent substance abuse in situations that are physically hazardous 3. Recurrent substance-abuse-related legal problems 4. Continued substance abuse despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (B) Has never met the criteria for substance dependence for this class of substance	(A) A pattern of psychoactive substance use that is causing damage to health; the damage may be to physical or mental health

Distinction Between Dependence and Harmful Use

However, from the perspective of the clinician, *the* most important issue is to be able to determine with regard to the range of substances, whether patients are dependent on them, or are engaging in harmful use. This differentiation is critical

Table 2 Criteria for dependence syndrome in DSM IV and ICD10

DSM IV (APA, 1994)	ICD10 (WHO, 1992)
(A) Diagnosis of dependence should be made if three (or more) of the following have been experienced or exhibited at any time in the same 12-month period	(A) Diagnosis of dependence should be made if three or more of the following have been experienced or exhibited at some time during the last year
1. Tolerance defined by either need for markedly increased amount of substance to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount of the substance	1. A strong desire or sense of compulsion to take the substance
2. Withdrawal as evidenced by either of the following: the characteristic withdrawal syndrome for the substance or the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms	2. Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use
3. The substance is often taken in larger amounts over a longer period of time than was intended	3. Physiological withdrawal state when substance use has ceased or been reduced, as evidenced by either of the following: the characteristic withdrawal syndrome for the substance or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms
4. Persistent desire or repeated unsuccessful efforts to cut down or control substance use	4. Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects	5. Progressive neglect of alternative pleasures or interests because of psychoactive substance use and increased amount of time necessary to obtain or take the substance or to recover from its effects
6. Important social, occupational, or recreational activities given up or reduced because of substance use	6. Persisting with substance use despite clear evidence of overly harmful consequences (physical or mental)
7. Continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem that was likely to have been caused or exacerbated by the substance	

in terms of decisions around the selection of appropriate treatment interventions (in terms of type and intensity) and suitability of settings.

Ongoing Process That Aids Communication and Coordination

Thus, assessment is an ongoing process, the summation of each phase of which can be communicated to the patient, carers, and other professionals. A phasic assessment can be utilized to monitor change, establish to what extent goals have been achieved, and coordinate care with other disciplines or agencies.

The Use of Investigations

In order to corroborate the verbal history provided by the patient, carers and professionals, and clinical findings, biochemical tests on blood, saliva, sweat, urine, and hair can be undertaken (Wolff *et al.*, 1999). In clinical practice, urinalysis, and more recently saliva, are most commonly used to test for drugs. Cannabis, methadone, and long-acting benzodiazepines may remain in the urine for a week or longer, but other drugs may not be found after 48–72 hours. Thus, if drugs are *not* detected, this does not necessarily indicate that the patient has *not* been using. If a patient is assessed as being dependent, the clinical picture may be that of a withdrawal syndrome: every drug has a specific set of criteria by which withdrawal can be diagnosed (Tables 3–6).

Since these criteria were established on the basis of an adult population, some may not apply to older people. For instance, older people may have substance-related problems without the development of tolerance; they may not develop dependence; cognitive impairment may interfere with noticing whether they need to take larger amounts over a longer period; negative effects may take a shorter time to develop; they may have fewer activities to give up; they may not appreciate that their problems are related to substance use.

Table 3 Symptoms of intoxication and withdrawal

Benzodiazepine intoxication	*Benzodiazepine withdrawal*
Euphoria, disinhibition, lability of mood	Confusion and convulsions
Apathy, sedation	Tremor, postural hypotension
Abusiveness and aggression	Nausea and vomiting
Impaired attention, amnesia	Agitation
Impaired psychomotor performance	Paranoid ideation
Unsteady gait, slurred speech, nystagmus	Tachycardia
Decreased level of consciousness, hypothermia	Rebound insomnia, tension
Opiate intoxication	*Opiate withdrawal*
Apathy, sedation, disinhibition, psychomotor retardation, impaired attention, impaired judgment	Craving
	Sneezing, yawning, runny eyes
	Muscle aches, abdominal pains
Interference with personal functioning	Nausea, vomiting, diarrhea
	Pupillary dilatation
Drowsiness, slurred speech, pupillary constriction	Goose flesh, recurrent chills
	Restless sleep
Decreased level of consciousness	
Cannabis intoxication	*Cannabis withdrawal*
Euphoria and disinhibition	Anxiety
Anxiety and agitation	Irritability
Suspiciousness and paranoid ideation	Tremor
Impaired reaction time	Sweating
Impaired judgment and attention	Muscle aches
Hallucinations with preserved orientation	
Depersonalization and derealization	
Increased appetite	
Dry mouth	
Conjunctival injection	
Tachycardia	
Stimulant intoxication	*Stimulant withdrawal*
Euphoria and increased energy	Lethargy
Hypervigilance; repetitive stereotyped behaviors	Psychomotor retardation or agitation
Grandiose beliefs and actions	Craving
Paranoid ideation	Increased appetite
Abusiveness, aggression, and argumentativeness	Insomnia or hypersomnia
	Bizarre and unpleasant dreams
Auditory, tactile, and visual hallucinations	
Sweats, chills, muscular weakness	
Nausea or vomiting, weight loss	
Pupillary dilatation, convulsions	
Tachycardia, arrhythmias, chest pain, hypertension	
Agitation	

TREATMENT INTERVENTIONS

Pharmacological Interventions

Pharmacotherapies are available to treat a variety of situations, such as:

- emergencies, for example, overdose, fits, dehydration, hypothermia;
- detoxification and withdrawal syndromes, for example, lofexidine, methadone, buprenorphine;
- substitution, for example, methadone, buprenorphine;
- relapse prevention, for example, naltrexone;
- comorbid substance problems;
- comorbid psychiatric disorders;
- comorbid physical disorders, for example, HIV, Hepatitis C, diabetes.

Readers are advised to access recent guidelines from the British Association of Psychopharmacology (BAP), which summarize the evidence base for the pharmacological treatment of substance misuse and comorbid conditions. The findings which follow are drawn from this document (Lingford-Hughes *et al.*, 2004).

Summary Recommendations from the BAP Guidelines

There is considerable evidence for the use of methadone, buprenorphine, and α-2 agonists (clonidine and lofexidine)

Table 4 Suggested outline for schedule of issues to be covered in assessment

Demographic characteristics	Age Gender Employment, retired, unemployment Nationality, religious affiliation, ethnicity, and culture Living arrangements, for example, with parent(s), spouse, relatives, friends, homeless, institutional care General environment, for example, deprivation, affluence, violence
Presenting complaint(s) or problems	May or may not be a substance problem or mental health issue
Each substance should be discussed separately: Alcohol Amphetamines Benzodiazepines Cannabis Cocaine Ecstasy Heroin and other opiates Methadone Nicotine Over-the-counter medication Prescribed medication	Age of initiation "first tried" Age of onset of weekend use Age of onset of weekly use Age of onset of daily use Pattern of use during each day Route of use, for example, oral, smoking, snorting, intramuscular, intravenous Age of onset of specific withdrawal symptoms and dependence syndrome features Current use over previous day, week, month Current cost of use Maximum use ever How is the substance use being funded? Periods of abstinence Triggers to relapse Preferred substance(s) and reasons
Treatment episodes for substance problems	Dates, service, practitioner details, treatment interventions, success or otherwise, triggers to relapse
Family history	Parents, siblings, children. History of substance misuse and related problems History of psychiatric problems, for example, suicide, deliberate self harm, depression, anxiety, psychotic illness History of physical illness Separation, divorce, death Family relationships, conflict, support Occupational history
Medical history	Episodes of acute or chronic illnesses: respiratory, infective, HIV, hepatitis, injury including accidents, surgery Admission to hospital, dates, problems, treatment, and outcome
Psychiatric history	Assessment by general practitioner for any "minor" complaints, for example, anxiety, depression Treatment by general practitioner with any psychoactive drugs Referral to specialist psychiatric services: dates, diagnosis, treatment, and outcome Mental Health Act assessments
Personal history	Occupational, sexual, marital relationships
Educational background	Age started and left school Achievements and aspirations
Vocational history	Ongoing activities and plans
Criminal activities	Involvement in criminal activities preceding or directly related to substance problems Cautions, charges, convictions Shoplifting, violence, prostitution
Social services	Child abuse and neglect Social service involvement
Social environment	Level of community support and network
Social activities	Sports, hobbies, community work, religious affiliation and activities
Financial situation	Debt to finance substance problems
Useful information	Current address Phone number including mobile phone General practitioner's name, address, and phone number Details of other professionals involved
Investigations	Biochemical, hematological, urinary, salivary, sweat, hair Special investigations
Collateral information	Family and friends Occupational colleagues, if appropriate Social services Criminal justice agencies Health services Voluntary agencies
Consent and confidentiality	

Table 4 (*continued*)

Current stressors	Bereavement, marriage, divorce, ongoing legal problems
How the client perceives the problems and what they want	Belief systems
Profile of strengths and risks	
Readiness to engage in treatment	
Mental state examination	
Physical examination	

Table 5 Testing for current drug use (maximum range)

Drug	Maximum range
Cocaine	12–72 hours
Amphetamines	2–4 days
Heroin	2–4 days
Codeine	2–4 days
Cannabis	30 days
Diazepam	30 days

Source: Adapted from Banerjee *et al.*, (2002) *Coexisting Problems of Mental Disorder and Substance Misuse*. London: Royal College of Psychiatrists Research Unit.

Table 6 Some features of withdrawal that necessitate immediate medical attention

- Ingestion of unknown quantities of substances
- Trauma
- Confusion or delirium
- Fever
- Tachycardia
- Tremulousness
- Hallucinations
- Paranoid behavior

Source: Adapted from Banerjee *et al.*, (2002) *Coexisting Problems of Mental Disorder and Substance Misuse*. London: Royal College of Psychiatrists Research Unit.

in the management of withdrawal states. However, *all* this available evidence relates to younger adults. There are differences in choice of medication, depending on the priorities around duration of treatment, adverse effects (brachycardia and hypotension due to α-2 adrenergic agonists), and withdrawal severity. Obviously, the patient's clinical condition, degree of dependence, preference, and practitioner experience will determine which drug to use.

Similarly, there is an established evidence base for methadone maintenance treatment and, more recently, for buprenorphine. Once again, this relates to younger people.

There is inadequate evidence for treatment with naltrexone and injectable opioids, and for using coercive methods.

For stimulant drugs such as cocaine and amphetamine, the guidelines do *not* recommend the use of dopamine agonists, antidepressants, or carbamazepine. Furthermore, there is no clear evidence to support substitute prescribing of dexamphetamines. In fact, "psychosocial" interventions are considered the "mainstay" of treatment, although the evidence is limited.

The guidelines also make recommendations for benzodiazepine dependence, whether licitly used on a prescription, or its illicit use. In early or mild dependence, "minimal" interventions, for example, relaxation or general practitioner advice are suggested. For more severe dependence, graded discontinuation is advised.

For "illicit" misusers, there is no evidence that continued prescribing is beneficial, other than to reduce illicit use.

It must be reiterated that the above advice is related to an adult population.

Psychological Interventions

The majority of interventions are based on learning theory models, but there is also the recognition that there are non-treatment routes to improvement (Crome and Bloor; 2005; Crome and Ghodse; in press). Furthermore, information-based approaches, for example, health education and information, are useful in less complex situations. These might include education about harm minimization, immunization, and vaccination.

In the addiction literature, the term counseling is used to incorporate brief or intensive interventions, be they supportive, directive, or motivational counseling, individual, family, or group behavioral treatments, as well as social network behavioral therapy. Counseling may aim to reduce the use of alcohol and drugs, as well as the negative consequences or related problems.

The term may encompass assessment, engagement and support, together with the development of therapeutic relationships. The nonjudgmental and empathic method of challenging decisions and assumptions in motivational interviewing is included in the gamut of techniques.

Important common objectives may include:

- problem solving: developing competence in dealing with a specific problem;
- acquisition of social skills: mastery of social and interpersonal skills by assertiveness or anger control;
- cognitive change: modification of irrational beliefs and maladaptive patterns of thought;
- behavior change: modification of maladaptive behavior;
- systemic change: introducing change into family systems.

Counseling is a widely used term and is a form of therapy or intervention, which includes a wide range of theoretical models. There are many different definitions,

each emphasizing specific aspects of the counseling role and processes practiced in a multiplicity of settings. It embodies psychodynamics, cognitive, behavioral, and person-centered approaches.

There are various options, the choice of which depends on the nature and extent of the problems and which approach may appear more appropriate and suitable for a particular drug user. The options include:

counseling
cognitive behavioral therapy
family dynamics
group therapy
motivational enhancement.

Nondirective counseling comprises the following components. The patient determines the content and direction of the counseling and explores conflict and emotions at the time. While allowing empathic reflection, the counselor does not offer advice and feedback.

A cognitive behavioral approach assumes that the patient would like to change, and analyzes situations that cause drug use, so that these can be altered. Problem-solving techniques, self-monitoring, anger management, relapse prevention, assertiveness training and the acquisition of social skills, and modification of irrational beliefs or patterns of thought or behavior are used. Individual, group, and family therapies used in the treatment of addiction problems are often based along cognitive behavioral lines.

Social network behavior therapy considers the social environment as being important in the development, maintenance, and resolution of substance problems. It maximizes positive social support, which is central to the process. The therapist offers advice and feedback and thereby facilitates change in the patient's social world; behavior is not interpreted, and engagement with significant others is the key in bringing about change and achieving goals.

Family therapy involves attempts to understand and interpret the family dynamics in order to change the psychopathology. Substance use is perceived as a symptom of family dysfunction and, therefore, altering the dynamics brings about change in substance misuse. Family members are viewed as contributory to the problems. Behavioral techniques may be used in family therapy as well as psychodynamic techniques.

Group therapies and 12-step programs. Participation in self-help groups is an important feature of many treatment programs where participants receive support from recovering members who often take members back to the negative consequences of substance misuse. A variant of group therapy is the 12-step approach. Central to the 12-step philosophy is the idea that recovery from addiction is possible only if the individual recognizes his or her problem, and admits that he or she is unable to use substances in moderation. Alcoholics Anonymous and Narcotics Anonymous are examples of the "12-step" philosophy where drug users have to abstain completely.

Recently, the most influential and popular form of treatment has been a "brief" or "minimal" intervention, designated *motivational interviewing*.

Motivational interviewing aims to build motivation for change. The focus is on a nonjudgmental approach and the patient's concerns about, and choices regarding future drug use, and it elicits strategies from the patient. Motivational enhancement directs the patient to motivation for change by offering empathic feedback and advice and information and selectively reinforces certain discrepancies that emerge between current behavior and goals in order to enhance motivation for change. Significant others play some role in the treatment but not a central role. It is, by and large, a personal therapeutic situation where the individual's motivation is seen as central. It aims to alter the decisional balance so that patients themselves direct the process of change.

The key characteristics are best described by the acronym FRAMES (Miller and Sanchez, 1994):

- personalized **f**eedback or assessment results detailing the target behavior and associated effects and consequences on the individual;
- emphasizing the individual's personal **r**esponsibility for change;
- giving **a**dvice on how to change;
- providing a **m**enu of options for change;
- expressing **e**mpathy through behaviors conveying caring, understanding, and warmth;
- emphasizing **s**elf-efficacy for change and instilling hope that change is not only possible, but also within reach.

This technique has not been evaluated in older substance misusers but evidence is accumulating with regard to the benefits and cost-effectiveness of this type of intervention (Dunn *et al.*, 2001; Project MATCH Research Group, 1997, 1998).

Treatment Effectiveness

Adult Population

The first relatively long-term, prospective, observational study on outcome in drug misusers in the United Kingdom, the National Treatment Outcome Research Study (NTORS), has been under way since 1995 (Gossop *et al.*, 2003). This study follows up 1075 drug misusers in two types of residential services (inpatient and residential units), and two kinds of community services (methadone reduction and methadone maintenance). The age range was 16–58, half of whom were responsible for caring for children. The older age-group has not been analyzed or reported on, separately.

Most important to note is that the specific nature of the treatment modalities provided has not been identified or described in any depth or in detail. Opiates, amphetamines, cocaine, nonprescription benzodiazepines and alcohol were assessed. The impact of treatment on psychological health, suicide, mortality, and crime was evaluated. In summary, the

study reported that drug use as well as injecting and sharing needles was reduced. Crime also decreased with concurrent improvement in physical and psychological health. However, 20% of the study population continued to use daily, and 40% continued to use once a week. Over the 5-year period, 62 people died, alcohol use remained at a constantly high level, and 80 were using two or more illicit drugs and were long-term users. There was a history of treatment for psychiatric disorder in the 2 years prior to treatment, and in the 3 months prior to treatment 30% had suicidal ideation.

At 5 years, between 33.3% and 50% of users achieved abstinence in community and residential services respectively. However, 20% were still using daily. While 40% used illicit drugs regularly, this had reduced from 66% at intake in the residential services and 80% in community services.

In summary, daily and regular use was found in 20–40% respectively. Likewise, injecting reduced from 60–40%, criminal activity halved, and 25% were drinking above safe limits. This evidence is encouraging despite the limitations in design described above. The study points to some value in the treatment programs, which are currently being implemented in the United Kingdom. Of course, this study was on an adult population.

Older People

Recently, Satre *et al.*, (2004) reported a 5-year alcohol and drug treatment outcome study as a comparative study of older adults (aged 55–77) versus younger and middle-aged people. They found that older adults were less likely to be drug dependent at baseline than younger (aged 18–39) and middle-aged (aged 40–54) adults, and had longer retention in treatment than younger adults. At 5 years, older adults were less likely than younger adults to have close family or friends who encouraged alcohol or drug use. Fifty-two percent of older adults had been totally abstinent from alcohol and drugs in the past 30 days, versus 40% of younger adults. Older women had higher 30-day abstinence rates than older men or younger women. Thus, although older adults had a favorable long-term outcome, these differences may be accounted for by variables associated with age, for example, type of substance dependence, treatment retention, social network, or gender. This data provides valuable information on which to base service provision, for example, persistence in treatment has long lasting benefits, the need for adequate social support, less likelihood of encouragement to use substances from family and friends.

Satre *et al.* (2003) also demonstrated that older patients are more likely to have an abstinence goal and a lower rate of psychiatric symptoms than younger people. This view has been substantiated by Oslin *et al.* (2002).

A further study by Brennan *et al.* (2003) indicated that older substance misusers are obtaining specialized outpatient mental health services, as are younger patients. In this study, older patients were less likely to be experiencing drug problems and psychiatric problems, but more likely to report alcohol and medical problems. This equality of gaining access was despite the fact that older people perceived the relative importance of treatment for psychological problems as less than younger people. Thus, the authors raise the interesting question of why older people appear to be more robust than younger people. Indeed, in this study, older patients had better outcomes than a matched sample of younger patients.

It is also worth mentioning in this context a study on the effects on mortality of brief interventions for problem drinking. In this meta-analysis Cuijpers *et al.* (2004), demonstrated that brief interventions appear to reduce mortality. This has far-reaching implications for public health measures, the role of primary care and, potentially, application to the drug-misusing population.

POLICY

There has been a plethora of policy initiatives around drugs in the United Kingdom. These include the following:

- Clinical guidelines on the management of drug misuse and dependence (1999).
- Tackling drugs to build a better Britain (1998).
- The national drugs strategy (Cabinet Office, 2000a,b).
- Models of care (NTA, 2002).

Attention should also be drawn to the Misuse of Drugs Act (1971) and the Misuse of Drugs Regulations (2001) (see Tables 7 and 8).

It is fair to say that these have been targeted at young people, with little or even *no* mention of older people. Furthermore, the National Service Framework for Older People (Department of Health, 2001) did not even raise the real possibility of dependence and addiction in older people, although some attention was given to the problem of prescription drugs. Hence, *no* suggestions about service delivery, training, and research in this invisible group were made.

To my knowledge, there is no designated service provider for older people with drug problems in the United Kingdom, and few elsewhere. The United States Department of Health and Human Services has published a useful guide on the assessment and treatment of substance use in older people (US Dept of Health & Human Services, 1998). This outlines guidance for treatment interventions and service delivery for older people. The key characteristics include availability, accessibility, and multidisciplinary team working across agencies. In this framework, geriatricians and primary care physicians and their teams have a vital role in the assessment and provision of brief interventions and onward referral (Crome and Day, 1999).

There is evidence that, as drug misuse increases in young people, and the elderly population increases, the drug problem in older people is likely to rise. There are unresolved questions about the types of service models that might be developed and evaluated (Gfroerer *et al.*, 2003). At present, this is a vision and a speculation. There is every reason why provision for this invisible, neglected, and stigmatized group should be established as mainstream.

Table 7 Summary of the classes of the misuse of drugs act, 1971

Class	Main drugs in each class	Maximum penalties for possession	Maximum penalties for possession with intent to supply
A	Heroin, cocaine (and crack cocaine); ecstasy, LSD, methadone, morphine, opium, dipipanone, pethidine, cannabinol, and cannabinol derivatives. Class B drugs when designed for injection become Class A.	6 months or a fine of £5000 or both (in a magistrate's court) Or, in a trial by jury 7 years or an unlimited fine or both	6 months or a fine of £5000 or both (in a magistrate's court) Or, in a trial by jury Life or an unlimited fine or both.
B	Amphetamines, barbiturates, cannabis[a] (herbal and resin), codeine, dihydrocodeine, and methylamphetamine.	3 months or a fine of £2500 or both (in a magistrate's court) Or, in a trial by jury 5 years or an unlimited fine or both.	6 months or a fine or of £5000 or both (in a magistrate's court) Or, in a trial by jury 14 years or an unlimited fine or both.
C	Benzodiazepines, buprenorphine, diethylpropion, anabolic steroids	3 months or a fine of £1000 or both (in a magistrate's court) Or, in a trial by jury 2 years or an unlimited fine or both.	3 months or a fine of £2500 or both (in a magistrate's court) Or, in a trial by jury 5 years or an unlimited fine or both.

Source: Reprinted from Young People and Substance Misuse, Crome I *et al.*, Copyright 2004, with permission from Royal College of Psychiatrists.
The tables have not been amended in light of the changes to (or relaxation of) the cannabis legislation, which took place on 29 January 2004, as the evidence on which this legislation was changed is currently undergoing review.
[a]Cultivation of the cannabis plant carries a maximum penalty of six months or a fine of £5000 or both in a magistrate's court, or in a trial by jury, 14 years or an unlimited fine or both.

Table 8 Summary of schedules of the misuse of drugs regulations, 2001

Schedule	Main drugs included	Restrictions
1	LSD, ecstasy, raw opium, psilocin, cannabis (herbal and resin)	Import, export, production, possession, and supply only permitted under Home Office licence for medical or scientific research. Cannot be prescribed by doctors or dispensed by pharmacists
2	Heroin, cocaine, methadone, morphine, amphetamine, dexamphetamine, pethidine, and quinalbarbitone	May be prescribed and lawfully possessed when on prescription. Otherwise, supply, possession, import, export, and production are offences except under Home Office licence. Particular controls on their prescription, storage, and record keeping apply
3	Barbiturates, temazepam, flunitrazepam, buprenorphine, pentazocine, and diethylpropion	May be prescribed and lawfully possessed when on prescription. Otherwise, supply, possession, import, export, and production are offences except under Home Office licence. Particular controls on their prescription and storage apply. Temazepam prescription requirements are less stringent than those for the other drugs in this schedule
4 Part 1	Benzodiazepines (except flunitrazepam and temazepam) and pemoline	May be prescribed and lawfully possessed when on prescription. Otherwise, supply, possession, import, export, and production are offences except under Home Office licence
4 Part 2	Anabolic steroids	May be lawfully possessed by anyone even without a prescription, provided they are in the form of a medical product
5	Compound preparations such as cough mixtures which contain small amounts of controlled drugs such as morphine. Some may be sold over the counter	Authority needed for their production or supply but can be freely imported, exported, or possessed (without a prescription)

Source: Reprinted from Young People and Substance Misuse, Crome I *et al.*, Copyright 2004, with permission from Royal College of Psychiatrists.
The tables have not been amended in light of the changes to (or relaxation of) the cannabis legislation, which took place on 29 January 2004, as the evidence on which this legislation was changed is currently undergoing review.

KEY POINTS

- Drug misuse in older people poses a considerable problem, which is likely to rise.
- There are substantial associated physical and mental health problems, which geriatricians are in a position to assess.
- Treatment interventions for substance misuse are effective and cost-effective.
- Models of service delivery comprise multidisciplinary teams working across agencies.
- The policy agenda must now take account of the current prevalence, projected increase, associated comorbidity, and cost-effectiveness, so as to implement the staff training and provision.

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PART III

Medicine in Old Age

Section 8

Special Senses

103

Disorders of the Eye

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INTRODUCTION

Age is the leading risk factor for visual impairment and blinding disorders of the eye. Five major disorders cause the greatest visual disability: cataracts, refractive error, macular degeneration, glaucoma, and diabetic retinopathy. The overall prevalence of refractive error caused by these five causes of visual impairment is remarkably consistent around the world. Figure 1 shows average values for the prevalence of these disorders in people aged 75 and over in the American population gleaned from multiple studies (AAO PPP, 2001; 2003a; 2003b; 2003c) (http://www.aao.org/aao/education/library/ppp/index.cfm).

Visual impairment is often described as a person's most feared disability, and with good reason. In the elderly, visual impairment is particularly devastating because it has been associated with dramatic reduction in quality of life (Lee and Coleman, 2004). As vision declines, people are forced to curtail driving. People who can no longer see clearly report having a reduction in mobility, and having difficulty walking and leaving their homes to participate in social and religious activities. They report a loss of ability to perform activities of daily living (ADL) such as dressing, shopping, and getting in and out of bed safely. Poor vision interferes with the ability to take medications properly. It is also a leading risk factor for falls and fractures which, in turn, are risk factors for placement in a nursing home and for loss of independence. In addition, other conditions appear to be strongly comorbid with low vision. These include dementia, depression, and delirium and other sensory losses, such as hearing and balance deficits. Thus, vision impairment has profound effects on the elderly and it is incumbent upon health-care providers to identify people at risk for leading causes of visual impairment, and to initiate treatments in a timely manner.

DEFINITIONS, TREATMENTS, AND RISK FACTORS

Refractive Error

Refractive error can be described as visual acuity with best lens prescription worse than 20/40. It is the most frequent eye problem and is usually corrected with prescription eyewear. The percentage of people whose visual acuity cannot be improved beyond 20/40 increases dramatically with age: 0.8% for those between 43 and 54 years old, 0.9% for those between 55 and 64, 5% for those between 65 and 74, and 21.1% for those 75 and older. This increasing degree of uncorrected refractive error is due to a number of variables. For example, there is normally an increase in the against-the-rule astigmatism with age and it is often exacerbated during surgery that breaches the conjunctiva such as cataract and glaucoma (Egrilmez *et al.*, 2004) surgeries. The long-term effects of refractive surgeries such as laser-assisted *in situ* keratomileusis (LASIK) that many people are now undergoing for the correction of myopia, hyperopia, and presbyopia are still unknown.

There is also a normal hyperopic shift in older adults that may be altered by cataract surgery (Guzowski *et al.*, 2003). Contrast sensitivity decreases with age, in part due to the increased prevalence of dry eye with age, and in part due to the smaller pupil size found in the elderly. Dark adaptation also decreases with age and with diseases such as diabetic retinopathy and cancer. Finally, cataracts, yellow lenses, and aberrations of the cornea, all of which increase with age, produce glare, or excess light scattered within the eye. This glare can be debilitating. It can cause difficulty with driving and other tasks conducted in bright light. It can also cause headaches. As people who have been faithful contact lens wearers for decades enter their 70s and 80s, it will be interesting to determine whether the rate of corneal aberrations rises.

There are many risk factors for refractive errors in the elderly. Many of the medical and social risk factors are listed in Tables 1 and 2.

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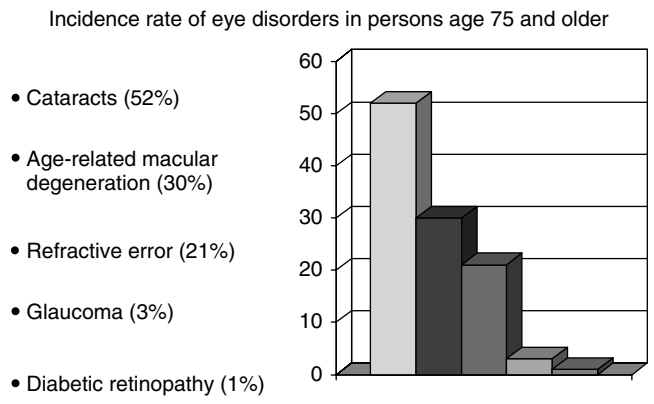

Figure 1 Over 50% of Americans aged 75 and older will suffer from visual impairment due to cataracts, 30% will lose central vision from age-related macular degeneration, 21% will have uncorrected refractive errors, 3% will report visual field loss due to optic nerve damage from glaucoma, and 1% will suffer vision loss due to diabetic retinopathy

Table 1 Medical risk factors for refractive errors

• Dry eye
• Increased glare
• Cataracts
• Yellowing of lenses
• Reduction in dark adaptation
• Decreased pupil size (miosis)
• Decreased contrast sensitivity
• Normal hyperopic shift with age
• Increasing against-the-rule astigmatism with age

Table 2 Social risk factors for refractive errors

• Cost of care
• Lack of access to care
• Living in a nursing home
• Lower expectations of patients and providers with age

Age-related Macular Degeneration

Age-related macular degeneration (AMD) is a disorder of the macula characterized by the presence of drusen, hypo- or hyper-pigmentation of the retinal pigment epithelium (RPE), local atrophy of the RPE and choriocapillaris, neovascularization of the macula, and a reduction or loss of central vision. AMD is the leading cause of severe, irreversible vision impairment in developed countries. Ninety percent of the AMD cases are of the nonexudative (dry or atrophic) type. Ten percent are of the exudative (or wet) type. Nonexudative AMD is characterized by the presence of drusen and loss of RPE and photoreceptors. Sight in the central visual field is lost gradually. Exudative AMD is characterized by a much more rapid loss of central vision due to neovascularization of the choroid and its accompanying hemorrhages that lead to retinal and RPE detachments and scarring. Although nonexudative AMD is more prevalent, most of the people with severe vision loss have exudative AMD.

Currently, there are no pharmaceutical treatments for AMD. However, there are several recommendations that can be made to people with AMD. Patients with early AMD should receive regular dilated fundus eye exams and should increase the consumption of antioxidants. They should be educated about how to use an Amsler grid to screen for the progression and encouraged to seek medical attention at the first sign of new symptoms. Dietary consumption of fresh fruits and vegetables is encouraged because they contain antioxidants such as Vitamin C, Vitamin E, carotenoids, selenium, and zinc, which neutralize damage caused by free radicals. Those who have unilateral AMD should be encouraged to take supplements in order to reduce their chances of developing AMD in the other eye. Results from the National Eye Institute Age-related Eye Disease Study (AREDS) showed that supplements containing high levels of antioxidants and zinc significantly reduce the risk of advanced AMD and its associated vision loss (Higginbotham *et al.*, 2004). The same nutrients had no significant effect on the development or progression of cataract.

There are surgical treatments for AMD. Two well-proven strategies for preserving residual vision are laser photocoagulation and photodynamic therapy. Other promising methods that are currently under study are submacular surgery, transpupillary thermotherapy, and pharmacological modalities like angiostatic steroids (Mohan *et al.*, 2003). These techniques target the more progressive disease that is no longer responsive to diet and supplements. Research into new treatments of AMD is ongoing. For example, apheresis, which is used to treat microcircuitry disorders such as myasthenia-gravis, is currently being tested for safety and effectiveness for treating nonexudative AMD. The hypothesis being tested is that decreasing blood plasma viscosity and red blood cell (RBC) aggregation might improve blood flow through the choriocapillaris and improve perfusion of the macula and preserve RPE and photoreceptors.

Understanding of both old and new risk factors is constantly being investigated and refined. Sunlight, long suspected to be a risk factor, is slowly yielding its complicated relationship with the onset of AMD (Tomany *et al.*, 2004) as is dietary fat consumption (Seddon *et al.*, 2003). Estrogens, despite extensive scrutiny, have not been implicated in the risk for AMD (Abramov *et al.*, 2004). Finally, researchers are in the process of uncovering molecular interventions for the treatment and eventual cure of AMD. Transgenic and knockout mice studies are providing new insights into choroidal neovascularization, the principal cause of vision loss in AMD, and gene searches are close to identifying genes such as the *fibulin 5* gene (Stone *et al.*, 2004) that may be responsible for the pathogenesis of AMD.

People with advanced AMD may be classified as legally blind and often require assistance with ADL even if the AMD is monocular because contrast sensitivity is affected, thereby reducing visual acuity in the unaffected eye. They are also at significant risk for depression. Vision can often be enhanced by the use of low vision aids such as magnifiers and bright lights. Motivated patients can be taught to read with the peripheral retina. Because functional status and quality of life are related, every effort should be made to encourage patients to seek rehabilitation.

Table 3 Confirmed risk factors for age-related macular degeneration

- Smoking
- Female sex
- Advanced age
- Caucasian race
- Low levels of antioxidants
- Exposure to sunlight in early adulthood

Table 4 Factors associated with AMD

- High fat diet
- Alcohol use
- Hormonal status
- Family history of AMD
- High levels of C-reactive protein
- High intake of saturated fats and cholesterol

Risk factors for and other factors associated with AMD are listed in Tables 3 and 4.

Diabetic Retinopathy

Diabetic retinopathy (DR) is the most frequent cause of blindness among adults aged 20 to 74 years. DR is a disorder of the retinal vasculature in which retinal changes such as waxy exudates, punctuate hemorrhages, and microaneurysms may occur as a result of uncontrolled systemic diabetes. DR can occur with both type I (insulin deficient) and type 2 (non-insulin dependent) diabetes mellitus. Despite the fact that type 1 diabetics develop the disease at an earlier age, a greater number of type 2 diabetics will develop DR because more than 90% of diabetics have type 2 diabetes. DR progresses from its mild, nonproliferative stage with increased vascular permeability, to severe, nonproliferative DR which is characterized by vascular closure, to proliferative DR with neovascularization in the retina and on the vitreous humour which tends to produce vitreal hemorrhages and resultant vision loss, retinal detachment, and possibly, glaucoma. Vision loss can result in several ways: (1) central vision can be lost due to macular edema or capillary loss; (2) neovascularization can lead to retinal detachment; (3) pre-retinal or vitreal hemorrhages can obstruct vision; (4) glaucoma can result in response to the damage caused by DR.

The retinal damage caused by DR cannot be cured. However, DR does respond favorably to early detection and treatment of diabetes and to case management of the disease (Norris *et al.*, 2002). Annual dilated fundus examinations are recommended for early detection and management of DR. Laser photocoagulation significantly reduces vision loss (ETDRS, 1991). Finally, for those who have experienced vision loss, low vision care and rehabilitation is recommended. These recommendations on how to minimize vision loss associated with DR are particularly significant in light of the research that shows that vision loss contributes significantly to poorer health, more disability, and increased frequency of falls in diabetics (Miller *et al.*, 1999) as well as restrictions in reading, mobility, work, and leisure activities (Lamoureux *et al.*, 2004).

Table 5 Risk factors for diabetic retinopathy

- Duration of diabetes
- Late diagnosis of diabetes
- No perception of vision problems
- Lack of frequent evaluation of vision
- Uncontrolled or poorly controlled blood sugar level (Hemoglobin A_{1c})
- Presence of other systemic diseases such as hypertension and hyperglycemia

Table 6 Factors associated with diabetic retinopathy

- Age
- Clotting factors
- Renal disease
- Use of angiotensin-converting enzyme inhibitors

Diabetics are at greater risk for comorbid conditions. The presence of diabetes mellitus increases the risk for the development of cataracts. In turn, the presence of cataracts complicates both the patient's and the provider's abilities to monitor vision changes due to DR. In addition, diabetics are at greater risks for complications during cataract surgery. Finally, comorbid conditions such as hypertension and hyperglycemia can worsen DR and should be treated (Fong *et al.*, 2003). Risk factors of and other factors associated with diabetic retinopathy are listed in Tables 5 and 6.

Glaucoma

Glaucoma is a general term that refers to a number of disorders of the optic nerve that are often accompanied by increased intraocular pressure (IOP) (ocular hypertension) and that results in a gradual and progressive visual field loss when the optic nerve is damaged. Glaucoma is the second leading cause of legal blindness in the United States and the leading cause of legal blindness in African-Americans. The destruction of the optic nerve that occurs as glaucoma progresses causes gradual loss of peripheral vision. As the disease progresses, the field of vision gradually narrows and blindness can result. Glaucoma has no early symptoms so about half of the people who are affected are unaware they have the disease. By the time people experience problems with their vision, they usually have a significant amount of optic nerve damage.

Early detection of glaucoma is critical. If glaucoma can be controlled, serious vision loss can be prevented. Comprehensive dilated eye examinations are recommended at least once every two years for African-Americans over age 40 and all people over age 60. Primary open-angle glaucoma (POAG) is the most common form of glaucoma and one of the nation's leading causes of vision loss. POAG has a characteristic loss of retinal ganglion cells and atrophy of the optic nerve that occurs in the presence of an open and normal looking angle. The visual field loss may be monocular but if it is binocular, it may well be asymmetric (AAO PPP, 2003c),

(http://www.aao.org/aao/education/library/ppp/index.cfm). Although there is a dearth of convincing evidence about causal relationships, there is evidence that macular degeneration, pseudo exfoliation, diabetes, and hypertension (Hennis *et al.*, 2003; Le *et al.*, 2003; Racette *et al.*, 2003) often occur in people with glaucoma, perhaps because all of these diseases represent increased risks of increased IOP. It may be that glaucoma is one more consequence of circulatory diseases.

Treatment to control IOP is helpful in reducing the visual field losses associated with glaucoma, regardless of whether the patient has elevated or normal (low-tension) glaucoma (Lee and Coleman, 2004). Drug therapy, in the form of eye drops, is normally initiated first, in large part due to the development of new drug therapies such as prostaglandins to lower IOP. The older drug therapy for glaucoma treatment, β-blockers, had so many side effects that surgery was often considered to be a reasonable alternative, despite the increased risk of infections and the large failure rate with its concomitant need to repeat the surgery several times. With the advent of prostaglandins, which have very few side effects (other than a tendency to darken iris and lash color), and of α-adrenergic drugs (which have some of the significant side effects of β-blockers) for the treatment of the more intractable cases, pharmaceutical control of IOP has become the standard of treatment. Even though African-Americans respond differently to eye drops than do Caucasians, the NEI (National Eye Institute) Ocular Hypertension Treatment Study (OHTS) showed that daily pressure-lowering eye drops reduced the development of primary open-angle glaucoma in African-Americans by almost 50% (www.nei.nih.gov/glaucomaeyedrops/).

Surgery is recommended if a patient becomes intolerant of the drugs or is not compliant with the drug schedule. Surgical procedures for glaucoma have become much more standardized in the past 10 years. Although glaucoma surgery can be done with manual or laser incisions, the most common types of surgery are done with lasers. The most common laser techniques are argon laser trabeculoplasty, argon or neodymium:YAG (Nd:YAG) laser iridotomy, and trans-scleral laser cyclophotocoagulation. The argon laser trabeculoplasty involves removing part of the trabecular meshwork in order to improve the outflow of aqueous humor from the anterior chamber. This technique works well in the treatment of POAG.

For patients with narrow anterior chamber angles or who have a closed angle, then surgery to open a hole in the iris is often recommended. This iridotomy surgery can be made manually or with either argon or Nd:YAG lasers. Care must be taken to not damage the corneal endothelium, which lies close to the iris.

When other surgical methods have failed to reduce IOP and the advancement of optic nerve damage, trans-scleral laser cyclophotocoagulation can be tried. This surgery selectively destroys the ciliary body, where aqueous humor is produced, thereby lowering IOP by reducing the amount of aqueous humor produced.

Table 7 Risk factors for glaucoma

- Age greater than 60
- Central corneal thickness
- Elevated intraocular pressure
- African descent over age of 40
- Family history (parent or sibling)

Table 8 Other factors associated with glaucoma

- Late onset menarche
- Migraine headaches
- Peripheral vasospasm
- Low diastolic perfusion pressure
- Presence of AMD, hypertension or diabetes
- High ratio of *n*-3 to *n*-6 polyunsaturated fat
- Suspicious optic nerve appearance (cup-to-disc ratio greater than 0.5)

The efficacy of surgical interventions, the number of times each of the surgeries needs to be repeated, and the order in which the surgery types are offered in combination, differ for black and white patients (Ederer *et al.*, 2004). Further study will undoubtedly fine-tune future surgical interventions.

Before determining whether the disease will be treated with eyedrops or surgery, an effort must be made to determine patient's health status and life expectancy, how difficult daily treatment of eyedrops will be, how expensive the drugs costs are, and what the possible side effects will be.

The use of marijuana as a complementary therapy for POAG glaucoma is not recommended. NEI studies have demonstrated that some derivatives of marijuana do result in lowering IOP for 3 to 4 hours when administered orally, intravenously, or by smoking. However, potentially serious side effects included increased heart rate, a decrease in blood pressure, impaired memory of recent events, and impaired motor coordination.

Efforts to better understand the pathogenesis of glaucoma have led to attempts to locate gene anomalies associated with glaucoma. Defects in the *myocilin* gene (MYOC) have been associated with POAG and defects in PITX2, FOXC1, and CYP1B1 are associated with anterior segment development (WuDunn, 2002).

The risk factors for and other factors associated with glaucoma are summarized in Tables 7 and 8.

Cataracts

Cataracts are a leading cause of blindness worldwide. They are opacities of the lens or the lens capsule. Cataracts are *named* by the location of the opacity; the opacity may occur in the nucleus (nuclear cataract), in the lens cortex (cortical cataract), or in the lens periphery (coronary cataract), or posterior (posterior subcapsular, posterior cortical, and posterior polar cataracts).

Cataracts are caused by the hardening of the lens that occurs as a part of normal aging. They also may occur as a result of blunt trauma, but the history of this type of cataract is a rapid onset and a rapid rate of progression. Normal

cataracts progress slowly and may be present for years before they are noticed.

Cataracts are not normally life threatening. No effective medical treatment for cataract exists, but a diet rich in lutein and zeaxanthin, carotene, and Vitamin A and long-term Vitamin C supplementation are thought to slow the progression of cataracts.

Once the patient reports a decreased quality of life or impaired function, elective surgery can correct the visual impairment. For patients with glaucoma, AMD, or diabetes, where visualization of the fundus is necessary for continuing management and treatment, surgery may be indicated before the patient reports a decline in functional status (AAO PPP, 2003a; 2003b; 2003c), (http://www.aao.org/aao/education/library/ppp/index.cfm).

When vision becomes cloudy enough to bother the patient, surgery can remove the clouded lens and replace it with an intraocular lens implant (IOL). Surgery is normally an outpatient procedure using local anesthetic. Phacoemulsification (ultrasonic cataract removal) is used to emulsify the lens for easy removal (although promising research on the use of lasers to break up the lens is ongoing (Bowman and Allen, 2003)). An IOL is then implanted within the empty lens capsule to serve as the new lens. Normally the incision is self-sealing. The surgical procedure is so safe that it has changed little in the past 10 years although lens implants of differing powers can reduce dependence upon glasses for either reading or distance work.

Many risk factors have been associated with cataracts although the studies have been largely observational. General risk factors for cataracts are listed in Table 9 and specific risk factors for cortical, nuclear, and posterior subcapsular cataracts are listed in Tables 10 to 12.

Table 9 General risk factors for all cataracts

- Age
- Diabetes
- Cost of treatment
- Low socioeconomic status
- Diet low in lutein and zeaxanthin
- Lack of education about cataracts

Table 10 Risk factors specific for cortical cataracts

- Iris color
- Hypertension
- Hyperglycemia
- Family history
- Abdominal obesity
- Low body mass index
- Exposure to UV-B radiation

Table 11 Risk factors specific for nuclear cataracts

- Smoking
- Iris color
- Family history
- Low education level
- Nonprofessional occupation
- Occupational sun exposure in third decade of life

Table 12 Risk factors specific for posterior subcapsular cataracts

- Smoking
- Hyperglycemia
- Inhaled corticosteroid use
- Systemic corticosteroid use
- Alcohol consumption
- Exposure to UV-B radiation

SUMMARY

Each type of eye disorder discussed above has unique risk factors, ranging from diet to environment. Increased age is associated with all of the eye disorders, that is, the frequency of the disorder in the population increases with age. In addition, some of the risk factors are shared by two of the eye disorders. Excessive exposure to sunlight is a risk factor for both cataracts and macular degeneration. Additionally, a particular symptom may have more than one cause. For example, glare may be caused by corneal aberrations or by the development of cataracts. A decrease in contrast sensitivity may be the result of decreased illumination to the retina because of a decreased pupil size, but it may also be caused by AMD, glaucoma or diabetic retinopathy. A decrease in dark adaptation may be caused by a miotic pupil or it may also be caused by cataracts. Thus, treatment of a specific visual deficit may require more than one approach because due consideration must be given to how different disorders contribute to the resulting morbidity.

In addition to having shared risk factors, there is some degree of comorbidity between the eye disorders. Either cataracts or glaucoma may often co-occur with DR and AMD often co-occurs with glaucoma. Interactions between diseases may complicate the treatments needed to prevent visual impairment and blindness. Finally, although there is little research about how comorbid eye disorders affect an already decreased level of function and quality of life, the quality of life of patients is dependent upon better understanding of the interactions between diseases and between their treatments.

For people who become blind from an eye disorder, there is some hope. Research on artificial vision techniques is ongoing. Artificial vision through the use of cortical implants is a promise of the future (Dobelle, 2000), although it is designed to promote mobility, not reading. These cortical implants are contraindicated for people with severe chronic infections and for those blinded by stroke or cortical trauma. However, cortical models for patients without viable optic nerves (e.g. glaucoma patients) and retinal prostheses for those without viable photoreceptors (e.g. AMD patients) are under development. Research such as this should considerably brighten the future of visually impaired people.

KEY POINTS

- Increasing age is a risk factor for loss of vision due to the following eye disorders: cataract, age-related macular degeneration, refractive error, glaucoma, and diabetic retinopathy.
- Poor vision due to refractive error and cataracts is often reversible.
- Loss of vision due to diabetic retinopathy, glaucoma, and age-related macular degeneration is not recoverable.
- Vision impairment caused by these eye disorders has a negative impact on functional status, mobility, independence, and cognitive status of elders.
- Education and visual rehabilitation play important roles in improving the quality of life of persons with visual impairments.

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The Epidemiology of Hearing in Aging Population

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SCOPE

Epidemiology is defined as "the study of how often diseases occur in different groups of people and why". The public health context needs a through consideration of the epidemiology of hearing impairment and disabilities as well as good, independent information on the current service provision for those with a genuine health need. To assess public-health priorities for the prevention, early identification of need and rehabilitation, a national and a local epidemiology of hearing impairment and disability are required. It is estimated that hearing impairment is the most prevalent disability in the developed countries (Davis, 1997). In some studies, it has been estimated to affect approximately 15% of adults, and its prevalence is expected to increase up to 25% by the year 2020 (Rosenhall *et al.*, 1999; Sorri *et al.*, 2001). According to some estimates, the current proportion of those suffering from hearing impairment is even higher than that comprising up to 18–20% of the adult population. (Uimonen *et al.*, 1999; Davis, 1989; Gates *et al.*, 1990; Quaranta *et al.*, 1996). Within the United Kingdom, it is estimated that 3.5% of the population have hearing aids (Taylor and Paisley, 2000).

The ongoing change in the society, for example, the fact that much of the workforce is changing from manual to communication work, where good hearing ability is a necessity, influences future needs for hearing services. Independent of the profession, present-day working requires good communication abilities. In the urban population, it is estimated that as high as 87.5% of the entire workforce is dependent on communications skills. The challenge presented to the health-care service is, with appropriate management, to maintain the hearing-disabled at work.

The aim of this chapter is to show that hearing disorders are a major and under-reported disability and handicap, underestimated in terms of their burden on society and traditionally undersupplied with appropriate health services to ameliorate that burden through improving quality of life.

Most of the data presented here was collected during the 1980s and 1990s in Great Britain and, therefore, has limitations in terms of its generality. However, the major conclusions are probably similar for most developed countries and there are some aspects that can be applied to developing countries as well. The main limitation to the work described was the very great difficulty in conducting rigorous work with populations that were very elderly, because of the difficulties in obtaining proper random samples in this population and in the restriction of mobility that makes laboratory-based studies difficult. In this context, "very elderly" means 80 years and over.

INTRODUCTION

There are three major disorders that arise from auditory-based pathology, (i) hearing impairment, (ii) tinnitus, and to a lesser extent (iii) vestibular dysfunction (*see* **Chapter 105, Auditory System** and **Chapter 106, Disorders of the Vestibular System**). While the first of these has been documented by some systematic population studies (Davis, 1995, 1989; Salomon, 1986; Brooks, 1989) and also by investigation of the elderly in nursing homes or residential settings (Alpiner, 1963; Martin and Peckford, 1978; Schow and Norbonne, 1989; Tolson *et al.*, 1992), tinnitus has been relatively underdocumented (Reich and Vernon, 1995) in the elderly, and vestibular dysfunction rarely documented (Davis, 1997). The consequences of our lack of knowledge concerning the extent of those who could benefit from rehabilitation for their disorder is a lack of prioritization of services for those people at a primary and secondary level of health care. Hearing impairment and tinnitus are not visible to society and their effects are therefore under-recognized.

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However, the effects exist and are suffered by the relatives and carers who try to communicate with the hearing impaired or tinnitus sufferer, on a regular basis. In addition to this chronic and long-term breakdown in communication facility, when there is an exacerbation of the disorders by an accompanied vestibular dysfunction or lack of orientation, the effects may indirectly be manifest in a greater number of accidents requiring emergency treatment or surgery and hospitalization (Davis, 1996). Hence, apart from social and mental health implications for the nuclear family, there may be indirect effects on physical functioning and vitality at a population level. A major challenge for current research is to separate the effect of hearing on quality of life from the effects due to other comorbidity factors.

Hearing disability should have a major public health priority because of the extent and nature of its impact on individuals and their families. The knowledge base concerning the need in the community has expanded over the last 20 years (Davis, 1995), and there has been a systematic attempt to develop outcome measures that reflect the impact of hearing impairment to guide and evaluate rehabilitation (Gatehouse, 1994; Dillon *et al.*, 1997). However, a major omission in that work concerns the very elderly population. Indeed, the perceived lack of rehabilitative success (Tolson *et al.* 1992; Hart, 1980) with this very elderly population has shifted the emphasis, in terms of personal rehabilitation in this group, to secondary prevention in the younger generations by fitting hearing aids 10–20 years earlier than is presently the case. Consequently, the subsequent generation should have benefited from earlier use *per se*, and, in addition, by adapting to the changes, should be better equipped, both cognitively and ergonomically, to cope with the demands of using hearing aid technology (Davis *et al.*, 1992; Stephens *et al.*, 1990). In addition, the complexities and cost of providing a thorough service to the very elderly have led to the idea that it would be more cost-effective to educate the carers to provide better acoustic environments and promote the use of good hearing tactics (Haggard, 1993) than to concentrate solely on increasing the provision of personal hearing aids, which, without proper rehabilitation and support, or an individual care plan, are likely to accumulate unused in drawers. There appears to be little systematic research into the most appropriate and cost-effective form of rehabilitation for this very elderly population. For instance, what are the communications needs of the very elderly and their carers? What would these people accept and how could their needs be met in a sustainable and cost-effective fashion? These are questions that need to be addressed but which will be given only the lowest level of input in terms of our knowledge base in this chapter.

The main data used in this review comes from the National Study of Hearing (Davis, 1995, 1989). This is a major population study carried out using random samples of the population by means of postal questionnaires ($n = 48\,313$) and clinical interviews expanded by audiological assessment of a representative subsample ($n = 2708$) during 1980–1986. This is supplemented by a more recent study carried out by Medical Research Council (MRC) Institute of Hearing Research (Gray, 1995) in Glasgow and Nottingham in 1994–1996, asking similar questions but in addition more details concerning the service received ($n = 11\,471$ at the postal questionnaire phase, $n = 1301$ people interviewed in their own homes including 546 people who had audiological assessment). In the Nottingham and Glasgow study, sampling was based on households, while the National Study drew its sample from individual electors.

Where comparisons are made between the samples over time, only those people living in Glasgow or Nottingham in the first study are used ($n = 12\,549$ at the postal phase).

PREVALENCE OF HEARING DISORDERS

The prevalence of hearing impairment is the number of people who have a specific degree of hearing impairment at a given time. This can also be expressed as a percentage of the relevant population. When generalizing between populations, care has been taken to ensure that the assumptions underpinning such generalizations are valid in terms of congruence of age, gender, and occupational distribution, together with an assessment of whether there are particular risk factors present in one of the sample populations. In terms of hearing impairment, it is particularly important to define the degree of impairment or disability, enabling comparison of like with like. Terms such as deaf or deafness should be avoided, as these tend to give rise to misleading and emotive statements. As hearing impairment is a chronic and progressive problem, often accompanied by tinnitus, and, sometimes, by vestibular dysfunction, the *incidence* of hearing impairments, which is the number of new cases of a given degree of severity of hearing impairment that arise in a year, is difficult to establish (Davis *et al.*, 1991). The prevalence is the important consideration for service provision. Given that the prevalence far outweighs the provision, the question becomes "the prevalence of what form of hearing impairment deserves our consideration?"

Figure 1 shows the broad extent of hearing impairment and reported hearing disability in the adult population (aged 18 and over) in the United Kingdom. It can be seen from this figure that almost 1 in 3 of UK adults has, at least, a mild hearing impairment in one ear, with 1 in 5 showing a bilateral hearing impairment. Great difficulty in hearing what is said in a background of noise is reported by 1 in 4 people, with 1 in 10 reporting that they have prolonged spontaneous tinnitus (PST) (Coles *et al.*, 1990). At a moderate degree of hearing impairment in the better ear, 7% of the adult population is impaired (Davis, 1995). This means a substantial number of people in the United Kingdom who may have the need for some associated services, that is, who may benefit from the provision of hearing services. Supplying those services is a substantial public health problem, substantial enough to warrant considerable debate. This has been discussed by several authors (Haggard, 1993; Davis *et al.*, 1992; Stephens *et al.*, 1990), and revolves around criteria concerning the extent to which the population

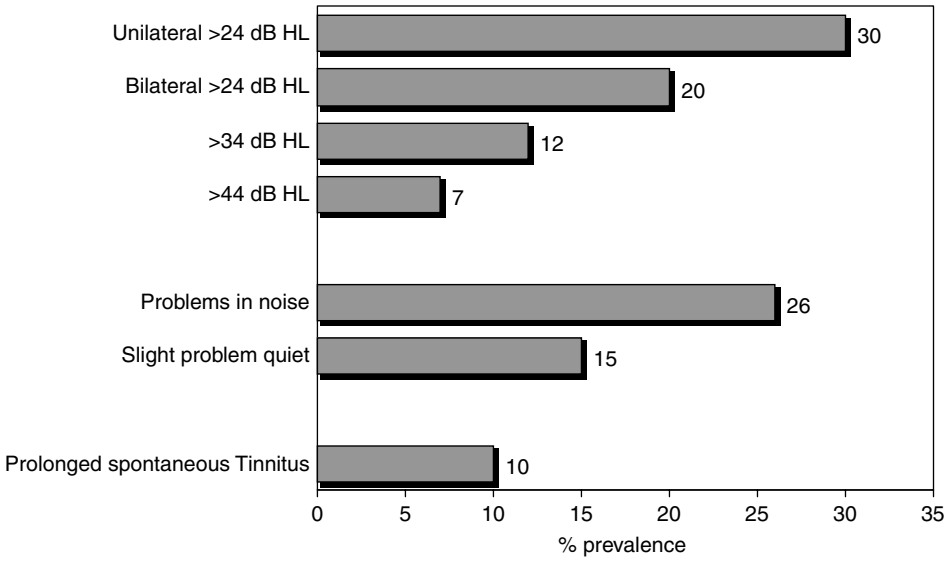

Figure 1 The prevalence of hearing impairment at different degrees of severity, hearing disability as shown by finding it "very difficult" to hear what someone says if there is a background of noise and also by having at least a slight difficulty hearing in quiet. The prevalence of tinnitus that is not only after loud sounds and which lasts for 5 minutes or more (PST, prolonged spontaneous tinnitus) is also shown

can benefit from intervention and a cost-effective analysis of such an intervention; obviously, hearing disability and handicap are the major targets of rehabilitation, both present and future. However, the extent of hearing impairment is the best predictor of need that can be assessed quantitatively. Both aspects will be presented in this chapter. Some authors (Davis *et al.* 1992; Stephen *et al.* 1990) think that the low threshold for provision of hearing aids should be set at about 25 dB HL in the better ear, measured as an average over the frequencies 0.5, 1, 2, and 4 kHz. Other authors (Haggard, 1993) consider more complex schemes and higher thresholds, but the differences are actually quite small operationally and relate mainly to the degree of impairment in the better ear.

Using the lower threshold definition, the prevalence in the adult population aged 18 and over of a hearing impairment in the better ear of 25 dB HL or greater is 20%. Taking more severe criteria, 12 and 7% are the prevalences for impairments of 35 dB HL or greater and 45 dB HL or greater, respectively. The pattern of hearing impairment does change with age (Davis, 1995), with the higher frequencies being more susceptible to aging and noise.

Figure 2 shows the prevalence of hearing impairment as a function of age-group (see Davis (1995) for the confidence intervals and a more detailed description). Within the figure, the data are derived from the National Study of Hearing 18–80 age-group and from a number of studies for the aged over 80 years (Davis *et al.*, 1992; Hart, 1980). These do not disagree widely with the estimates made by Soucek and Michaels (1987) and by Tolson *et al.* (1992). The estimates for the 71–80 age-groups are reasonably accurate in terms of their relatively bias-free derivation. Those for the over 80s have been derived from 862 people using a variety of testing procedures, and are thus more open to criticism. Gatehouse and Davis (1992) suggest that at least some of the prevalence in the elderly may be due to central response-based processes rather than peripheral perceptual processing (i.e. it takes a stronger signal for an elderly person to give a response). For public health purposes, this makes very little difference until differential rehabilitation is considered. In any case, it is unlikely that a response bias would make over 10 dB difference to the hearing thresholds in the over-80-year olds.

The major effects on the prevalence of hearing impairment have been shown by Davis (1989). By far the most important was the age-group, with occupational group and occupational noise exposure having major effects throughout the severity range. In terms of gender, at mild–moderate impairments, men have a higher prevalence at 25 dB HL (odds ratio 1.4 : 1). The effect of age-group, as seen in Figure 2, is large and

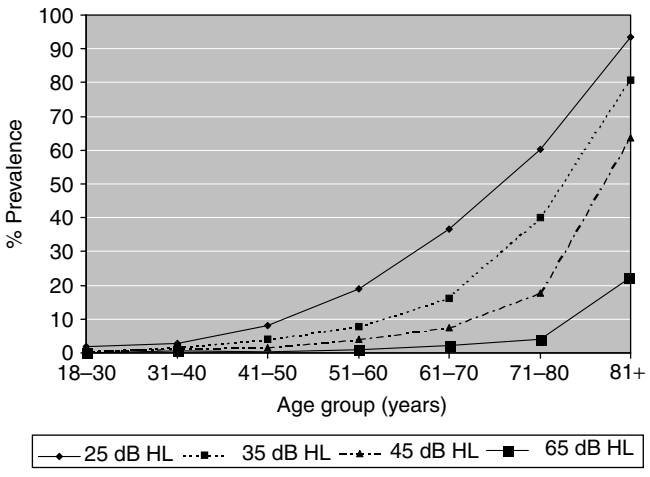

Figure 2 The prevalence (%) of different degrees of hearing impairment as a function of age in the Great Britain population

dominates any other factor. Thus, almost 1 in 5 people aged 51–60 have a hearing impairment in the better ear and 1 in 5 of the over 80s has a severe hearing impairment, which will render speech almost inaudible without amplification. At least 80% of the over 80s would benefit from a hearing aid, if they could use one, and 40% of the population aged 71–80 would benefit likewise. The problem of hearing impairment in the elderly is thus a major issue in terms of the numbers of people that are involved. The UK National Study of Disability estimated that hearing disability was the third most prevalent disability, and the figures from the National Study of Hearing show that it is in fact the most prevalent disability in the aged (see Davis (1989) for a discussion of this difference) and should be given a greater priority than at present.

While there is no doubt that hearing impairment and disability are major chronic problems for the population at present (Davis, 1995) with the probability of 8.759 million people in the United Kingdom having a hearing impairment as described previously, the situation may deteriorate because of demographic changes in the population (Davis, 1997, 1991). Figure 3 shows an extract of the predictions for the number of people with hearing impairment in the United Kingdom, United States, developed countries and developing countries for 1995 and 2015.

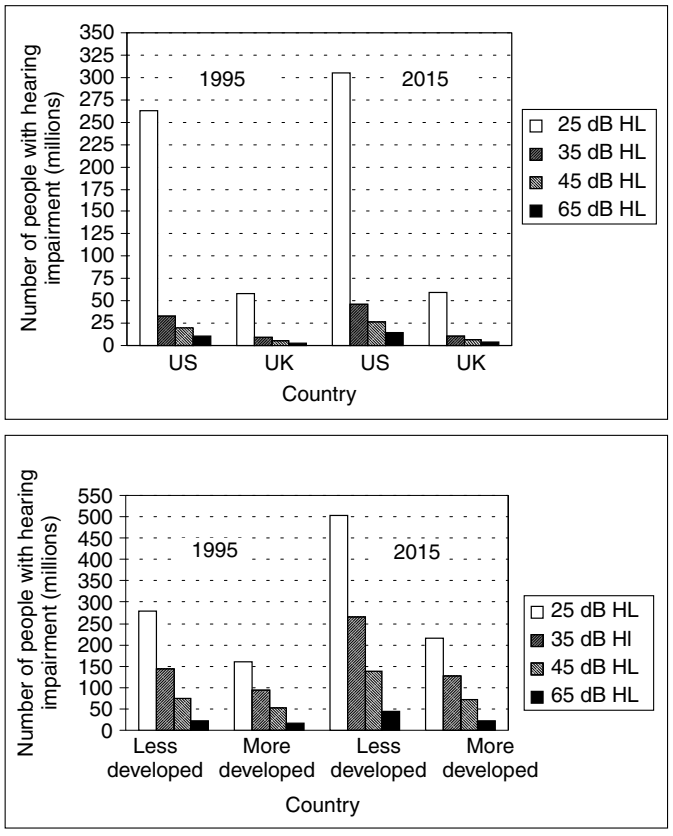

Figure 3 Shows the predictions for the number of people with hearing impairment as a function of country and severity of hearing impairment using the 1994 revision of the UN projected world populations in 1995 and 2015

Figure 3 is derived from the National Study of Hearing in Great Britain by convolving the age and sex distribution of different countries (in 5-year bands) with the prevalence of hearing impairment. The increase seen in the overall prevalence is therefore due to the structure of the population alone and assumes no change in etiology or risk factors over the time period. However, as most of the people who will be contributing to the statistics are already in middle age, they have had their most dangerous time for noxious exposure. There will probably be a more rapid growth in those with hearing problems in the less developed countries, as life expectancy will increase over the next 20 years. However, it is noticeable that the proportion of people who have hearing problems is greater in the more developed countries where life expectancy is already high. Another key factor for health/hearing services planning is that the expected number of hearing-impaired people in the United Kingdom will rise by over 20% in the next 20 years. Using the data for Great Britain, with 8.58 million hearing impaired in 1994, the numbers who were aged 18–60 were 2.131 m, aged 61–80 years were 4.486 m and aged over 80 years were 1.963 m. At $\geq$45 dB HL there were 0.471 m, 1.132 m and 1.337m, and at $\geq$65 dB HL there were 0.136 m, 0.294 m and 0.469 m respectively for 18–60, 61–80 and over 80 (Davis, 1995). Thus, as the severity criterion increases, there is a larger and larger proportion of the very elderly in the hearing-impaired group.

Figure 4 shows the prevalence of reported hearing disability in the population (Davis, 1995) in the 1980s. The question "How well can you hear someone talking to you when that person is sitting on your left-/right-hand side in a quiet room" was used with responses "No, slight, moderate and great difficulty" and an option for "Can't hear at all". A response of slight difficulty in hearing in an ear relates to a median hearing impairment of about 35 dB HL, the moderate and worse to 50 dB HL and the great and worse to 75 dB HL (averaged over 0.5, 1, 2, and 4 kHz). Figure 4 shows that at all degrees of reported hearing disability, there is an increase with age. Thus, at 61–70 years, about 15% report difficulty on the better ear, with about 25% at 71–80 and 40% for the over 80s. Comparing the reported hearing disability to the measured hearing impairment, it is noticeable that far fewer people have a reported better-ear hearing disability compared with a measured hearing impairment. Furthermore, the ratio of reported problem to measured impairment is not constant across age, giving fair correspondence up to 50 years and then giving progressive discrepancies. Thus, older people are far less likely to report a hearing disability for a given level of hearing impairment. However, it could be argued that they are less likely to benefit from rehabilitation unless they recognize that problem.

Figure 4 also reports the prevalence of tinnitus that lasts for five minutes or more and was not only after loud sounds, adjusted for the proportion of the sample who did not complete all three parts of the question (this was particularly so in the elderly). It is noticeable that the prevalence of tinnitus increases with age until 60 years of age, when it reaches a peak of 1 in 5 people. The factors that influence

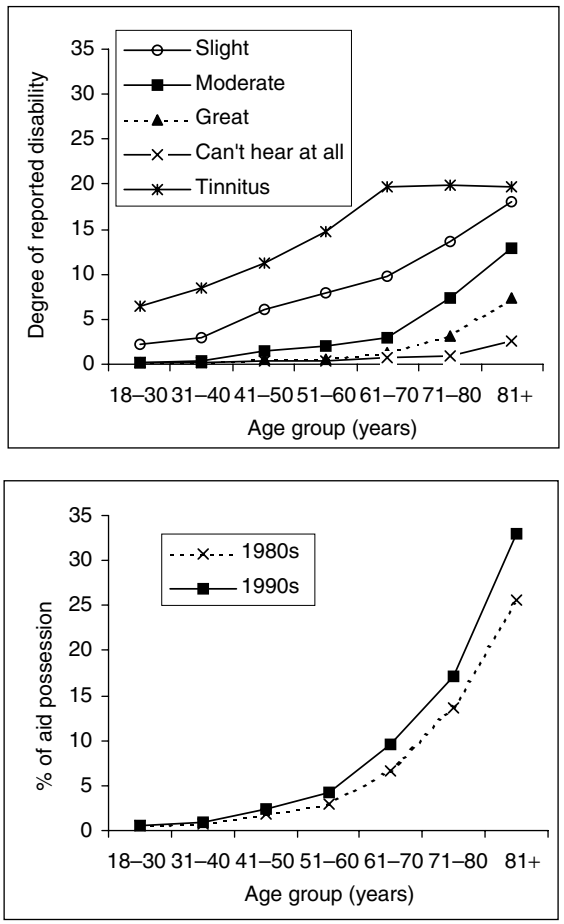

Figure 4 Prevalence (%) of different degrees of reported hearing disability, tinnitus, and hearing-aid possession as a function of age in the population of Great Britain

tinnitus report are systematically explored in Davis *et al.* (1992). Davis and Roberts (1996) explored the quality-of-life implications for those with prolonged spontaneous tinnitus and/or a reported hearing disability. They examined the scores on the SF-36 and showed that both reported hearing disability and tinnitus affect the scores on the SF-36 in a differential way, with tinnitus that is severe giving the largest deficits, particularly in terms of the vitality, social function, and mental health. Using the 1990s sample, the largest effect of reported hearing disability was concerned with the social function score and is shown in Figure 5.

The terms "hearing difficulty" and "disability/handicap" were obtained from the subject- and situation-specific hearing questionnaire devised by Gatehouse and Davis (1992), and the factor effect shown here is for a shift in 10% of the scores on this questionnaire that only uses items that are relevant to individual patients/hearing aid users. Figure 5 shows that the effect of a slight reported hearing disability is a deficit in 6 points of the social function score (range 0–100%), and that a moderate reported disability is a deficit of 14% with about 30 points for a great disability. However, those who use their hearing aids most or all of the time do get this deficit from the hearing disability offset by up to 12%. Those who use the hearing aid only some of the time do not get a significant benefit. This may be for a number of reasons including the fact that there needs to be a reasonable amount of time to adapt to the input from the aid (cognitive plasticity). Also, there were significant beneficial effects of "using a hearing aid most or all of the time" for body pain and mental health scores.

SERVICE PROVISION (*see* Chapter 105, Auditory System)

Services for hearing-impaired people have very different modes of organization and service delivery in different countries, and are very much a function of the ways in which health care is funded, structured, and delivered. In the United Kingdom, for example, hearing aid services are located in hospitals and are free at the point of delivery as

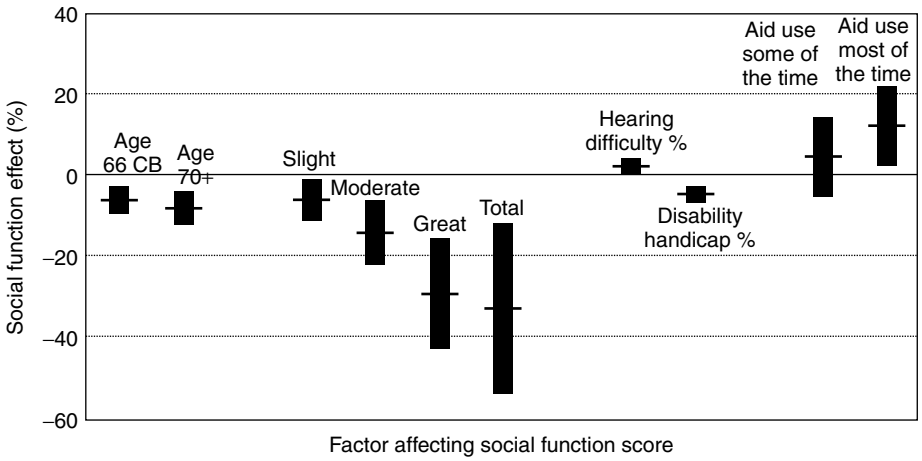

Figure 5 The effect (with confidence interval) of age, hearing disability, difficulty handicap, and hearing-aid use on the social function score of the SF-36 using a general linear model to estimate the effects

part of the UK National Health Service (NHS), funded by direct taxation. Prior to the Modernisation of NHS Hearing Aid Services (MHAS) program, four basic analog models accounted for more than half of the aids distributed, and only 2% were digital. Ten to fifteen percent of hearing aid users have a bilateral aid in the United Kingdom, compared to up to 60% in other European countries (Barton *et al.*, 2001). It has also been estimated that 150 000 people have a private aid in the United Kingdom (Taylor and Paisley, 2000), over 25% of the number estimated to be provided by the NHS. This figure is higher than that in the European countries (Barton *et al.*, 2001) and it has been argued as too high, as private aids enable people to receive the benefits of private technology and avoid having to wait as long as they might with the NHS while providing the option of a hearing aid in both ears (Audit Commission, 2000).

THE NEW SERVICE

As a result of the MHAS program, patients are fitted to nationally agreed protocols that ensure that the technology is used to specifically tailor the hearing aid to each individual's hearing loss. The audiologist spends longer with each patient, and there are now standardized national systems to monitor patient outcomes.

In addition to the equipment and hearing aids, NHS services were given additional funding to recruit extra staff to fit the new hearing aids; furthermore, in order to be able to fit the new hearing aids to their patients, a comprehensive national training package was delivered, including hands-on training within the individual hearing aid department. This has effectively meant that every audiologist in England has been fully trained to fit digital hearing aids to NHS patients.

EVIDENCE-BASED CHANGE

Modern digital hearing aids provide users with an "intelligent" amplifier, the performance of which is programed and fine-tuned by an audiological professional to meet their individual needs. The hearing aid will constantly adapt to changes in the sounds it picks up. In addition, it offers the user a means of choosing the most helpful settings for each listening environment that they encounter in daily life.

The differential benefit to patients was measured using a standardized questionnaire (*The Glasgow Hearing Aid Benefit Profile*). This questionnaire captures how much of the time each person uses their hearing aid, how much it helps in different everyday situations and how satisfied they are with the result. The composite score is shown in Figure 6.

An independent evaluation of the MHAS program by the MRC found that people fitted with high-quality digital hearing aids in the modernized service reported 41% greater overall benefit compared to those with analog aids. They were using their aids for more time, finding them more helpful, and more satisfied with the result.

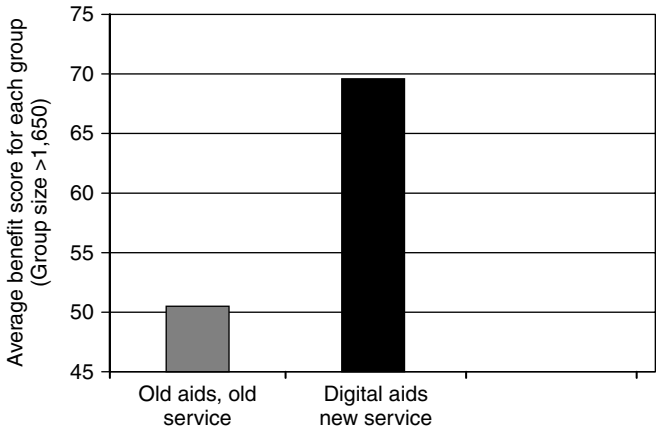

Figure 6 Average benefit of modern digital hearing aids

DISCUSSION

The public health priority of hearing impairments and tinnitus in adults should be substantially higher than it presently appears, because hearing disorders comprise the most prevalent chronic impairment in the population, with over 8 million people in the United Kingdom (i.e. about 20%) having an impairment. The major factor associated with this high prevalence is age, with noise being the major preventable factor, especially in young people. Because age is the major factor, prevalence of hearing impairments in the whole population will increase over the next 20 years by up to 20% because of the change in demographics (Doyle and Gough, 1991). The data show that the need is great at most levels of severity of hearing impairment and particularly for the over-60s. Demand and supply seem to be increasing, which will be driven by the changing demographics of the aging population over the next 20 years. The implications for hearing-aid and rehabilitation budgets are quite substantial even if the same annual incidence of referral for a hearing aid is maintained and not increased using screening, education, or awareness programs so that some of the unmet need can be fulfilled.

There seems to be no reason why elderly people cannot cope with rehabilitation for their hearing disorders, both hearing and tinnitus, unless other factors affecting morbidity interfere. The elderly benefit as much from hearing aids as those who are younger and have about the same usage rates, unless there are other problems that interfere with maintenance of their hearing aids. There is no evidence that central dysfunction handicaps the elderly who are not hospitalized. However, the usage rates are disappointingly low in this group. The implications for service provision are, perhaps, that the hearing aid service for the elderly should be situated increasingly in the community and thought should be given as to how individual care plans can be enacted, which take a client-oriented approach to individual facets of the

disability that are presented by clients. There is little evidence on the effectiveness of different styles of rehabilitation on their costs and benefits. The comments received from the 318 individuals who had a hearing aid in the 1990's study suggest that more thought should be given to meeting specific needs (including detailed training in tactics and handling skills) and less emphasis be placed on technology as the primary means to these ends.

In terms of research requirements, there is an urgent need to build up a better evidence base in order to suggest guidelines for better and more acceptable rehabilitation services for the elderly who have a hearing problem. There are very few studies of whole population samples or randomized control trials on which to base good practice. Such trials should be given an urgent priority to consider why take-up and access are so poor and also to determine what factors can increase systematic use of hearing aids for example, early detection and intervention.

KEY POINTS

- Prevalence of hearing impairment is expected to increase by up to 25% by 2020.
- The major factor associated with its high prevalence is age.
- A study of the prevalence is most important for service provision.
- The quality of digital hearing aids in the modernized service in the United Kingdom reported 41% greater overall benefit compared to analog aids.
- The elderly benefit as much from hearing aids as those who are younger and have same usage, unless there are other problems that interfere with maintenance of their hearing aids.

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Auditory System

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INTRODUCTION

The auditory system is one of the special senses, which, together with the visual system, is largely responsible for the way in which we perceive our environment. In addition to audition, the system encompasses the vestibular apparatus with special senses for the detection of gravity and movement (*see also* **Chapter 106, Disorders of the Vestibular System**). The auditory system is responsible for the detection of sound energy, its effective transfer from the surrounding air to the inner ear fluid and the subsequent conversion of this physical stimulus to a psychoacoustic sensation, which we perceive as sound.

Abnormalities of the auditory system can result in a variety of symptoms, the most frequent of which are hearing impairment and tinnitus. Assessment of the auditory system is directed toward

1. the identification of the pathological processes and their anatomical location;
2. quantifying the impairment and disability;
3. reducing the handicap by the most appropriate means.

ACOUSTICS AND HEARING

The transmission of sound through air involves the oscillation of air molecules, producing regions of alternating pressure changes traveling away from the sound source. If these sound waves reach a normal functioning ear, a noise is heard. The human ear is capable of detecting sound wave oscillations of varying frequency and amplitude. Variations in frequency of vibrations are perceived as variations in pitch of sound; similarly, variations in amplitude of vibrations are perceived as a variation in loudness.

Pitch

The frequency of sound wave vibration is measured in Hertz (Hz or cycles per second). Some human ears are able to detect a sound frequency as low as 20 Hz, but hearing is not normally tested for sounds below about 100 Hz. Similarly, sound is not easily detected at frequencies above 10 000 Hz although some individuals can hear up to 20 000 Hz. Pure-tone audiometry (PTA) assesses the ability to hear tones presented to each ear individually and is normally done using between 7 and 11 pure tones in the range between 125 and 8000 Hz.

Loudness

Sound pressure is a physical measure that relates to the perception of loudness. The sound pressure level at which the human ear is able to detect sound is approximately 10 million times smaller than the loudest level that can be tolerated. As a result, it is not practical to refer to actual sound pressure levels when measuring the variations in the threshold and tolerance of sound amongst the human population. The alternative and more practical method is the decibel (dB) scale. The basis of this scale is the comparison of a sound pressure to a reference sound pressure level, usually that at the threshold of normal human hearing (2×10^{-4} dynes cm^{-2}), and converting the ratio into a logarithmic scale (the Bel), then dividing by 10 (the decibel). Using this scale, a sound pressure at the threshold of normal hearing is represented by a decibel score of 0 dB. If the sound pressure being tested is less than the reference level, such that the test to reference ratio is less than 1, the resulting decibel score will be negative. A 10-fold increase in sound pressure level equates to an increase of 20 dB.

Sound frequencies in the midrange of normal human hearing are heard better than those at the extreme ends of the range. In order to simplify the graphical representation of normal hearing levels, a decibel scale is used that uses different reference sound pressure levels for each frequency tested, thus providing a means of representing normal hearing as a horizontal line on an audiogram chart. The decibel scale

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used is known as the *Hearing Level scale* (dB HL) and was initially achieved by testing otologically normal, young adults.

MEASUREMENT OF HEARING LOSS

Clinical assessment of hearing usually begins with free-field voice tests and tuning fork tests. The approximate loudness of the whispered voice is 15 dB at 2 ft and 35 dB at 6 in. Similarly, a conversational voice is approximately 50 dB at 2 ft and 60 dB at 6 in. A loud voice is about 75 dB at 2 ft. Using these figures as a guide, it is possible to estimate the hearing loss by simple voice tests, presenting simple words or numbers to one ear at a time and occluding the opposite ear and rubbing the tragus to help mask the nontest ear.

Tuning Fork Tests

Common tuning fork test that can be helpful in differentiating conductive from sensorineural deafness are the Rinne and Weber tests.

Rinne Test

This test compares the effective transmission of sound through the normal route of the outer and middle ear (air conduction) against the transmission through bone. A tuning fork placed onto the mastoid bone transmits sound to the cochlea through the skull. In the presence of a functioning cochlea, a sound will be heard until the loudness of the tone reduces to the individual's hearing threshold. If the tuning fork is then placed next to the ear canal and heard, it indicates that the normal conductive mechanism is intact. Alternatively, the perceived loudness of sound is compared by alternating the position of the tuning fork between the mastoid and ear canal. In the presence of a conductive deafness, the sound may appear louder by bone conduction than by air conduction. The magnitude of conductive deafness at which the perceived loudness shifts from air to bone conduction is about 20 dB HL (Browning and Swan, 1988). By convention, the "normal" result (air conduction perceived as louder than bone conduction) is a Rinne positive result. If bone conduction sounds louder than air conduction, the result is Rinne negative.

Sound transmission through bone means that sound presented anywhere on the skull will travel to both ears. If a sound source is placed on the right mastoid bone, sound will be transmitted to the right and left cochlea. Therefore, even if the right cochlea is not functioning, the sound will be heard – by the left ear. When the sound is presented to the right ear by air conduction, no sound will be heard because the left ear will not detect the sound. In this situation, the sound will appear louder by bone conduction than air conduction, by virtue of the fact that the opposite ear has detected sound transmitted across the skull. This can be mistaken for a conductive loss and is known as a *false Rinne negative* result.

Weber Test

When a tuning fork is placed centrally on the skull, sound is transmitted to both ears equally. Whether the sound is perceived equally depends on the sensitivity of hearing in both ears. The transmission of sound to the cochlea by bone conduction is not only directly through the skull vault to the cochlea, but also via the skull to the middle ear and then through the ossicular chain to the cochlea. As a result, the transmission of sound by bone conduction is affected by abnormalities of the middle ear. When sound reaches the middle ear through the skull, it will travel through the ossicular chain in both directions, resulting in some loss of sound outwards through the ear canal. Any process that affects the transmission of sound through the middle ear (i.e. a conductive deafness) will reduce the loss of sound from the middle and outer ear. This is one explanation for the phenomenon of increased loudness in the ear with a conductive deafness when the sound of a tuning fork is presented to the vertex of the skull. The magnitude of conductive deafness at which the perceived loudness shifts from midline to the affected ear is about 12 dB(HL) (Stankiewicz and Mowry, 1979).

In the absence of a conductive deafness, the loudness of the tone will be determined by the relative sensitivities of both cochlea. Therefore, the lateralization of the Weber test may be because of a conductive loss in the affected ear or a sensorineural loss in the opposite ear.

Pure-tone Audiometry

Hearing thresholds can be assessed using audiometry. The commonest method used is pure-tone audiometry (PTA), which measures the subjective threshold of hearing of various pure-tone frequencies. The results are usually presented graphically and normally include both air conduction and bone conduction. Air conduction refers to the detection of sound as presented through the normal anatomical pathway, via the outer ear. The sound may be presented either through standard earphones, or alternatively through insert earphones or using free-field sound from speakers. Bone conduction measures the threshold of sound applied directly to the skull.

The pure-tone audiogram graphically represents the magnitude of hearing loss at different frequencies. It is convenient to summarize the average hearing loss as a single figure, and by convention, the thresholds over the midrange of 0.5, 1, 2, and 4 kHz are used. On this basis, hearing impairment can be described according to the severity of the average loss (see Table 1; Browning, 1998).

In healthy state, the air conduction is similar to bone conduction. In broad terms, hearing loss may be due to abnormalities of the sound conduction mechanisms affecting the outer or middle ear, resulting in a conductive deafness, or

Table 1 Classification of deafness based on pure-tone average hearing thresholds at 0.5, 1, 2, and 4 kHz)

Pure-tone average (dB)	Description
0–24	Normal
25–50	Mild
51–70	Moderate
71–90	Severe
91–110	Profound
>110	Total

alternatively, may be due to abnormalities of the cochlea or neural pathways resulting in a sensorineural deafness. Differentiation between conductive and sensorineural deafness identifies the anatomical part of the auditory pathway at fault and in turn allows a suitable management plan to be made. Most conductive losses are associated with identifiable changes affecting the outer and middle ear, including the tympanic membrane.

Acoustic Admittance and Tympanometry

The ability to measure the ease with which sound energy travels through the middle ear has been developed into a clinical application that is easily used to assess so-called acoustic admittance of the ear. Acoustic tympanometers are used to measure admittance, a parameter that is influenced by changes in the stiffness, mass, and resistance of the tympanic membrane and middle ear. The test is performed automatically using a sealed probe inserted into the ear canal, which measures the changes in intensity to an 85 dB SPL (sound pressure level) tone at 226 Hz as the pressure in the ear canal between probe tip and drum are adjusted from −400 daPa to +200 daPa, relative to atmospheric pressure. Acoustic admittance will vary as the pressure changes, because of the splinting effect of the increase or decrease in pressure on the eardrum. When the pressure in the outer ear is similar to the middle ear pressure, the acoustic admittance will be highest. A graphical representation of this series of measurements is the tympanogram, and is clinically useful because it provides information about middle ear pathologies and can identify normal and abnormal contraction of middle ear muscles. Examples of different tympanograms are shown in Figure 1.

The normal pattern, known as a *type A curve*, has a distinctive peak in the vicinity of atmospheric pressure. The height of the peak represents the acoustic admittance of the middle ear and is affected by changes in stiffness and mass. A low peak is seen in conditions that fix the ossicles such as otosclerosis. A flat curve is known as a *type B tympanogram*, and is seen in the presence of middle ear fluid, but can also occur if there is a perforated drum or impacted wax. If the peak of the tympanogram is shifted to the left, it indicates that acoustic admittance is best when the pressure in the outer ear canal has been reduced below atmospheric, and, by inference, corresponds to the middle ear pressure. A peak below −100 daPa is a type C tympanogram and may occur in the presence of Eustachian tube obstruction associated with a negative middle ear pressure due to a failure to replace middle ear air lost by absorption through the middle ear mucosa.

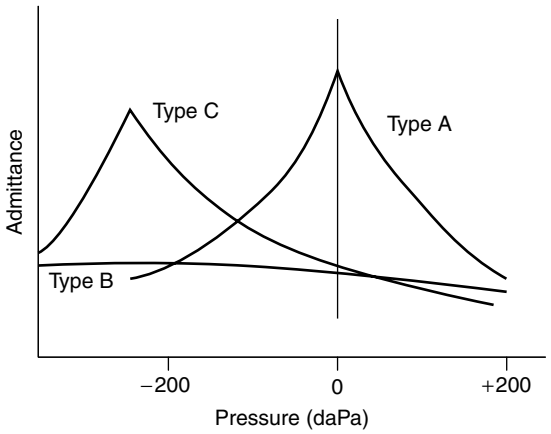

Figure 1 Classification of tympanogram shapes. (a) Normal tympanogram with peak centred at atmospheric pressure. (b) Flat curve due to middle ear fluid. (c) Negative peak due to eustachian tube dysfunction associated with a negative middle ear pressure

Tympanometry can be used to assess the integrity of the stapedius muscle contraction by virtue of the fact that this muscle can be made to contract in response to a loud sound; contraction alters the middle ear mechanics, resulting in reduced acoustic admittance. The introduction of a loud sound and measurement of acoustic admittance constitutes an acoustic reflex test, the afferent arm of which is the stimulation of the acoustic nerve and the efferent arm is triggered by a bilateral brain stem (superior olivary complex) reflex to the facial nerve, which supplies the stapedius muscle. The test will assess the integrity of both the 7th and 8th cranial nerves and can be performed ipsilaterally (stimulus and tympanometry in same ear) or contralaterally (stimulus and tympanometry probe in opposite ears).

Speech Audiometry

The assessment of speech perception is perhaps a more appropriate test of hearing than PTA when assessing impairment. A speech audiometer can assess the ability to perceive and understand the complex and rapidly changing spectrum of sound that constitute speech. The test is usually performed using headphones and asking the patient to repeat words presented at varying loudness levels. Words may be presented as single words from standard word lists (e.g. Boothroyd word lists) or as sentences. When using sentences, key words in the sentence are used for scoring. The ability to understand words presented within the context of a meaningful sentence is easier than words presented in isolation. Speech audiometry can also be assessed using visual presentation as well, combining the speech signal with a recorded image of the speaker in a standard audiovisual test.

Because of the varied ways in which speech tests are performed and reported, the results must be interpreted within

the context of the test material and with the PTA results. The results of speech audiometry tests are reported as either the highest score that can be achieved by the individual no matter how high the volume, or as a decibel level indicating the loudness level at which the individual correctly hears half the test words. The highest score that can be achieved is known as the *optimal discrimination score* (*ODS*) and in normal individuals, it is achieved using a loudness level about 30 dB above the pure-tone threshold. Results of speech audiometry can also be presented graphically as a performance-intensity function graph, as shown in Figure 2.

Such a graph will indicate whether the individual achieves 100% speech recognition score and the loudness level at which the maximum score is achieved. The normal shape to the speech audiogram performance-intensity graph is a rapid increase in speech recognition over a 20–30 dB increase in loudness, to the maximum speech recognition level of 100%. Two common abnormalities are seen using this type of graph, a shift to the right in the presence of a conductive loss or a reduced speech recognition score seen in sensorineural deafness.

Speech audiometry is particularly useful when assessing hearing disability and the value of interventions such as hearing aids or surgery. Because speech recognition is a phenomenon largely regulated by neural processing beyond the cochlea, abnormalities affecting the cochlear nerve or central auditory pathways will have a greater affect on speech recognition than on the detection of pure tones, which is a much more basic audiological function. Therefore, hearing loss caused by a retrocochlear pathology will result in a greater-than-expected loss of speech discrimination, than that predicted by the pure-tone audiogram. With retrocochlear pathology, the discrimination of speech may in fact deteriorate with increasing loudness, resulting in another type of speech audiogram curve where the speech recognition score decreases after reaching its peak, so-called rollover (Figure 2). Speech audiometry is therefore useful in that it reflects the site of the disorder as well as degree of disability.

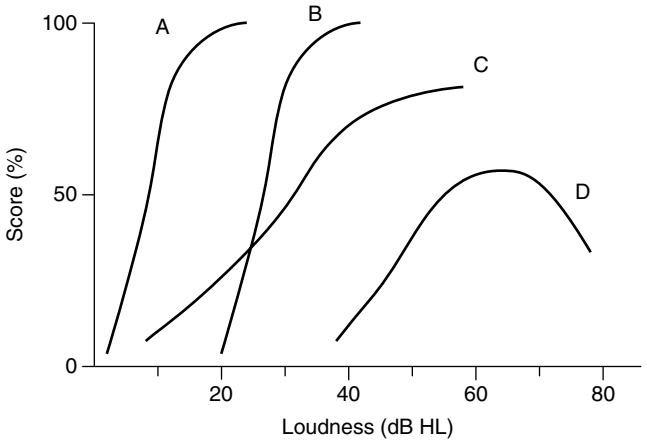

Figure 2 Speech audiometry, examples of various performance-intensity curves. (a) normal hearing individual reaching maximum score of 100%. (b) conductive deafness causing displacement of curve to the right by 25 dB. (c) sensory deafness in a patient whose score reaches 80% at 50 dB. (d) neural deafness in a patient with rollover, representing deterioration in discrimination with increasing loudness

THE SYMPTOMS OF EAR DISEASE

Hearing Loss

One of the commonest symptoms of ear disease is hearing loss. The broad classification of hearing loss is conveniently categorized according to the anatomical site within the auditory pathway affected. Deafness caused by any abnormality affecting the transmission of sound to the cochlear is a conductive deafness, whereas abnormalities of the cochlea or subsequent neural pathways result in sensorineural deafness. The distinction is useful as it conveniently allows the clinician to focus on the different potential pathological processes and management approaches that are required for the two types of deafness.

Conductive Hearing Loss

Most causes of conductive deafness can be identified on otoscopy. Common causes are listed in Table 2.

Wax (Cerumen)

Wax is an uncommon cause of deafness because it either has to completely occlude the ear canal or impinge against the eardrum. Wax is produced by the ceruminous glands, found in the outer third of the ear canal. Wax will become impacted if attempts are made to clean ears using blunt objects such as cotton tipped probes or tissues. Wax can become impacted by hearing aid molds if there is excessive wax production.

Wax should be removed either by syringing or manual removal using suitable wax hooks, ear forceps, or microsuction. Hard occlusive wax is best softened first, using oil or sodium bicarbonate. Syringing should not be performed in the presence of a known perforation or if the ear is effectively the only hearing ear, in which case, patients are best referred to an otologist for careful manual removal (Aung and Mulley, 2002).

Table 2 Causes of conductive deafness according to site

Site	Description
Pinna	Atresia, perichondritis
Ear canal	Wax occlusion, otitis externa, osteoma, foreign body, tumor (“ceruminoma”)
Tympanic membrane	Myringitis, perforation, calcification (tympanosclerosis)
Middle ear	Otitis media, ossicular fixation (otosclerosis or ankylosis), ossicular disruption, tumor (e.g. glomus)

Otitis Externa

The accumulation of infected debris and soft tissue occlusion of the ear canal in otitis externa may result in conductive deafness. Infection may be bacterial, viral, or fungal. Acute bacterial otitis externa is a very painful condition. Discomfort and irritation of the ear canal precedes the most severe period of pain, and discharge often precedes the onset of deafness. The mainstay of treatment is removal of debris and wax, usually by gently syringing or microsuction, and instillation of topical antibiotic and steroid drops. Ear swabs for bacteriology should be taken beforehand so that recalcitrant infection can be treated appropriately. The commonest bacterial pathogens are Staphylococcal and Pseudomonas (Roland and Stroman, 2002), over 90% of which remain sensitive to aminoglycosides and quinolones. Therefore, topical gentamicin or ciprofloxacin (0.3% solution) is often effective. Topical treatments are only effective after the removal of infected debris and discharge.

Fungal otitis externa is most often seen following prolonged antibiotic treatment. Careful cleaning and removal of fungal hyphae and spores will maximize the chances of resolution. Topical antifungal treatments using clotrimazole or clioquinol are important adjuncts. Systemic treatment is only needed in invasive infection in immunocompromised patients.

Myringitis

Inflammation or infection of the tympanic membrane is not uncommon, and tends to be mistaken for otitis media by virtue of the fact that the appearances can be similar.

Acute myringitis is usually viral in origin and may be accompanied by bullae on the outer surface of the drum. A common form of myringitis is characterized by hemorrhagic bullae associated with severe, sudden onset otalgia and conductive hearing loss, so-called *myringitis haemmorhagica bullosa*. It may be associated with sensorineural deafness in up to 40% cases. Granular myringitis has the typical appearance of vascular granulations on the outer surface of a de-epithelialized drum. This may respond to the application of topical steroid, repeated cauterization using silver nitrate carefully applied using an otological microscope or it may require surgical skin grafting (Blevins and Karmody, 2001).

Otitis Media

Infection or inflammation of the middle ear cleft is a common cause of conductive deafness. The distinction between inflammatory and infective otitis media is useful in that treatment options and symptoms differ between the two pathologies, although both coexist much of the time. Infective otitis media is usually followed by an inflammatory process before full resolution, characterized by a middle ear effusion that may take a few weeks to fully resolve. Conversely, inflammatory otitis media is characterized by the production of a sterile middle ear effusion, which may become secondarily infected.

Acute Infective Otitis Media

Acute infection of the middle ear cleft is usually viral. This may take the form of infection of the middle ear cleft itself or nasopharyngeal infection affecting Eustachian tube function. Secondary bacterial infection can occur, resulting in a prolonged episode requiring systemic antibiotics. Viral to bacterial conversion in acute otitis media occurs in about 10–20% of cases. In the majority of cases, therefore, all that is required is analgesia until the acute viral episode resolves after 2–3 days. Bacterial otitis media is characterized by increasing pain and toxicity, often culminating in tympanic membrane perforation and mucopurulent discharge from the ear. Common bacterial pathogens are *Streptococcus pneumoniae, Hemophilus influenzae*, and *Moraxella catarrhalis*. First-line treatment should be with amoxicillin or erythromycin for 5 days (O'Neill, 1999).

Chronic Otitis Media

Chronic middle ear infections are conveniently divided into those associated with cholesteatoma and those associated with middle ear mucosal disease and tympanic membrane perforations, the latter type is referred to as *tubotympanic otitis media*. The distinction between these types of chronic infection is not absolute and both may coexist. Historically, a distinction was made because cholesteatoma was thought to have a greater likelihood of leading to intracranial infection, but this is not the case. The serious complications of facial nerve palsy and meningitis are just as common with mucosal disease (Sing and Maharaja, 1993). The actual risk of developing intracranial infection from active chronic otitis media is between 0.5 and 1% over a 60-year period (Nunez and Browning, 1989).

Conductive deafness in chronic otitis media has a number of potential mechanisms. A number of causes may coexist, requiring a combined medical and surgical approach (see Table 3).

Management of Chronic Otitis Media

Examination of the ear should begin by carefully looking for a postaural scar. Acute mastoid infections were much more common years ago, and many elderly patients will have undergone mastoid surgery as children. Many of these will have been cortical mastoidectomies, whereby infection in the

Table 3 Pathological causes of conductive deafness in chronic otitis media and the otological procedures for their correction

Pathology	Treatment
Perforated drum	Myringoplasty
Disrupted ossicular chain	Ossiculoplasty
Mucosal edema	Topical steroid
Active infection	Antibiotics
	Mastoid surgery with Tympanoplasty
Tympanosclerosis and fixed ossicular chain	Ossiculoplasty

mastoid was drained through a postaural incision removing bone from the outer table of the mastoid, but not opening the cavity into the ear canal. Surgery to deal with cholesteatoma usually leaves an open cavity communicating with the ear canal, allowing inspection and cleaning of the cavity.

Findings on otoscopy direct the investigations and management principles. It is usually possible on inspection to determine if there is active infection or not. With inactive chronic otitis media, the commonest findings are: dry perforations of the tympanic membrane, patchy calcification of the drum (tympanosclerosis), retraction of the tympanic membrane. Retraction of the pars tensa may occur in the central portion of the drum or near the margin, most often the posterior margin. Deep retractions can mimic perforations, the distinction being that retractions are lined with a thin layer of dry squamous epithelium, whereas moist middle ear mucosa can be seen through perforations. Retraction of the pars flaccida in the upper part of the drum (the attic) is more often associated with accumulation of squamous epithelium and recurrent infection and may be the precursor of cholesteatoma or the only external feature of an extensive mastoid cholesteatoma. It is advisable to inspect the ear with an otological microscope where there is a marginal or attic retraction.

Purulent discharge should be cultured and treated using systemic antibiotics such as amoxicillin initially. Persistent infection usually signifies loculations of infected debris, inappropriate antibiotic, or poor penetrance into the middle ear cleft. Careful cleaning and removal of debris from the ear is essential in these cases. The outer ear canal can be dry mopped using cotton wool wrapped/mounted on a probe such as a Jobson Horne probe. It is much more difficult to clean debris lying against the drum or in the middle ear cleft, and this usually requires microsuction using the otoscopic microscope. Topical antibiotics can then be administered. Many of these contain potentially ototoxic antibiotics and are not recommended by manufacturers or the Committee on Safety of Medicines (CSM) in the presence of a perforation. Nevertheless, specialists have used topical aminoglycosides for many years to good effect and consider the presence of pus and active infection in the middle ear to be a greater risk to the hearing than the short-term use of these drops (Lundy and Graham, 1993). A nonototoxic alternative is ciprofloxacin 0.3% or ofloxacin 0.3% (both available as ophthalmic solutions but unlicensed for otitis media), especially as *Pseudomonas* is a common pathogen in chronic otitis media (Ghosh *et al.*, 2000).

Referral to a specialist is recommended in the presence of persistent granulations on the tympanic membrane or middle ear mucosa, or if there is continued drainage despite topical antibiotics.

Complications of Otitis Media

Complications of otitis media are uncommon but can be serious. They fall into two broad groups – extracranial and intracranial.

Extracranial Complications

Acute Mastoiditis. Because the mastoid air cells are confluent with the middle ear space, infection within the mastoid is almost inevitable following otitis media. Improvements in imaging over the last few years have highlighted the frequency of mastoiditis and serve as a reminder that most cases of mastoiditis go undiagnosed and are successfully treated along with the otitis media. Treatment should be modified if there is involvement of the periosteum of the postauricular area with associated erythema and protrusion of the pinna. These features indicate spreading infection and demand a change in antibiotic therapy as well as consideration of intravenous administration. If the tympanic membrane is intact, a myringotomy with drainage of middle ear pus will aid resolution and provide material for microbiology. Progress beyond this stage with osteitis results in increasing fever, postauricular swelling, and downward protrusion of the pinna and requires surgical drainage (mastoidectomy).

Chronic Mastoiditis. Chronicity following simple acute otitis media is uncommon. A more common scenario is an acute infection on a background of chronic disease. Bacterial infection in chronic mastoiditis is more often mixed, anaerobic bacteria can be isolated in the majority of cases, and *Pseudomonas* is quite prevalent.

Acute Labyrinthitis. The pathological progress of inner ear infection allows a distinction to be made between so-called serous labyrinthitis and suppurative labyrinthitis. Serous labyrinthitis results from bacterial toxins and other chemical changes disrupting the normal chemical equilibrium within the perilymph of the inner ear. It is potentially reversible and therefore results in temporary vertigo and a fluctuating sensorineural hearing loss. Conversely, suppurative labyrinthitis refers to bacterial invasion and manifests itself with severe vertigo and profound hearing loss. Meningitis may develop if infection spreads along perilymph channels to the internal auditory canal or through the cochlear aqueduct to reach the CSF. Labyrinthitis secondary to otitis media is today a very rare occurrence, in contrast to a reported 4% incidence at the turn of the last century (Whitehead, 1904).

Facial Palsy in Otitis Media. Only about 5% of all facial palsies are caused by otitis media (Table 4 – causes of facial palsy). Facial weakness rarely occurs in acute otitis media,

Table 4 Causes and incidence of acute facial palsy, excluding true idiopathic ("Bell's palsy"), which still accounts for about 20% of facial palsies (Reproduced from Peitersen E, Bell's palsy, *Acta Otolaryngol Suppl*. (2002) **549**, 4–30, by permission of Taylor & Francis)

Causes	Incidence (%)
Herpes simplex virus type 1	75
Herpes zoster virus	15
Trauma	4
Otitis media or cholesteatoma	5
Rare and unusual conditions	1

but it may occur when the facial nerve canal is dehiscent in the middle ear. In chronic otitis media, the thin bone overlying the facial nerve may be eroded by osteoclastic activity resulting in neuropraxia. The overall incidence of facial nerve palsy increases with age, from approximately 1 per 10 000 at the age of 20 to about 6 per 10 000 at age 60. Facial nerve weakness resulting from middle ear infection will sometimes respond to the treatment targeted toward the middle ear infection.

One of the most important prognostic predictors is the degree of paralysis. Over 90% of partial palsies make a full recovery, whereas the likelihood of recovery reduces to about 60% if the palsy is complete. The rate of recovery of complete facial palsy secondary to middle ear infection improves with surgical intervention. In acute otitis media, a myringotomy should be performed to aspirate middle ear mucopus, sending pus for microbiology. In chronic otitis media, surgery should be performed after radiological investigations, with CT being the most appropriate as it demonstrates bone erosion and cholesteatoma; surgery can then be targeted appropriately.

Petrositis. Extension of infection into the petrous part of the temporal bone may be a cause of persistent otorrhea associated with deep otalgia. Irritation of the trigeminal nerve as it crosses the apex of the petrous temporal bone results in orbital pain and more extensive involvement of the ophthalmic division of the trigeminal nerve. The abducent nerve may also be involved, resulting in a lateral rectus palsy. The combination of trigeminal pain, 6th nerve palsy and deep otalgia constitutes Gradenigo's Syndrome. Diagnosis is confirmed by radiology and requires immediate antibiotic therapy, although the duration of medical treatment before considering surgery is controversial. Access to the petrous apex is difficult and therefore surgery should only be considered if there is a deterioration clinically and radiologically, despite appropriate medical treatment.

Intracranial Complications

Intracranial complications are rare in otitis media, occurring in about 0.3% of all cases (Kangsanarak *et al.*, 1995). When intracranial complications do occur, they are often multiple.

Meningitis (see Chapter 148, Infections of the Central Nervous System). This is the commonest intracranial complication of otitis media, accounting for about a half of all intracranial complications. Treatment must be directed primarily toward the meningitis (Heyderman *et al.*, 2003), using intravenous cefotaxime or cefriaxone. A CT scan will determine whether there are associated complications and whether surgery to drain the ear or mastoid is necessary.

Intracranial Abscess (see Chapter 148, Infections of the Central Nervous System). Subdural, extradural, and parenchymal brain abscesses are less common than meningitis and require the input of neurosurgeons. The mortality of patients with intracranial abscess formation following chronic otitis media is close to 10%.

Lateral Sinus Thrombosis. Thrombosis of the lateral (sigmoid) sinus is diagnosed by MRI or CT scan. Thrombosis may extend into the internal jugular vein and very rarely results in septic emboli. It requires aggressive antibiotic treatment and may require surgery to deal with the mastoid infection and infected clot if symptoms persist. Altered venous drainage may result in raised intracranial pressure and so-called "otitic hydrocephalus", with papilloedema, vomiting, headache, and 6th nerve palsy. It is a misnomer as the ventricles are reduced in volume because of the generalized raised intracranial pressure. It occurs more often in younger patients and is treated by CSF drainage and anticoagulation.

Sensorineural Deafness

Hearing loss in the elderly is predominantly a form of degenerative deafness to which the term "presbycusis" applies. The potential causes of sensorineural deafness increase with increasing age by virtue of the fact that many of the causes are more likely to have occurred in the older population. With increasing age, people are more likely to have been exposed to noise, ototoxic drugs, ear infections, vascular disorders, neural disorders, and trauma. The term presbycusis is reserved for those cases of hearing loss for which there is no identifiable cause and in whom the cause is thought to be related to a degenerative change associated with aging.

What is "Normal" in the Aging Population?

Various epidemiological studies have examined the pattern of hearing loss in the aging population (*see* **Chapter 104, The Epidemiology of Hearing in Aging Population**). Age-related hearing loss (ARHL) affects virtually all people to a varying degree. Studies have shown that the loss with age is greater in men than in women and greater in manual workers even after allowing for noise exposure (Davis, 1989). Figure 3 illustrates the mean hearing thresholds in the typical UK adult male and female population based on the MRC National Study of Hearing (Davies, 1995).

The greatest change in hearing with age disproportionately affects the higher frequency hearing thresholds. The audiograms in Figure 4 illustrate the expected range of hearing in the cohort of men aged 40–49 years compared to the 70–79 year age-group. The shaded areas represent the range of hearing in the 25–75th percentile of these population cohorts (data from MRC National Study of Hearing (NSH) database).

These audiograms demonstrate how the individuals with the least amount of ARHL in the 70–79 year age-group have similar hearing to those individuals with the worst ARHL in the 40–49 year age-group.

The pathological processes responsible for ARHL have been divided into four main groups – sensory, neural, strial, and cochlear conductive (Schuknecht, 1993).

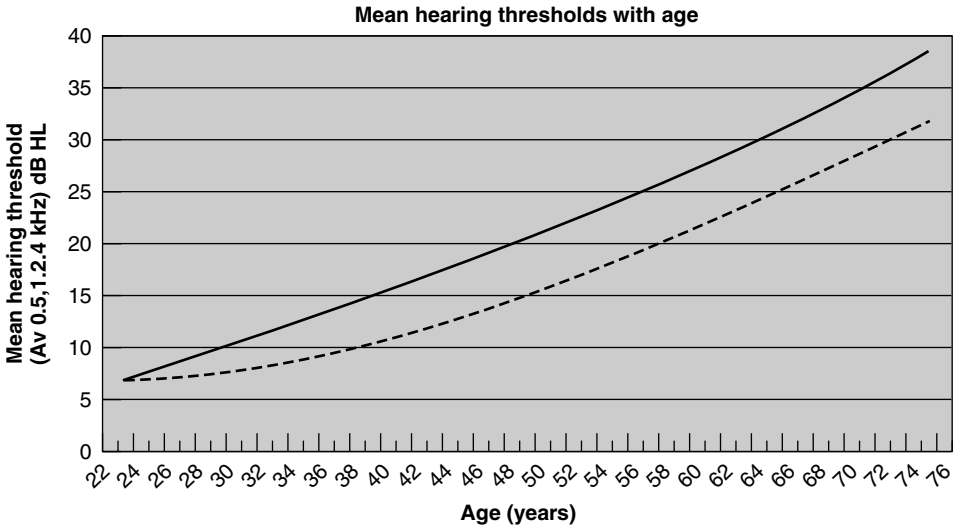

Figure 3 Graph showing mean hearing thresholds against age for men (solid line) and women (dashed line); data from UK MRC National Study of Hearing

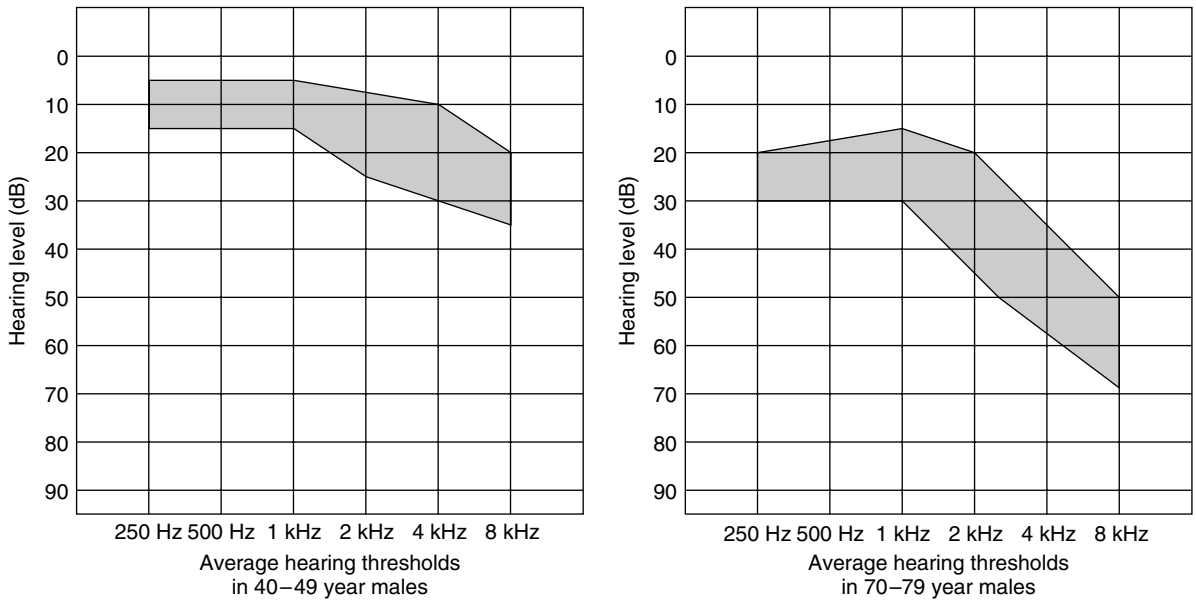

Figure 4 Audiograms illustrating the range of hearing (25th – 75th centiles) in two 10-year cohorts of men, aged 40–49 years and 70–79 years (based on MRC National Study of Hearing)

The different types are based on patterns of histological change associated with characteristic patterns of hearing loss. This is a useful classification in that it helps with the understanding of pathophysiology and may be useful in explaining why similar magnitudes of hearing loss can result in markedly different degrees of discriminatory loss.

Sensory Presbycusis

Sensory presbycusis is predominantly caused by loss of sensory epithelium within the organ of Corti. Most of the loss tends to occur near the basal end of the cochlea, accounting for high-frequency loss. There is relative sparing of the neuronal and supportive elements within the cochlear, which accounts for the reason why many of these types of hearing loss may have quite good speech discrimination.

Neural Presbycusis

Neural presbycusis, on the other hand, is associated with a loss of speech discrimination, which is more marked for a given loss in pure-tone threshold compared to sensory

presbycusis. Loss of cochlear neurones is almost inevitable with increasing age, although pure-tone threshold appears not to be affected until about 90% have disappeared. The commonest pattern of pure-tone loss is similar to that seen in sensory presbycusis, a high-frequency loss.

Strial Presbycusis

Degeneration and atrophy of the stria vascularis is believed to affect the homeostatic control of inner ear endolymph and glucose metabolism and has been described as a pathological feature in some forms of familial hearing loss. The pattern of hearing loss affects all frequencies equally, producing a so-called flat loss on PTA. Preservation of the neuronal population results in good speech discrimination relative to the pure-tone hearing loss.

Cochlear Conductive Presbycusis

A fourth pathological variety of presbycusis is proposed on the basis that some individuals with a significant hearing loss have no obvious histopathological changes other than changes to the cochlear likely to result in changes to its mechanical properties, such as fat deposition and calcification in the basilar membrane. Altered electromechanical properties affecting the outer hair cells, which are responsible for the cochlear amplification process, may contribute to this type of hearing loss. These changes are proposed as an explanation for some cases of high-frequency loss without significant loss of sensory epithelium or neuronal population.

Patterns in Hearing Loss

Progressive Bilateral Loss

Overall, it is estimated that about half of all patients with progressive bilateral sensorineural deafness have a genetic cause, and of these, the majority are nonsyndromic (70 vs 30% syndromic), and the majority of these are autosomal recessive (75 vs 25% autosomal dominant). In the remaining patients, environmental factors and certain diseases may be implicated, for instance, noise-induced deafness, ototoxic drug exposure (e.g. aminoglycosides) and viral or bacterial infections. Progressive bilateral deafness is the commonest pattern of hearing loss seen in the adult population. In the majority of cases, the etiology is unknown, but because the prevalence of this type of impairment increases with age, the cause is often thought to be an age-related degeneration ("presbycusis"). Age-related deafness tends to affect the higher frequencies first, the commonest pattern of hearing loss on a pure-tone audiogram being a sloping line downward to the right, which, if severe, is sometimes referred to as a *ski-slope* loss.

The loss of predominantly low frequency hearing is unusual, although it is associated with Meniere's syndrome. The term Meniere's syndrome refers to the triad of sensorineural hearing loss, tinnitus, and episodic vertigo, and has been associated with the pathological changes of endolymphatic hydrops in which the endolymph compartments within the inner ear are expanded relative to the perilymph compartments. Although Meniere's syndrome often affects both ears, it does so in a varied way such that some patients will have an asymmetric loss (see the following text).

Very few general diseases have a proven association with bilateral sensorineural deafness, but they include diabetes (Tay *et al.*, 1995), Paget's disease, and neurosyphilis.

Asymmetrical Hearing Loss

In most individuals with a hearing impairment, there is no noticeable difference between the two ears. An average difference of about 15 dB between ears will be detectable by most people, and the majority of cases of asymmetric hearing loss in the population are due to a conductive deafness. The incidence in the UK population of asymmetric sensorineural deafness is about 3% (MRC NSH data). In the majority of cases, the cause of the hearing loss cannot be identified even after extensive investigations. In about 5% of cases, the deafness can be attributed either to a congenital cause, head injury, previous labyrinthitis, or noise exposure, or to ototoxic drugs. Rather surprisingly, ototoxicity from aminoglycoside drugs predominantly affects one ear in 60% of cases (Lerner *et al.*, 1983).

A small number of patients with asymmetrical sensorineural deafness will have an acoustic neuroma. This benign tumor arising from shwann cells of the vestibular nerve is more correctly termed *vestibular schwannoma* and accounts for 6% of all intracranial tumors. The peak incidence is in the 7th decade, with a slightly higher incidence in females compared to males in the 8th decade. The commonest presenting symptom is an asymmetric hearing loss (90%), or unilateral tinnitus (70%). As the tumor enlarges, it may compress the facial nerve or affect the trigeminal nerve resulting in some facial weakness or paresthesia. Some tumors will enlarge, so as to become life threatening, and, therefore, this is a condition that needs to be identified and treated if necessary. Age alone should not dictate whether or not a patient with appropriate symptoms is investigated. Knowledge of the diagnosis, even if no treatment is offered, may help in patient management. Once established, the most appropriate investigation of a patient with asymmetrical hearing loss is an MRI scan. Specialized audiometric investigations such as auditory brainstem responses (ABR) have a high sensitivity and specificity (over 90%) in the diagnosis of acoustic neuromas; however, the false negative rate of ABR, especially for small neuromas, is unacceptably high and approaches 17% (Wilson *et al.*, 1997). Nevertheless, it may be useful in patients who cannot undergo MRI. CT may not detect small tumors (<10 mm), but may be useful in elderly patients in whom the aim is limited to detecting larger space-occupying lesions. Once diagnosed, management options are interval scanning, surgery, or radiotherapy. Up to two-thirds of acoustic neuroma remains stable over a follow-up period of 35 months (Tschudi *et al.*, 2000) and about 1 in 10 will regress (Luetje, 2000). No study exists

that systematically compares the different modalities of management (surgery, radiosurgery, interval scanning). Although surgery will achieve total removal in well over 90% of cases, radiosurgery appears to achieve control of tumor growth in most cases. With both modalities, damage to adjacent neural structures is possible, facial nerve palsy being one of the commonest complications. Operative mortality remains at about 1%.

Sudden Hearing Loss

Sudden hearing loss should be considered a medical emergency if the loss is sensorineural, although for the majority of cases the definitive diagnosis will remain unknown. A sudden loss is defined as 30 dB or more sensorineural hearing loss over at least three adjacent audiometric frequencies occurring within 3 days or less. About one in every 10 000 to 15 000 people will suffer from this condition, with the highest incidence occurring between 50 and 60 years.

Suggested causes of idiopathic sudden sensorineural hearing loss include viral infections, immunologic, vascular compromise, and intracochlear membrane breaks. Serial audiometric testing provides documentation of the progression or resolution of the hearing loss and response to treatment. Few laboratory studies have been shown to be helpful, although initial screening tests should be directed based on history and suspected conditions and aim to identify potentially treatable conditions. Test might include: full blood count, erythrocyte sedimentation ratio (ESR), glucose, cholesterol/triglycerides, T3, T4, TSH, VDRL, and Lyme titer. MRI is useful in evaluating for acoustic tumors, multiple sclerosis, and cerebrovascular accidents. About 10% of all acoustic neuroma present with a sudden hearing loss.

Autoimmune hearing loss may be associated with or part of systemic autoimmune diseases such as Cogan's syndrome, Wegener's granulomatosis, polyarteritis nodosa, temporal arteritis, Buerger's disease (thromboangitis obliterans), and systemic lupus erythomatosis.

Traumatic breaks in the membranous labyrinth are accepted causes of sudden hearing loss. Cochlear membrane breaks may be either intracochlear, as is thought to occur in Meniere's syndrome, or involve the labyrinthine oval and/or round windows with a resultant perilymph fistula. The patient's history will usually elicit an inciting event such as a blow to the head, sneezing, bending over, lifting a heavy object, exposure to sudden changes in barometric pressure (such as during flying or diving), or exposure to a loud noise. Initial treatment should include 5 days of strict bed rest with the head of bed elevated 30°. The patient should avoid straining or forceful nose blowing. Stool softeners may be given. If no improvement is seen after 5 days, surgical therapy, including middle ear exploration with patching of the perilymphatic fistula should be considered.

Because the majority of cases of sudden sensorineural deafness are idiopathic, treatment options are limited. Despite this, there is a long list of suggested options described, which include steroids, cyclophosphamide, methotrexate, diuretics, antiviral agents, vasodilators, and low-molecular-weight dextran, although there is little supportive evidence for their use (Wilkins *et al.*, 1987). Some studies have found that steroids had a significant effect on the recovery of hearing in patients with hearing loss between 40 and 90 dB (Moskowitz *et al.*, 1984; Wilson *et al.*, 1980), whereas patients with profound hearing loss do not appear to benefit significantly from steroid use.

Tinnitus

Although a common symptom, tinnitus rarely becomes a significant clinical problem, but when it does, it requires careful evaluation and a combination of counseling and consideration of various management strategies.

Tinnitus is a symptom whereby an individual has a conscious perception of sound originating from within the individual. The perceived sound varies considerably between patients. One useful characteristic that may indicate the source of the tinnitus is that of pulsation, which may represent transmitted vascular sounds indicative of cardiovascular pathology. Another unusual description that suggests a physical origin to the tinnitus is that of a repetitive clicking or "a chirping cricket" that may occur in myoclonus of middle ear muscles (usually tensor tympani) or palatal muscles.

Physiological tinnitus accounts for less than 5% of all cases presenting to a tinnitus clinic, and the majority of these result from the perception of vascular sounds. A pulsation or humming noise may originate from arterial or venous flow in or around the ear, or from stenosis of the carotid artery. Occasionally, transmitted cardiac sounds, especially murmurs associated with aortic stenosis, can cause troublesome pulsatile tinnitus. Rarely, vascular malformations or tumors such as glomus tumors of the middle ear (*glomus tympanicum*) or jugular fossa (*glomus jugulare*) will present with pulsatile tinnitus.

Pathophysiological tinnitus occurs in situations where auditory function is temporarily disturbed by external factors. The three commonest factors are noise exposure, pharmacological, and toxemic. Excessive noise exposure has long been associated with tinnitus. Short-term noise exposure can result in temporary tinnitus as a result of probable chemical and neurological effects within the cochlear. The duration of noise exposure that may produce tinnitus varies according to the noise level, typically from being a few hours exposure to noise at 90 dB to a few milliseconds of high-intensity explosive sounds. Prolonged and repetitive exposure to loud sound may result in longer periods of temporary tinnitus, eventually leading to permanent tinnitus and hearing loss, with the greatest loss being close to 4 kHz.

Drug-induced tinnitus may be temporary or permanent. Although there are a large number of drugs associated with tinnitus, most cases of drug-induced tinnitus are associated with those listed in Table 5. They broadly fall into two groups, those associated with permanent tinnitus and deafness as a result of ototoxic effects and those producing

Table 5 Drugs capable of causing either permanent or temporary tinnitus

Permanent tinnitus	Temporary tinnitus
Aminoglycosides	*Nonsteroidal anti-inflammatory drugs*
Gentamicin	Ibuprofen
Neomycin	Diclofenac
Streptomycin	Indomethacin
Tobramycin...	
Other antibiotics	*Antidepressants*
Rifampicin	Venlafaxine
Vancomycin	
Chloramphenicol	
Erythromycin	
Polymyxin	
Cytotoxic agents	*Hypnotics*
Cisplatin	Benzodiazepine
Vincristine	
Loop diuretics	*Antimalarials*
Frusemide	Quinine
Bumetanide	Primaquine

temporary tinnitus, often as a result of effects on the central nervous system.

As well as inducing tinnitus as a result of pharmacological changes to the auditory system itself, some drugs are associated with tinnitus as a consequence of a hyperexcitable state brought on during rapid drug withdrawal. This is not uncommon with benzodiazepines.

Tinnitus may occur in patients with systemic illness, who are toxic and in whom the illness causes a temporary tinnitus. Many of these individuals have an underlying abnormality predisposing them to tinnitus.

Pathological tinnitus occurs as a result of physical or psychological disorders, which can broadly be divided into disorders of the auditory pathway, or disorders affecting other associated systems. Auditory disorders can be further classified as those affecting the conductive mechanism, the cochlea, the peripheral neural pathway or the central auditory pathway. The associated systems that can give rise to tinnitus include transmitted sounds from muscular structures (e.g. palatal myoclonus in which there is episodic twitching of the soft palate), respiratory sounds transmitted through a patulous Eustachian tube and vascular sounds. Vascular tinnitus may be "physiological" or may be secondary to turbulent blood flow through normal or abnormal structures adjacent to the ear. A history of pulsatile tinnitus, which is synchronous with the pulse, requires further radiological investigations including carotid assessment and, if the carotids are normal, magnetic resonance angiography if a skull base vascular tumor or vascular malformation is suspected.

The auditory disorders giving rise to tinnitus are usually associated with hearing loss, the identification and investigation of which usually locates the site of the abnormality. Conductive tinnitus may result from the reduction of ambient background noise consequent to the conductive deafness. Tinnitus is an uncommon association with isolated conductive losses; it is more often seen in sensorineural deafness. Individuals with sensorineural deafness and tinnitus may experience a deterioration in the tinnitus if they develop an additional conductive loss, as a result of accumulation of wax or debris in the ear canal, for instance.

Tinnitus arising from disorders of the cochlea and/or cochlear nerve account for the majority of tinnitus cases. An association between the severity of hearing loss and the prevalence of tinnitus means that tinnitus is more likely to occur in the aging population, with up to 70% of patients with presbycusis attending audiology clinics admitting to having some degree of tinnitus (Spoendlin, 1987). There is also a broad association between the perceived loudness of the tinnitus and the severity of the hearing loss. Despite these associations, not everyone with a sensorineural deafness suffers from tinnitus. Various studies have estimated the prevalence of tinnitus within different groups and populations. The NSH in the United Kingdom found that 7% of the adult population consult their family doctor at some point of time because of tinnitus. The commonest group that seek advice are aged 55–65 years (MRC Institute of Hearing Research, 1987), about 40% of patients attending tinnitus clinics are aged over 60 years, and a quarter of these (10% of attendances) are aged over 70 years (Hazell *et al.*, 1985). Many of the reports and studies of tinnitus prevalence gather data from specialist clinics and therefore from a highly selected population, which tends to bias the data. Unselected epidemiological studies have indicated that less than 0.5% of the UK population suffer troublesome tinnitus, whereas 35% of the adult population have suffered nontroublesome tinnitus (MRC Institute of Hearing Research, 1987).

Investigation

The history may direct the examination and subsequent investigations, which should include general examination of the cardiovascular and neurological systems, concentrating on the head and neck. This should include auscultation of the neck and ears and, cranial nerve examination including baseline audiology. Assessment of the tinnitus is of some value in that pitch and loudness matching using an audiometer will give an indication of the characteristics complained of.

Although a variety if blood tests have been advocated in the investigation of tinnitus, they must be interpreted with caution; there are no specific blood investigations necessary for the investigation of tinnitus in isolation. Radiological investigations may be necessary where there is clinical evidence or suspicion of a vascular cause or pathology within the temporal bone affecting the VIIIth nerve.

Treatment

In the vast majority of cases, tinnitus cannot be eliminated, and treatment is directed toward ameliorating the effects, with only about 5% of cases having an identifiable cause that can be treated. The majority of patients with tinnitus also have a hearing loss and anything that can be done to reduce this may also benefit the tinnitus by virtue of

increasing the awareness of ambient background noise. For the time being, there is no routine specific medical treatment for tinnitus. It has been known for sometime that intravenous lidocaine can reduce or eliminate tinnitus and there have been reports of its use in severe tinnitus (Marzo *et al.*, 2004), but its effects are temporary and the potential risks outweigh its benefits for routine use. These reports have increased interest in the local application of similar drugs to the round window membrane or middle ear cavity via a small catheter inserted into the middle ear (Adunka *et al.*, 2003; Schwab *et al.*, 2004), the results of which indicate little or no benefit on the tinnitus, although there does appear to be a short-term benefit in the control of vertigo in Meniere's disease.

The mainstay of tinnitus therapy is psychological support and counseling, once treatable causes have been eliminated. Professional counseling is usually available at local audiology departments, with much of the work now being done by audiological physicians supported by hearing therapists. Counseling can be supported by literature and there are many suitable booklets and information leaflets on this subject. The availability of material on the Internet has also enabled patients to understand more about tinnitus and access useful self-help advice. The quality and suitability of this information is varied, and should not be recommended unless appropriate. Some information may be difficult to understand and can lead to rather negative and pessimistic conclusions. In the United Kingdom, patients can be encouraged to join local self-help groups, which are often set up by local members of the British Tinnitus Association. The association also provides useful information on the Internet (http://www.tinnitus.org.uk) and can provide support material and audio recordings for relaxation in the form of tapes and CDs. Additional help is sometimes provided by way of tinnitus maskers. These devices provide a source of noise that the patient finds more acceptable than the tinnitus; they do not (as the name suggests) cancel the tinnitus sound. Complete masking is unusual, most patients report being able to perceive the sound of the tinnitus as well as the masking noise. The use of environmental sounds to relieve the tinnitus may seem an obvious alternative, yet many elderly patients will not have thought of this. Tinnitus is often more troublesome in a quiet environment and can be particularly troublesome at night. The presence of background noise from a clock, fan, or radio can be beneficial, and the use of a flat under-pillow speaker to deliver low volume sounds can help in relaxation and sleep. Many tinnitus support associations provide recordings of sounds that can be useful in relaxation.

Surgical treatment of tinnitus is very limited, although many patients with both profound deafness and tinnitus who have received a cochlear implant have reported improvements in the tinnitus. The prevalence of tinnitus amongst these patients is high (approximately 80% have significant tinnitus), but between 50 and 70% report improvements or resolution of tinnitus after implant surgery (Tyler, 1995; Ito and Sakakihara, 1994).

The Management of Hearing Loss in the Elderly

The nature of progressive hearing loss in the elderly, by virtue of its slow relentless progress, results in a degree of adaptation. This may be all that is needed in the early stages, when the odd misunderstanding creeps into conversation and may be followed by a simple explanation. Also, the listener may be able to modify the listening environment, for example by sitting closer to family and friends, especially in noisy environments.

As hearing loss worsens, adaptations occur that become more noticeable to others. The volume of the television and radio increase, people are asked to repeat themselves more and more; slowly but surely, frustration grows and situations with difficult listening environments are avoided. Group conversations become an ordeal. Frustration turns to embarrassment or, worse, bitterness, and loneliness.

The magnitude of the hearing loss does not in itself determine the disability caused by the loss because this is also determined by the patients' listening requirements. Various self-assessment questionnaires have been used to assess disability and are useful in assessing the benefit of any intervention.

Amplification

Apart from hearing aids (detailed below) there are many other sources of amplification to help hearing-impaired adults. These include personal listening devices that can be used in isolation or act as a link between a hearing aid and television, radio, or other sound sources. Many of these are available on the NHS in the United Kingdom and are provided through audiology departments on the advice of various professionals, including hearing therapists, audiologists, otologists, and audiological physicians.

Hearing Aids

Hearing aids are amplification devices that allow the users to perceive sounds that would otherwise have been at intensity levels below their auditory thresholds. The basic components of most simple hearing aids are a microphone, a transducer and amplifier, and a receiver or loudspeaker. Most hearing aids are powered using a small battery housed in a hidden battery compartment. Air conduction hearing aids have a custom-made earmold taken from an impression of the patient's ear. Rarely, earmolds cannot be tolerated or used, in which case a bone conducting hearing aid can be used. These transmit sound to the mastoid bone through a bone conduction vibrator held in place by either a spring headband or surgically implanted attachments.

Air Conduction Hearing Aids

These are hearing aids that deliver sound to the ear through a receiver or speaker in the ear canal, the sound traveling

through the air of the ear canal. The commonest variety is the "behind the ear" (BTE) configuration, which consists of a small hearing aid behind the pinna onto which a custom-made earmold is fitted. Most hearing aids fitted in the United Kingdom on the NHS are of this type.

Some patients prefer small discrete aids that fit into the ear canal. The hearing aid components are fitted within the hearing aid mold. These aids vary in size with some small enough to fit well within the ear canal ("in the canal" (ITC)); others are slightly larger, sitting in the conchal bowl of the pinna ("in the ear" (ITE) or modular hearing aids) and still being visible. ITE and modular aids tend to need more frequent repairs than BTE hearing aids, with the added disadvantage that patients often have to have another ear mold made in order to manufacture a new aid. The BTE aids can be replaced off the shelf and immediately fitted onto the patient's existing ear mold.

Digital hearing aids are those that process the sound signal digitally before converting it back into an analog sound signal. They too come as BTE, ITE, or ITC types. They can process and adjust sounds in various ways, providing additional benefits for some patients. Analog hearing aids may still be preferable to digital aids in some situations; for instance, there appears to be little benefit in using digital over analog aids in many cases of conductive deafness.

The external features of a typical BTE hearing aid is shown in Figure 5. The introduction of digital aids has increased the variety of aids available and in use by patients. Most aids have a battery compartment, which, in small aids, may serve as the on/off switch. The aid may have a separate selection switch including the on/off control. Analog aids with conventional control switches will have three positions: M, T, and O. "M" is used to select the microphone (i.e. switching on the aid), "T" for using the induction loop in the aid, and "O" for Off. When set to the "T" setting, the aid can pick up a signal from an induction loop system and will inactivate the external hearing aid microphone. This has the advantage of cutting out any background noise. The presence of a "loop system" is normally indicated in public places such as banks and post offices; they are often used in churches, theaters, and cinemas. Hearing aid–compatible telephones also use a loop system and can improve the clarity of sound when using the "T" setting.

Figure 5 Modern, behind the Ear (BTE) hearing aids. On the left is one with conventional patient controls including a volume control wheel. On the right is a digital aid that can be programed to a number of different settings. The button marked with an asterix is used to cycle through the different programs. B indicates the battery compartments

Digital aids have the capacity to be programed to manipulate sounds to the advantage of the listener according to the magnitude and frequency location of the hearing loss. Two or more programs can be loaded into the aid, so an additional feature on digital aids is the ability to select different programs, for instance, one for common everyday use and another for listening to music.

Most hearing aids have a volume control wheel, although many digital aids will automatically adjust volume and some will not have a manual volume control. With some digital aids, it is possible to disable the volume control wheel (useful in confused elderly patients who "fiddle" with their aids), a point to remember if patients report an apparent fault with this control.

Candidature

Any patient with hearing difficulty is a potential candidate for a hearing aid. A simple predictor of hearing aid use is the degree of disability for everyday speech (Davies *et al.*, 1991). Also, those patients unable to hear a forced whisper at 70 cm in their worst ear are likely to accept a hearing aid. The mean hearing threshold at which patients seek amplification is about 45 dB HL, and over 50% of patients with an average loss of 55 dB HL or more will accept and use bilateral hearing aids. That is not to say that hearing aids cannot provide significant benefit to those with lower hearing thresholds, but reluctance to use hearing aids for various reasons means fewer people than predicted ask for aids. It is estimated that only about 35% of patients with hearing thresholds of 45–55 dB HL have hearing aids (Davies, 1997).

The UK National Study of Hearing, carried out by the MRC Institute of Hearing Research (Davies, 1995) found that approximately 20% of individuals in the age bracket 71–80 years had hearing thresholds worse than 45 dB. The overall prevalence of individuals reporting hearing difficulties in the United Kingdom population is 16%, but in the 75-and-over age-group, 52% report difficulties with their hearing (General Household Survey, 2002; Office of National Statistics, UK). Less than half of these wear hearing aids (23%) (see Figure 6).

Approximately 1 in 10 people given a hearing aid are, for various reasons, nonusers. The percentage of hearing aid users who continue to have hearing difficulties despite using hearing aids is not age dependant, with about 60% of all age-groups reporting some ongoing difficulties. This is perhaps a reflection that patient expectations are often unreasonable, many expect hearing aids to restore hearing to near normal. This will never be achieved by amplification alone, especially where there is associated central neural degeneration affecting discrimination and central processing.

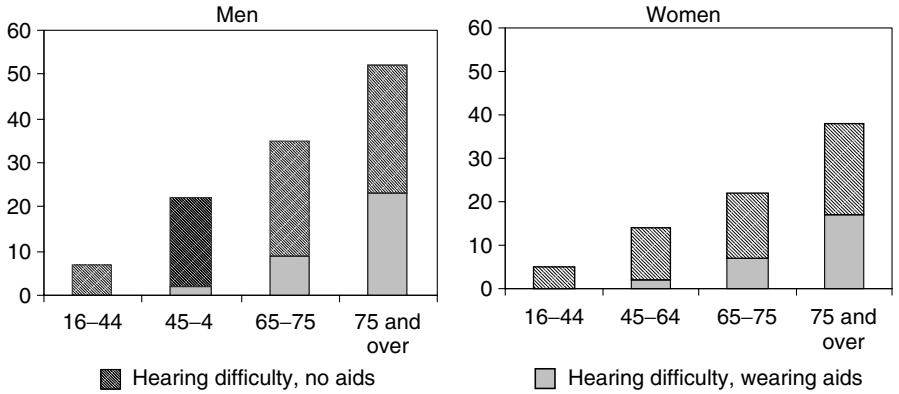

Figure 6 Percentage by age of men and women reporting some difficulty with hearing. Based on: Living in Britain, General Household Survey 2002, Office of National Statistics

Part of the process of hearing aid fitting should involve careful counseling and support in other ways so as to reduce the residual disability after appropriate hearing aid fitting. With this type of approach, about 95% of patients fitted with hearing aids will continue to use them on a regular basis.

Other Types of Hearing Aids

Bone conducting hearing aids provide a means of directing sound to the ear through the skull. They can be attached either to a headband or on the end of spectacle arms, directing sound to the mastoid bone behind the pinna. They are used only if air conduction aids cannot be used because of atresia of the ear canal or a chronic persistent discharge from the ear.

Bone anchored hearing aids work in similar situations, but are attached to a surgically implanted receiver (abutment). The abutment is a metal stud onto which the custom-made hearing aid attaches. This is useful if the need for a bone conducting aid is a long-term one.

Cochlear Implants

In situations where the hearing loss is so severe that there is little residual hearing, and the patient is unable to benefit from conventional hearing aids, cochlear implants may be used. Cochlear implants consist of an internal component, which has to be surgically implanted, and an external processor worn behind the ear or as a body worn device. The internal component consists of a receiver placed under the skin behind the ear and an electrode array inserted into the cochlear itself. The number of electrodes on the array varies according to the design of the device, most commonly used implants having between 12 and 22. The external component consists of an external coil that transmits the signal to the internal receiver, a speech processor and microphone. In the BTE variety of cochlear implants, the microphone is situated on the speech processor and is similar to a BTE hearing aid.

In order to benefit from a cochlear implant, the auditory nerve must be intact, and there must be a residual population of spiral ganglion cells within the cochlea. Insertion of the electrode into the cochlea is only possible if the cochlea is patent, although obliteration by disease (labyrinthitis following meningitis, or otosclerosis) is not a contraindication, a specially designed split electrode being used in such circumstances.

The outcomes from cochlear implantation are varied and can be difficult to predict beforehand. Suitable candidates are adults who have lost their hearing in both ears and gain little or no benefit from the most appropriate, properly fitted, and adjusted hearing aids. Adults with speech recognition scores on speech audiometry of less than 30% may be considered. One of the best predictors of successful outcome is the period of deafness, with those deafened for over 20 years unlikely to do well.

Not only must patients be well enough to undergo the surgery, which lasts about 2 hours, they should have realistic expectations and the ability to attend regular rehabilitation sessions. The implant itself functions like a complex hearing aid, requires batteries, and has external controls to change the sensitivity settings and switch the implant on and off.

Most implant users have the ability to follow conversation with the aid of lip-reading, many will learn to understand speech without lip-reading, and some are able to have an interactive conversation over the telephone.

It is now accepted that cochlear implantation is a safe and effective intervention, is available in most countries and provided by public services in many including the NHS in the United Kingdom (Summerfield and Marshfield, 1995).

KEY POINTS

- Hearing assessment should be performed using clinical evaluation, supplemented by audiometry; speech

audiometry will provide a better indication of disability than PTA. PTA will indicate the likely site of pathology.
- Conductive hearing losses are usually associated with identifiable conditions on otoscopy and may be treated by a number of methods, including medical, surgical, and amplification.
- Sensorineural deafness is common in the elderly population and requires investigation if asymmetrical or sudden in onset.
- Mild forms of tinnitus are common, are most often associated with a hearing impairment. Most require limited investigations, counseling, and amplification.
- Hearing aid technology has improved the quality of rehabilitation of deafened adults; some complex and severe hearing losses may be treated using bone anchored hearing aids or cochlear implants.

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Disorders of the Vestibular System

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INTRODUCTION

Man has developed a sophisticated system for maintaining balance, which requires the integration and modulation of visual, vestibular, and proprioceptive information within the central nervous system (CNS) (Figure 1). Pathology of any one of the three sensory inputs or of the central vestibular pathways may give rise to disequilibrium, as may many pathological processes that affect directly or indirectly the systems essential for perfect balance (Table 1). Dizziness is a frequent complaint in elderly, and the prevalence of balance problems at age 70 has been reported in 36% of women and 29% of men, increasing with advanced age to 45–51% at ages 88–90 (Jonsson *et al.*, 2004). Dizziness and vestibular abnormalities are reported to be a major risk factor predisposing to falls among the elderly (O'Loughlin *et al.*, 1993) and the significance of this lies in the high morbidity and mortality associated with falls in this age-group (Downton, 1993). In addition, fear of falling may constitute an independent risk factor for disability, leading older people to unnecessarily restrict their daily living activity (Burker *et al.*, 1995; Staab and Ruckenstein, 2003). However, with the correct diagnosis many vestibular disorders are treatable, leading to improved quality of life. Thus for the geriatrician, an understanding of the pathophysiology of the vestibular system and its central connections is particularly important if the common complaint of disequilibrium is to be managed successfully.

VESTIBULAR ANATOMY

The inner ear is a minute, complex, fluid-filled structure surrounded by a bony labyrinth located deep in the temporal bone. The cochlea corresponds to the acoustic end-organ, whereas the vestibular end-organs consist of the three semicircular canals, the saccule, and the utricle. The semicircular canals are called the *horizontal* (or *lateral*), the *posterior*, and the *superior canal*. The two ends of all semicircular canals open into the vestibule, near the utricle. One end of each semicircular canal has a dilated portion, called the *ampulla*, containing the sensory epithelium, that is, the hair cells. The utricle and the saccule correspond to the otolith organs and both contain a small area of sensory epithelium, called *maculae*. All vestibular sensory epithelium is covered with a gelatinous mass, which, in the saccule and the utricle, contains calcium carbonate–rich crystals termed *otoconia*.

A force parallel to the surface of the sensory epithelium provides the maximal stimulus. The semicircular canals with their ampullary tissue sense angular acceleration, whereas the saccule and the utricle sense linear acceleration. The planes of the two otolith organs lie approximately at right angles to each other. The utricular macula is oriented roughly horizontally and the saccular macula is roughly vertical. Accordingly, the saccule is well equipped to sense vertical head acceleration and the constant pull of gravity, whereas the utricle senses linear head motion in the horizontal plane. The utricle also plays an important role in signaling the spatial upright when the head is tilted with regard to gravity. The ampullae in the semicircular canals are insensitive to the static gravitational vector or position of the head in space. However, when an appropriate angular force is introduced, the fluid in the semicircular canal is displaced along the lumen of the canal leading to changed activity in the sensory epithelium of the ampullae.

PHYSIOLOGY AND AGING OF THE VESTIBULAR APPARATUS

In a normal subject holding the head in the anatomical position, the sensory epithelium in each ear generates resting neural activity, which passes via the VIIIth cranial nerve and the vestibular nuclei within the brainstem to the cortex.

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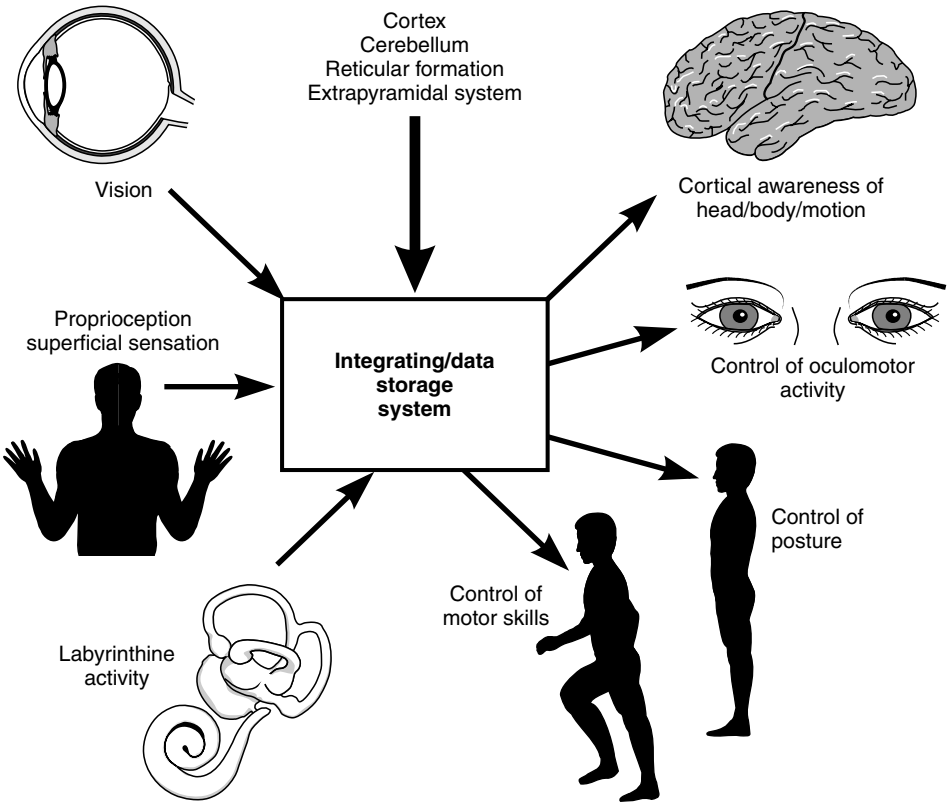

Figure 1 Mechanisms subserving balance in man (Reproduced from Savundra P and Luxon LM, 1997. Copyright Elsevier)

Head movements result in linear and/or angular accelerations, which stimulate the vestibular sensory epithelium and modulate the neural activity in an equal but opposite manner in each ear (Figure 2). Hence, an asymmetry of information is generated, which passes into the CNS. This asymmetric vestibular input allows cortical awareness of head position in space and provides the stimulus for compensatory eye and body movement (Savundra and Luxon, 1997). Pathology involving the peripheral labyrinth, VIIIth cranial nerve, or central vestibular connections may result in an asymmetry of vestibular information, which is "misinterpreted" by the brain and perceived as vertigo and instability.

The incidence of vertigo has been reported to rise with advancing age, in parallel with the incidence of hearing loss (Enrietto *et al.*, 1999). Histopathologic age-related changes reported in the human vestibular sensory organs include progressive hair-cell degeneration, otoconial degeneration in the otolith organs, and decreasing number of vestibular nerve fibers (Rauch *et al.*, 2001; Nadol and Schuknecht, 1990). In addition, age-dependent changes in both caloric and rotation-test responses have been demonstrated (Enrietto *et al.*, 1999; Kazmierczak *et al.*, 2001). However, vestibular symptoms result from an asymmetry of afferent information arising within the vestibular apparatus and degenerative changes tend to occur symmetrically. It is therefore unlikely that disequilibrium in the elderly is solely consequent upon vestibular degenerative changes and is more probably multifactorial in origin (Baloh, 1992). Accordingly, dizziness in the elderly is often the result of central pathology and/or sensory deficits: visual impairment (not correctable); neuropathy; vestibular deficits; cervical spondylosis; and orthopedic disorders, interfering with joint mechanoreceptors.

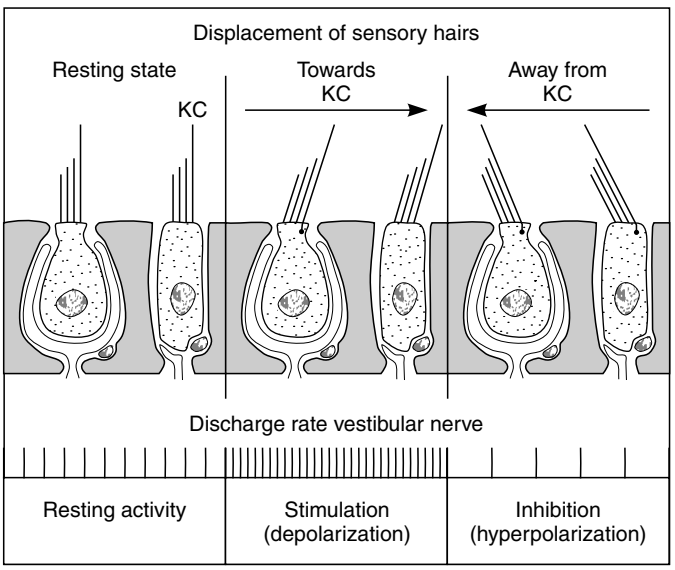

Figure 2 Schematic illustration of the relation between hair-cell orientation and the pattern of stimulation of the innervating fibers in the mammalian crista. KC = kinocilium (Reproduced from Wersall J *et al.*, 1967. Copyright Elsevier)

Table 1 Causes of dizziness in the elderly

General medical	
Hematological	Anemia
	Polycythemia
	Hyperviscosity syndromes
Cardiovascular	Postural hypotension
	Carotid sinus syndrome
	Dysrhythmias
	Mechanical dysfunction
	Shock
Metabolic/endocrine	Hypo- and hyperglycemia
	Thyroid disease
	Chronic renal failure
	Alcohol
Neurological	
Supratentorial	Trauma
	Neoplasia
	Epilepsy
	Cerebrovascular disease
	Syncope
	Psychogenic
Infratentorial	Vertebrobasilar insufficiency
	Subclavian steal syndrome
	Wallenberg's syndrome
	Anterior inferior cerebellar artery syndrome
	Degenerative disorders including neuropathy
	Tumor, including those of the vestibulocochlear nerves
Infective disorders	Ramsay–Hunt
	Neurosyphilis
	Tuberculosis
Foramen magnum abnormalities	
Cerebellar degeneration	
Basal ganglion disease	
Multiple sclerosis	
Otological	
Drug-induced/ototoxic	
Degenerative (e.g. positional vertigo)	
Posttraumatic syndrome	
Infection	
Vascular	
Tumors	
Menière's syndrome	
Otosclerosis and Paget's disease	
Autoimmune disorders	
Others	
Migraine	
Multisensory dizziness syndrome	

Following an acute unilateral vestibular upset, the patient experiences vertigo, but usually the symptoms are relatively short lived and resolve in 6–12 weeks, as a result of processes collectively known as *cerebral compensation*. Functional recovery depends on the degree of vestibular loss and cerebral compensation. The restoration of perfect balance involves reduction or abolition of the asymmetry in postural and ocular motor tone and recalibration of the gain of dynamic vestibular reflexes, in order to ensure symmetrical compensatory vestibulospinal and vestibulo-ocular reflex action during movement of the head and body. However, in some patients recovery does not occur. The persisting symptoms are usually less dramatic and the vertigo may not be rotational, but may consist of more vague symptoms of floating, rocking, or a sense of depersonalization. Such symptoms may be continuous, but may also present as episodic attacks of disequilibrium frequently triggered by an intercurrent illness or a psychological upset such as bereavement (Figure 3). It is well established that vestibular compensation is dependent on a variety of brainstem, cerebellar, and cortical structures, together with sensory inputs including vision, somatosensory afferents, and remaining labyrinthine input, which are involved in the normal perception of space, body posture, and locomotion. The causes of failure of compensation or intermittent decompensation are not clear, but cerebellar damage, impairment of proprioception, visual impairment, mild cerebral dysfunction, and psychological disorders have all been cited as possible contributing factors. Thus, the age-dependent changes in sensory inputs and CNS function noted above would suggest that central compensation for vestibular deficits in the elderly is likely to be less efficient.

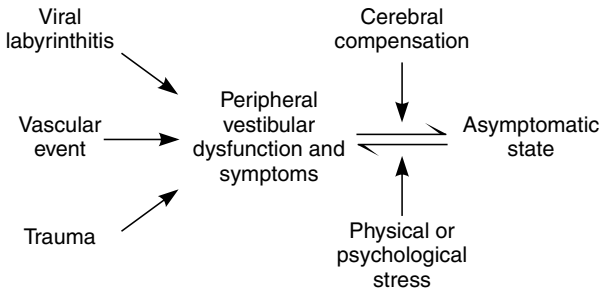

Figure 3 Diagram to illustrate normal sequence of events leading to recovery from a peripheral vestibular abnormality and factors relevant in decompensation

CLINICAL ASPECTS AND DIAGNOSTIC STRATEGY

Vertigo defined as "an hallucination of movement" is a cardinal manifestation of a disordered vestibular system; while dizziness is a lay term, defined in the *Concise Oxford Dictionary* as "a feeling of being in a whirl, or in a daze, or as if about to fall", associated commonly with a multiplicity of general medical disorders. This semantic distinction is volunteered rarely by the elderly patient who more frequently complains of feeling faint, swimmy, or lightheaded. Hence, for practical purposes, all complaints of disorientation are considered most easily within a single diagnostic approach.

History

In the history, the character, time course, and associated symptoms of the dizziness/vertigo are valuable pointers in elucidating the underlying diagnosis.

Character of Dizziness

Classically, the vertigo/dizziness of peripheral labyrinthine origin is manifested as acute, unprecipitated, short-lived attacks of rotational disequilibrium, associated with nausea and vomiting and more rarely diarrhea, while the vertigo/dizziness of central vestibular origin is described as a more insidious, protracted sense of instability. Exceptions to the former include epilepsy and vertebrobasilar artery ischemia, while exceptions to the latter include uncompensated peripheral vestibular disorders, bilateral vestibular failure, and psychogenic disequilibrium. Additional common symptoms with peripheral vestibular dysfunction are a sensation of being pulled downward or sideways or of the room tilting and a sensation of swimming, floating, and lightheadedness. However, if a clear description of subjective or objective motion is given, the suspicion of vestibular pathology is raised, whereas symptoms of lightheadedness, swimminess, or faintness are more likely to be attributable to a general medical/neurological disorder.

Time Course

Acute rotational vertigo of less than 1-minute duration is most commonly associated with the diagnosis of benign positional vertigo or paroxysmal type (see the following text), while acute rotational vertigo of less than 1-hour duration may suggest the diagnosis of vertebrobasilar insufficiency. Vertigo of several hours' duration (less than 24 hours) is most commonly associated with migraine and Ménière's disease (see the following text). Acute rotational vertigo of several days' duration, with gradual resolution of symptoms, points to a viral or vascular vestibular neuritis, although persistence of such symptoms in the elderly patient may indicate poor compensation from a peripheral vestibular insult or a fixed neurological deficit as a result of a vascular event within the brainstem.

Apart from the duration of the vertigo the time course of the episodes is also of diagnostic value. A single acute episode with gradual resolution over days or weeks would point to a peripheral vestibular pathology, such as a viral neuritis or an ischemic event. In the elderly patient, cerebral plasticity is reduced, as noted previously, and hence compensation from such a single insult may be protracted and intercurrent illness may result in an exacerbation of symptoms. Repeated short episodes with complete and rapid recovery in-between would suggest migraine, Menière's disease, or, most commonly, benign positional vertigo. It should be emphasized that in these conditions, the episodes also tend to occur in clusters, with intervals of months, or even years, of freedom.

Associated Symptoms

Within the labyrinth and VIIIth cranial nerve, the vestibular and cochlear elements are in close anatomical proximity. Hence pathology in these sites gives rise commonly to both cochlear and vestibular symptoms. Frequently, the elderly patient will not volunteer a complaint of tinnitus or hearing loss, as they attribute the symptoms to their age, and it is therefore important to enquire specifically. Within the CNS, the vestibular and auditory pathways diverge, and vestibular symptoms of brainstem or cerebellar origin are rarely associated with cochlear symptoms, but commonly associated with neurological symptoms and signs. Loss of vestibular function leads to impaired gaze stabilization during fast head movements, that is, oscillopsia (Bronstein, 2004). Typically, the patients complain of blurred vision or bouncing images while walking or riding in a car. The vestibular system is sensitive to fast, high-frequency head movements (1–10 Hz) and cortical–optokinetic reflexes are too slow to compensate for this functional loss above 2–3 Hz. Many patients with vestibular dysfunction report a worsening or triggering of dizziness with certain visual stimuli, such as rapidly changing images, fast-moving traffic, crowds, and striped material. This symptom is called *visual vertigo* (Bronstein, 2004). In addition, anxiety disorders, depression, and panic attacks have been described in association with peripheral vestibular disease and it is likely that in some patients vestibular dysfunction may play an important role in the etiology of these disorders (Burker *et al.*, 1995; Staab and Ruckenstein, 2003).

Examination

A full general examination is essential with special reference to the fundi, visual fields and acuity, a general neurological examination, and examination of the cardiovascular and peripheral vascular systems. On the basis of a comprehensive history and a thorough examination, the diagnosis of many neurological and general medical disorders will be excluded. The diagnosis of vestibular disorders giving rise to vertigo/dizziness is based on a neuro–otological examination, which may be divided into:

- an examination of the external ear and tympanic membrane together with clinical tests of auditory acuity/whispered-voice tests and tuning-fork tests;
- an assessment of vestibulo-ocular function;
- an assessment of vestibulospinal function, as part of the overall balance.

Otological Examination

In all patients with vertigo, particularly in ethnic minorities, immigrants, and immunosuppressed patients, it is essential to exclude active, chronic middle-ear disease with labyrinthine erosion. A labyrinthine fistula should be suspected in all patients with vertigo and previous surgery for middle-ear disease. Clinical tests of auditory function, including tuning-fork tests, are important when attempting to localize pathology, since the presence of an auditory deficit may suggest an underlying labyrinthine or VIIIth nerve pathology.

Vestibulo-ocular Examination

A detailed account of vestibular physiology and pathophysiology is beyond the scope of this chapter, but a clear understanding of these subjects is essential if an informed assessment of vestibular function and vestibular investigations are to be made (Eggers and Zee, 2003).

As has been outlined earlier, an asymmetry of vestibular activity may result from unilateral peripheral vestibular, VIIIth nerve, or brain-stem pathology. This asymmetry is "monitored" by the brain and, via the pathways subserving the vestibulo-ocular reflex, results in a slow vestibular-induced drift of the eyes in the same direction as the peripheral labyrinthine lesion. For reasons that are not fully understood, this slow drift is interrupted by rapid saccadic eye movements, which are generated within the brainstem in the opposite direction. This combination of slow and fast eye movements is known as *spontaneous vestibular nystagmus* and is characteristic of acute peripheral vestibular lesions. Initially, the nystagmus present with fixation but is more prominent without fixation. As a general rule, nystagmus with fixation (nystagmus seen on routine neurological examination) disappears within 1–2 weeks after the acute lesion. By contrast, spontaneous nystagmus can be recorded in the dark for as long as 5–10 years after the acute episode. Spontaneous vestibular nystagmus will usually beat away from the affected side, unless the lesion is irritative.

By definition, the direction of the nystagmus is defined by the fast phase, for clinical purposes. Thus, a right peripheral vestibular lesion gives rise to horizontal left beating nystagmus, which obeys Alexander's law. This states that the nystagmus is always in one direction irrespective of direction of gaze and that the intensity of the nystagmus is greatest when the eyes are deviated in the direction of the fast phase.

For purposes of accurate record keeping, nystagmus should be described in the following terms: 1° nystagmus describes nystagmus which is beating in the same direction as gaze deviation; 2° nystagmus describes nystagmus in the midposition of gaze; and 3° nystagmus describes nystagmus which is beating in the opposite direction to the direction of gaze (e.g. to the right, when the eyes are deviated to the left).

Bidirectional nystagmus (e.g. first degree nystagmus to the right on looking to the right and first degree nystagmus to the left on looking to the left), vertical nystagmus (i.e. upbeat nystagmus and/or downbeat nystagmus), and dysconjugate nystagmus (a differing nystagmic response in each eye) indicate CNS disease, requiring further investigation.

Clinically, *spontaneous nystagmus* should be sought in every patient complaining of dizziness/vertigo. The eyes should be examined in the midposition of gaze, with eyes 30° to the right and 30° to the left. Care must be taken that this angle is not exceeded, otherwise physiological end-point nystagmus may be observed and this may be confused with pathological nystagmus. In addition, vertical nystagmus with the eyes 30° upwards and 30° downward should be sought.

The presence of *positional nystagmus* is a most valuable and most frequently overlooked sign, and should be sought by a briskly performed Hallpike maneuver (Figure 4). The patient is made to sit close to the top end of a flat examination couch. The head is held firmly between the examiner's hands and turned 30–45° to the right or left. The patient is then carried rapidly backward with the head over the edge of the couch and the eyes carefully observed. If nystagmus develops, it is observed until it disappears, or for 2 or 3 minutes, until it is clear that the nystagmus is persistent. The patient is then returned to the upright position and the procedure repeated in the opposite direction. In broad clinical terms, the positional nystagmus which may develop can be divided into two main types, as identified in Table 2, although there are cases which do not clearly fit into either category, and those should be investigated, as should the "central" category, for neurological disease. If the positional nystagmus is of peripheral labyrinthine origin, after a latent period of a few seconds in the head-back position, severe vertigo develops which lasts for less than a minute, but during which the patient may feel extremely distressed and nauseated. The nystagmus is rotatory in nature and directed toward the undermost ear. Symptoms and signs adapt and fatigue on repeated testing. Thus, care must be taken that the procedure is carried out correctly at the first attempt. Moreover, it is important to establish this condition, as it is a troublesome cause of vertigo for which highly effective treatment is available (see the following text).

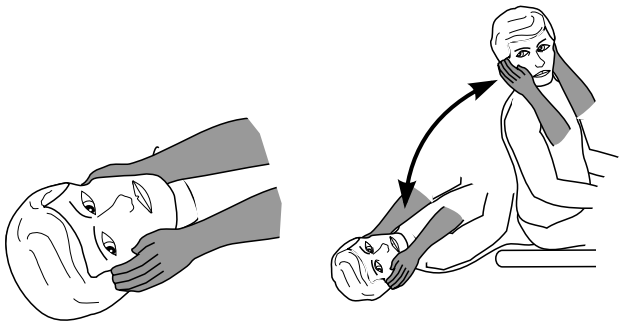

Figure 4 The Hallpike maneuver for inducing positional nystagmus

The vestibular system, via the vestibulo-ocular reflex (VOR), provides one system for the control of eye movements and gaze stability. Visual stimuli provide another mechanism for stabilizing gaze, that is, smooth pursuit and optokinetic reflexes, and under certain circumstances the two

Table 2 Characteristics of positional nystagmus

	Benign paroxysmal type	Central type
Latent period	2–20 seconds	None
Adaptation	Disappears in 50 seconds	Persists
Fatigue ability	Disappears on repetition	Persists
Vertigo	Always present	Typically absent
Direction of nystagmus	To undermost ear	Variable
Incidence	Relatively common	Relatively uncommon

systems may conflict. For example, watching a tennis tournament, as the head turns to the right to follow a ball flying through the air, the vestibulo-ocular reflex would tend to result in a compensatory eye movement to the left, whereas the subject wishes to keep the eyes fixed on the ball moving to the right. In this situation, the visual stimulus overrides the vestibular stimulus by modulation of neural activity at the level of the vestibular nuclei. This is known as *visual suppression of the vestibular responses* and clinical examination of this function allows assessment of central vestibular integrating ability. The simplest clinical means of assessing vestibulo-ocular reflex suppression is by observing the effect of optic fixation upon rotationally induced vestibular nystagmus. This may be simply accomplished in the clinic by observing the patient's eyes, while the patient is oscillated on an office chair while fixating his/her own thumbs (Bronstein, 2004). If the eyes remain fixated on the target, VOR suppression is intact. On the contrary, if clear nystagmus is elicited by the rotation, VOR suppression is abnormal indicating CNS pathology.

Vestibulospinal Assessment

Vestibulospinal function cannot be assessed in isolation and tests are nonspecific and insensitive, compared with tests of vestibulo-ocular function, but they may provide an indication of the extent of the patient's disability and interaction of vestibulospinal activities with other systems. The *Romberg test* is performed by asking the patient to stand in the upright position with feet together, arms by the side, and eyes closed. A tendency to sway to one side usually suggests peripheral vestibular pathology, while an inability to stand with the feet together is more characteristic of cerebellar ataxia. Baloh *et al.*, (1998) have demonstrated that there is a marked increase in postural sway in elderly patients with unilateral vestibular hypofunction, in comparison with younger patients with the same disorder. Anxious elderly patients frequently tend to fall backward like a wooden soldier and this is indicative of a nonorganic component to their symptoms, but it must be emphasized that this is almost always observed in the presence of an underlying abnormality, which will be elucidated on full examination.

Gait testing is assessed by asking the patient to walk toward a fixed point in a normal manner, but with eyes closed. Again, a tendency to veer in one direction is most commonly the result of an ipsilateral peripheral vestibular disturbance, but may on occasions be observed with cerebellar disease. This latter diagnosis is most commonly associated with a broad-based, ataxic gait.

Having briefly reviewed vestibular physiology and pathophysiology and outlined the aspects in the history and examination, which may enable the clinician to identify a vestibular abnormality, the remainder of this chapter will be devoted to a review of the more common causes of vestibular pathology in the elderly and the therapeutic options available.

PERIPHERAL VESTIBULAR DISORDERS

Viral Vestibular Neuritis

Single episodes of acute rotational vertigo associated with nausea and vomiting and with or without cochlear symptoms, are a common occurrence in all age-groups. The attacks are usually unprecipitated, but may be preceded by an upper-respiratory-tract infection, and are therefore presumed to be of viral origin, although there is little definitive evidence for this (Nadol, 1995). Additional possible causes of vestibular neuritis include other infectious agents, vascular, or immune-mediated disorders.

The vertigo may last for a few hours or several days, and the patient may then be extremely unsteady for a period of weeks, during which time cerebral compensation produces a degree of symptomatic recovery. However, in the elderly patient, the plasticity of the CNS is compromised, and recovery is often slower and is rarely complete.

Ramsay–Hunt Syndrome (*see* Chapter 148, Infections of the Central Nervous System)

The Ramsay–Hunt syndrome, or herpes zoster oticus is an example of a mononeuritis of the VIIth cranial nerve. The patient experiences a deep burning pain in the ear, which is followed within a few days by a vesicular eruption in the external auditory canal and on the concha. The patient often develops facial paralysis. In addition, some patients present with hearing loss, tinnitus, vomiting, vertigo, and nystagmus indicating VIIIth nerve involvement (Sweeney and Gilden, 2001).

Bacterial Infection

Chronic middle-ear disease is a prevalent condition in the elderly, and it cannot be overemphasized that in any patient with vestibular symptoms in whom there is the slightest suspicion of middle-ear disease or history of previous middle-ear surgery, the presumptive diagnosis must be of labyrinthine erosion. Labyrinthine fistulae are often the result of bony erosion by cholesteatoma with the lateral semicircular canal being the most commonly affected site (Minor, 2003). Rarely, labyrinthine fistulae may be caused by syphilitic osteitis, tuberculous otitis media, chronic perilabyrinthine osteomyelitis, or glomus jugulare tumor.

Otitis externa is a common benign disorder, but in debilitated elderly patients, particularly diabetics and other immunosuppressive conditions, it may present in a more malignant form (Rubin Grandis *et al.*, 2004). The causative organism is mainly *Pseudomonas aeruginosa*. The disease spreads rapidly, invading surrounding soft tissues, cartilage, and bone structures with occasional involvement of adjacent cranial nerves causing hearing loss and vertigo. Prolonged treatment with effective antibiotics, carbenicillin, or gentamicin, has improved the previously poor prognosis.

Neoplasia

Vestibular disorders as a direct result of neoplasia are uncommon, even in the elderly. The nonmetastatic complications of carcinomatous encephalomyelitis may involve the vestibular nerve (Gulya, 1993), while cochlear and vestibular symptoms have been reported in 10% of patients with carcinomatous meningitis (Alberts and Terrence, 1978).

Secondary tumor involvement of the inner ear by bloodborne metastases from hypernephroma, lung-, prostate-, breast-, and uterine carcinoma have been reported and direct extension of nasopharyngeal carcinoma may occur. Aural tumors are rare, with the exception of cholesteatoma, as outlined previously. Morrison (1975) reported that 20% of patients with acoustic neurinoma were over the age of 60 at the time of presentation. Cochlear symptoms (tinnitus and hearing loss) are the most common presenting symptoms of acoustic neurinoma, but 10% of patients complain of vertigo, dizziness, and/or unsteadiness. A unilateral asymmetric hearing loss must be investigated, and brain-stem auditory-evoked responses provide the best screening technique. If these are abnormal, a computed tomography (CT) scan or, preferably, a magnetic resonance (MR) scan, should be obtained.

The diagnosis and management of this condition in the elderly does not differ from that of any other patient, but early diagnosis is essential, as excellent surgical results are achieved with small tumors (below 20 mm in size) (Tos *et al.*, 2003). However, it has been shown that small tumors do not invariably enlarge with time (Piazza *et al.*, 2003) and the high sensitivity of MR scanning may mean that clinically insignificant tumors may be detected. In the elderly patient, it is reasonable to monitor growth of small acoustic neuromas, but this must be balanced against the significantly decreased mortality/morbidity associated with surgery for smaller tumors.

Vascular Disorders

Both the peripheral and central vestibular apparatus are supplied by the vertebrobasilar circulation and, as cerebrovascular disease is common in developed countries (the risk factors being diabetes mellitus, hypertension, and a raised hematocrit), disequilibrium in the elderly is commonly ascribed to vascular pathology. Ischemia of the internal auditory artery may give rise to three differing clinical syndromes: vestibular disorders alone, cochlear disorders alone, or combined vestibulocochlear symptomatology. An isolated acute episode of rotational vertigo, as outlined in the description of viral vestibular neuritis, may be of vascular origin. The diagnosis is usually presumptive and is based on evidence of vestibular dysfunction in a patient with other manifestations of vascular disease. Risk factors (diabetes mellitus, hyperlipidemia, hypertension, myxedema) should be sought and treated appropriately.

Trauma

The elderly are particularly prone to falls (O'Loughlin *et al.*, 1993), and vestibular abnormalities as a result of even trivial head injury are now well recognized (Luxon, 1996). Damage to the vestibular system may be the result of direct injury, for example, labyrinthine concussion and/or temporal bone fracture, or of secondary shearing forces in the brainstem and cerebellum. Falls may cause cervical trauma in the elderly, which may also give rise to vestibular disturbances (Luxon, 1996).

Two posttraumatic vestibular syndromes may be identified.

Unilateral Auditory and Vestibular Failure

This is associated with transverse fractures of the temporal bone, in which severe vertigo and hearing loss are accompanied by bleeding from the ear, nausea, and vomiting. The patient prefers to lie completely still with the affected ear uppermost. Over a period of 6–12 weeks there is marked improvement in the disequilibrium, although in the elderly patient, as noted earlier, this may be slower and less complete than in a younger person. There is no recovery of the auditory deficit.

Benign Positional Vertigo of Paroxysmal Type

This is the most common clinical syndrome after head injury, but may also be seen in the elderly as an idiopathic disorder or secondary to vestibular neuritis. Recent work has led to the theory of canalithiasis (Figure 5), which explains the majority of the characteristic features of benign positional nystagmus (Brandt and Steddin, 1993; Baloh, 1996). This theory proposes that debris from the otolith organ lies in the most dependent portion of the posterior canal and, upon assuming the critical head position, the clot moves in an ampullofugal direction and, thus, has a "plunger" effect within the narrow posterior semicircular canal. This causes

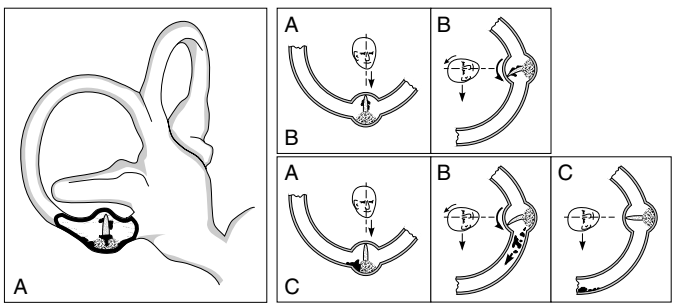

Figure 5 Diagram to illustrate the pathophysiological mechanisms of cupulolithiasis and canalithiasis. (A) Illustration of cupula in ampulla of posterior semicircular canal, with debris attached to and surrounding the cupula. (B) Illustration of the effect of gravity on the cupula and debris as proposed by the theory of cupulolithiasis. (C) Illustration of the effect of gravity on the cupula and debris as proposed by the theory of canalithiasis. (Reproduced from *Vestibular Research*, vol 3, Brandt T and Steddins S, pp 373–82, Copyright 1993, with permission from IOS Press)

movement of the cupula in an ampullofugal direction, with a brief paroxysm of vertigo and nystagmus as a result.

The clinical course of posttraumatic benign positional vertigo is that some days or weeks after even a trivial head injury, momentary, short-lived episodes of vertigo occur, on assuming specific head positions, particularly associated with neck extension. Frequently, the only abnormal clinical sign is benign positional nystagmus of paroxysmal type on performing the Hallpike maneuver (see earlier text). The vertigo associated with this condition is particularly severe and the elderly patient is frequently extremely afraid, as the attacks are very sudden and may cause drop to the ground and vomiting. This leads to anxiety, partly from fear of embarrassment if this should happen in a public place, and partly from fear of being incapacitated at home, unable to reach help. Not infrequently, this diagnosis is overlooked and the clinician merely observes an extremely anxious elderly patient, who finds difficulty explaining such brief yet severe symptoms. It is therefore extremely important that the Hallpike maneuver is performed and a clear explanation of the benign nature of the condition given.

In 1980, Brandt and Daroff (1980) reported complete relief of symptoms in 66 or 67 patients with benign positional vertigo as a result of precipitating head positions "on a repeated and serial basis". They suggested that the mechanism of improvement using this therapy lay in rapid and aggressive vertigo-provocative movements, which loosened and dispersed otholitic debris from the cupula of the posterior semicircular canal (cupulolithiasis) (Figure 5). However, on the basis of our current knowledge, it seems more likely that these maneuvers cleared debris from the most dependent part of the posterior semicircular canal into the utricle, where they no longer interfered with semicircular canal dynamics.

More recently, single positional maneuvers (Epley, 1992) have been described in which specific movements of the head allow the offending debris in the posterior canal to be moved by gravitation into the utricle (Figure 6). The patient is instructed to sit upright for 48 hours after this procedure, which has been reported to be effective in 80–85% of patients on the first attempt at treatment and in a further 10% upon a second attempt. Relapses may occur, but the maneuver should then be repeated. Pretreatment sedation is not required except for the most anxious of patients, and the maneuver is as effective in older people as in younger people.

In a small percentage of patients it would appear that the particle repositioning procedures are not effective and, in intractable cases, plugging of the posterior semicircular canal (Ludman, 1984) or section of the posterior and ampullary nerve (Ludman, 1984) should be considered.

Menière's Disease

Menière's disease was first described in 1861 by Prosper Menière and is characterized by episodic vertigo,

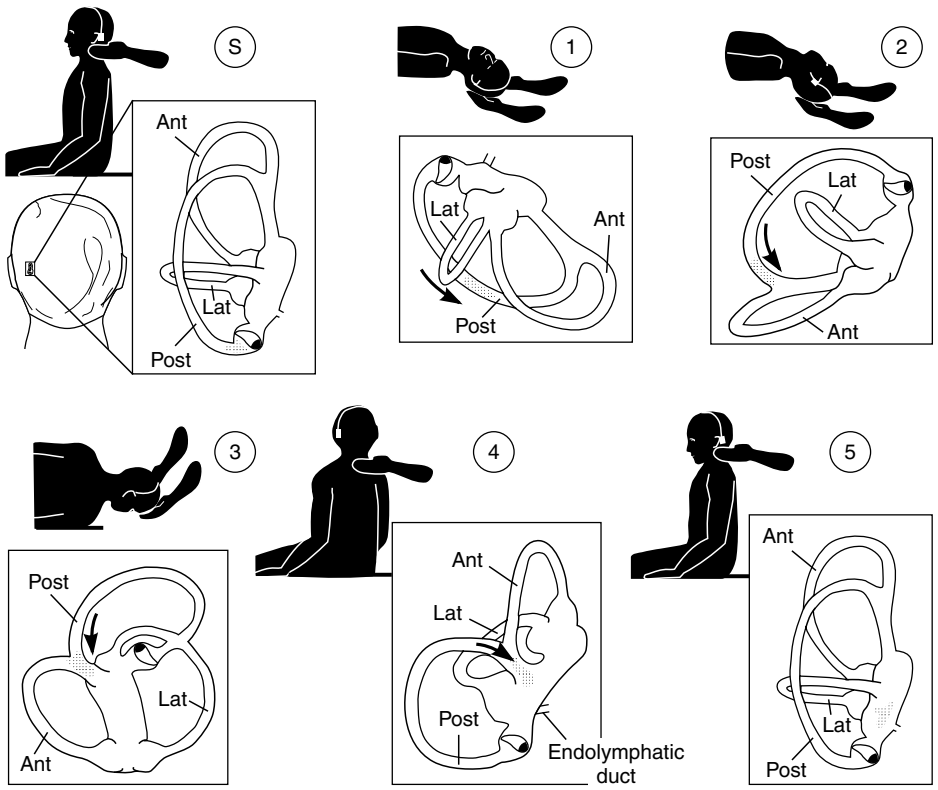

Figure 6 Diagram to illustrate particle repositioning procedure for canalithiasis of lest posterior semicircular canal, as described by Epley (1992). S = sitting. 1–5 = Stages of maneuver. Semicircular canals: Ant = anterior, Post = posterior, Lat = lateral (Reproduced from Epley JM., 1992. Copyright Elsevier)

low-frequency hearing loss with tinnitus, and fullness. Menière's disease does occur in the elderly (Ballester *et al.*, 2002) and the pathological underlying process is thought to be due to increase in endolymph volume, that is, endolymphatic hydrops (Paparella and Djalilial, 2002). If the Menière-like episodes of vertigo cannot be controlled by diuretics and a salt-free diet, the treatment of choice is labyrinthectomy, provided that there is no usable hearing.

Iatrogenic Vestibular Dysfunction

Iatrogenic dizziness may be surgical or medical in origin and it is well established that otological surgery carries a risk of inducing dizziness/vertigo postoperatively. Moreover, vestibular disturbances after nonotological surgery have been documented (O'Mahoney *et al.*, 1995).

Drug-induced dizziness is a very significant problem in the elderly and many, if not all, drugs may produce dizziness, although it is often impossible to identify the underlying mechanism causing disequilibrium. Anemia secondary to gastrointestinal bleeding, hypoglycemia, cardiovascular effects including reduction in cardiac output, dysrhythmias, and postural hypotension, and ototoxicity should all be considered. The most common drugs giving rise to dizziness in the elderly are shown in Table 3.

Ototoxic damage is of particular importance, as it is irreversible. The vestibulotoxic effect of the aminoglycoside antibiotics is common knowledge, and in the elderly, they should be used only as a lifesaving measure. It is well established that age is an important factor in the susceptibility to aminoglycoside ototoxicity, and for this reason blood levels of these drugs should be measured meticulously in the elderly, especially in the presence of concurrent diuretic therapy and/or any change in the overall medical state. Moreover, although standard vestibular tests are not feasible in a severely ill patient, recent methods of assessing vestibular function at the bedside have been developed and are of particular value in potential ototoxicity (Bronstein, 2004; Schubert and Minor, 2004).

Table 3 Drugs causing dizziness/vertigo

Psychotropic drugs	
Antidepressants	Tricyclics, MAOIs, SSRIs
Tranquilizers	Benzodiazepines, phenothiazines
Anticonvulsants	Phenytoin, carbamazepine, gabapentine, lamotrigine
Analgesics	Paracetamol, acetylsalicylate, NSAIDs, opioids
Cardiovascular drugs	
Antihypertensives	Diuretics (thiazides and loop), β-blockers, calcium-channel blockers, ACE inhibitors, methyldopa, hydralazine
Antiarrhythmic	β-Blockers, verapamil, mexiletine, flecainide, amiodarone, disopyramide
Antiangina	Nitrates, calcium-channel blockers, β-blockers, potassium-channel activators
Antimicrobials	Aminoglycosides, tetracyclines, macrolides, chloroquine, isoniazid
Antiallergic drugs	Nonsedating and sedating antihistamines
Hormone replacement/substitute	Hypoglycemics, corticosteroids, HRT
Chemotherapeutic agents	Cisplatin, busulfan, cyclophosphamide, vinblastine, methotrexate

MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin re-uptake inhibitor; NSAID, non-steroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme inhibitors; HRT, hormone replacement therapy.

CENTRAL VESTIBULAR DISORDERS

Cerebrovascular Disease

Cerebrovascular disease is most commonly secondary to atheroma, although giant cell arteritis should be considered in the elderly. The vertebrobasilar circulation supplies the peripheral vestibular apparatus as described earlier, but also supplies the vestibular nuclei. These nuclei occupy a large area in the lateral zone of the brainstem and are particularly susceptible to a reduction in the blood flow of the main basilar artery and the cerebellum, which is extremely important in modulating information required for balance at the level of the vestibular nuclei. The vertebral and internal carotid arteries provide the brain with a rich blood supply and the terminal branches anastomose to form the circle of Willis. This forms an anatomical safeguard against ischemia arising from narrowing of one vessel and, in addition, there are autoregulatory mechanisms within the cerebral circulation protecting it from fluctuations in the systemic blood pressure. Nonetheless, cerebrovascular disease is one of the most common causes of chronic disability and death. In addition, white-matter changes due to vascular ischemic damage produce gait disorders as well as cognitive impairment, both of which predispose to falls.

Vertebrobasilar Artery Ischemia

Episodic vertigo in an elderly patient is ascribed commonly to vertebrobasilar insufficiency, in the knowledge that cerebrovascular disease is common in the elderly and also on the basis that vertigo and/or dizziness has been reported as the first and most frequent symptom of this condition (Luxon, 1990; Caplan, 2003).

The classical symptoms of vertebrobasilar insufficiency include dizziness/vertigo, dysarthria, numbness of the face, hemiparesis, headache, dysphagia, sensory disturbance cerebellar ataxia, and visual disturbances. The diversity of symptoms and signs reflects the close proximity of cranial nerve nuclei and motor and sensory tracts, within the small confines of the brainstem. The duration of transient ischemic attacks in the vertebrobasilar territory may be variable, but by definition must be without actual infarction and less than 24 hours. They may recur at variable intervals and may or may not be stereotyped.

Classical attacks of vertebrobasilar artery ischemia associated with vertigo do not present a diagnostic problem. However, a study of 50 patients, of whom two-thirds were over the age of 60 with well-defined episodes of vertebrobasilar insufficiency, failed to identify episodic vertigo in isolation as a frequent occurrence in this condition (Luxon, 1990). In this context, it is important to emphasize that dizziness or vertigo, accompanied by only VIIIth nerve manifestations, is unlikely to be of vascular origin. Moreover, tinnitus and deafness are unusual manifestations of vertebrobasilar ischemia and, if present, are accompanied almost always by other symptoms and signs of brain-stem involvement. Despite the presence of vestibular and oculomotor abnormalities in vertebrobasilar ischemia, no characteristic pattern of neuro–otological findings has emerged in this disorder (Luxon, 1990). Hence, isolated episodes of rotational vertigo in an elderly patient should not be ascribed to vertebrobasilar insufficiency, unless there is other neurological evidence to support this diagnosis.

Completed Strokes (see Chapter 71, Acute Stroke)

Completed strokes in the vertebrobasilar territory may involve the vestibular nuclei and there are a number of well-recognized syndromes. The Wallenberg or lateral medullary syndrome may result from occlusion of the posterior inferior cerebellar artery or the vertebral artery (Fisher, 1967). The syndrome is characterized by acute rotational vertigo with nausea and vomiting and ipsilateral dissociated sensory loss in the distribution of the facial nerve, together with contralateral truncal loss and ipsilateral cerebellar ataxia, bulbar palsy, and Horner's syndrome. Specific visuo–vestibular abnormalities have been identified with Wallenberg's syndrome, including spontaneous rotatory nystagmus, with the fast phase directed toward the normal side; tonic deviation of the eyes toward the side of the lesion, with loss of fixation; voluntary and involuntary saccades of larger amplitude in the direction of the lesion; and asymmetry of smooth pursuit, optokinetic, and vestibular responses as a result of the interaction between spontaneous nystagmus and/or slow eye movements.

Pontine/medullary and cerebellar hemorrhages may involve the vestibular apparatus. In the former, there are multiple brain-stem signs and vertigo is usually a fleeting event, although a common presenting symptom, before the patient becomes unconscious (Barinagarrementeria and Cantu, 1994). Cerebellar hemorrhage presents with acute vertigo, vomiting, and an inability to stand, in the presence of cerebellar signs. The importance of rapid diagnosis lies in the ability to correct this condition surgically. Without rapid intervention, the patient dies from brain-stem compression.

Cervical Vertigo

Cervical vertigo is defined as vertigo induced by changes of position of the neck in relation to the body (Brandt, 1996). There is much controversy as to the underlying pathophysiology of cervical vertigo, but sympathetic irritation resulting in vertebrobasilar ischemia, intermittent vertebral artery compression by osteophytes caused by cervical spondylosis and deranged sensory input from the cervical kinesthetic receptors have been postulated.

It is a widely held belief, particularly in the elderly, that vertigo and nystagmus may result from vertebrobasilar ischemia, secondary to compression of blood vessels, as a result of arthritic changes in the neck. This seems unlikely noting the observations that unilateral, or indeed bilateral, compression of the vertebral arteries in the presence of a normal circle of Willis and internal carotid arteries produces only minimal brain-stem ischemia. It should be emphasized that radiological findings may prove misleading, as 75% of people over the age of 50 years show osteoarthritic changes in the cervical vertebrae, which are not directly related to symptomatology (Pallis *et al.*, 1954). Neuro–otological tests in patients suspected of having cervical vertigo are frequently normal and no specific assessment objectively defines the condition. The diagnosis will be facilitated with the development of a specific test defining specific abnormalities.

Neoplasia

Dizziness and/or vertigo are early or initial symptoms in 25% of brain-stem tumors. In later life, metastases are the most common neoplasms involving the brainstem and/or cerebellum, which give rise to vestibular dysfunction. Brain-stem lesions typically present with progressive cranial nerve palsies together with long tract signs, while midline cerebellar lesions give rise to truncal ataxia and oculomotor abnormalities, including impaired smooth pursuit, saccadic dysmetria, and rebound nystagmus (Savundra and Luxon, 1997). Hemispheric cerebellar lesions cause ataxia of the ipsilateral limbs with truncal ataxia.

Temporal-lobe tumors give rise to "disequilibrium" more frequently than in any other cortical site. This is not surprising in view that the temporal lobes exert a modifying influence upon the vestibular nuclei.

Cerebellopontine angle lesions and, in particular, acoustic neurinomas have been mentioned above, but are a rare cause of vestibular symptoms. Acoustic neurinomas, despite the misnomer, arise mainly on the vestibular division of the VIIIth cranial nerve. As they expand in the cerebellopontine angle, there is involvement of the Vth and VIIth cranial nerves, together with ipsilateral cerebellar signs and ultimately lower cranial nerve involvement. If surgical intervention is not undertaken, brain-stem compression results in death.

Infection

Although tuberculosis is no longer a common disorder in developed countries, the possibility of a tuberculoma in the

brainstem, cerebellopontine angle, or temporal lobe should be borne in mind, especially in elderly immigrants and in elderly, debilitated, or alcoholic patients.

Neurosyphilis may involve the vestibular apparatus at all stages of the disease and a review of neurosyphilis reported that 30% of patients were over the age of 60 at the time of presentation (Luxon *et al.*, 1979). A high index of suspicion is necessary if rare cases in the elderly are not to be missed.

Neurological Conditions

Many neurological disorders may affect the central vestibular connections, and a discussion of each is beyond the scope of this chapter. The reader is referred to a more extensive review of causes of balance disorders (O'Mahoney and Luxon, 1997). In the elderly, of special note are Parkinson's disease, cerebellar disease, and multisystem atrophies.

Migraine is an important cause of various forms of episodic vertigo and may occur at any time throughout life (Dieterich and Brandt, 1999). The vertigo may last a few minutes or several hours, and in 32% of patients vertigo and headache are not contemporaneous. The symptoms often resolve with effective antimigrainous treatment.

The importance of the cerebellar connections on the vestibular system in terms of maintaining balance and eye position has been emphasized. Neuro-otological abnormalities in cerebellar disease are well defined (Baloh *et al.*, 1986). Cerebellar degeneration may be seen in the elderly in association with malignancy (paraneoplastic syndrome), phenytoin intoxication, hereditary ataxias, alcoholism, and myxedema. Early diagnosis may lead to effective treatment in these groups.

Of importance in the elderly, Paget's disease may give rise to basilar impression which may be accompanied by vertigo (Davies, 1968). The neurological symptoms produced by spinal cord and cerebellar compression together with obstruction of the fourth ventricle usually overshadow the vestibular disorder.

This review of vestibular disorders in the elderly has concentrated on the more common vestibular pathologies affecting this age-group, but it must be emphasized that any vestibular disorder may occur and conditions such as endolymphatic hydrops, migraine, and multiple sclerosis should not be overlooked.

MANAGEMENT

The initial management of a patient must be directed at establishing the presence of an underlying diagnosis for which specific treatment may be instituted. A number of elderly patients will be found to have minor visual impairment, which should be corrected if possible. If there is proprioceptive impairment that is predominantly in the lower limbs, it may be helpful to provide a walking stick to provide additional proprioceptive information through the upper limbs. In addition, assistive devices and interventions for preventing falls should be considered. The management of peripheral vestibular dysfunction consists of counseling and vestibular rehabilitation exercises. Drug therapy may be of value in the management of acute vertigo, but has no place in the long-term management of chronic vestibular symptoms, as it delays compensation.

Symptoms of disequilibrium are especially disturbing for the elderly not only because they fear some sinister pathology but also because they are terrified of the consequences of repeated attacks of vertigo during which they may be unable to summon outside assistance. It is therefore extremely important to obtain a detailed history, carry out a full examination and appropriate investigations, and give a simple and clear explanation of the underlying cause of symptoms of disequilibrium and the therapeutic options that are available.

Chronic vestibular symptoms may be caused by central vestibular pathology or uncompensated peripheral vestibular disorders. The management of central vestibular dysfunction remains poorly understood, but a trial of cinnarizine, clonazepam, or carbamazepine may prove of value. The sedative side effects of these drugs should be recalled in the elderly and the dose titrated against sedation. In patients with a sense of instability and falls, which are frequently associated with basal ganglia disorders and cerebellar disease, physiotherapy to teach alternative gait strategies may prove invaluable in enabling the patient to regain a sense of confidence and improve their mobility.

Vertigo associated with peripheral vestibular disorders may either be attributable to specific conditions, for which there is a recognized treatment regime, or a specific etiology may not be identified despite the evidence of peripheral vestibular dysfunction on standard vestibular tests. The treatment of specific otological disorders is no different in the elderly to any other age-group and the reader is referred to standard otology texts.

Persistent vestibular symptoms due to peripheral labyrinthine dysfunction are frequently amenable to vestibular rehabilitation, and it cannot be overemphasized that destructive surgical procedures should not be considered, particularly in the elderly, until detailed neuro-otological investigation determining site of lesion and exhaustive medical management have been tried. There is no reason to assume that a patient will compensate more efficiently from a total labyrinthine destruction than from a partial impairment of vestibular function, particularly when it is likely that the failure of compensation in the elderly may be due to mild central processing disorders or unsuspected psychological factors.

Acute vertigo associated with nausea and vomiting requires immediate treatment with an antiemetic such as prochlorperazine, by buccal absorption, intramuscularly or by suppository, or metoclopramide intramuscularly, such that nausea and vomiting are alleviated. This enables the administration of a vestibular sedative, of which cinnarizine 15 mg 8-hourly is the treatment of choice. Again, in the elderly patient, sedative side effects must be carefully monitored and the dose adjusted accordingly.

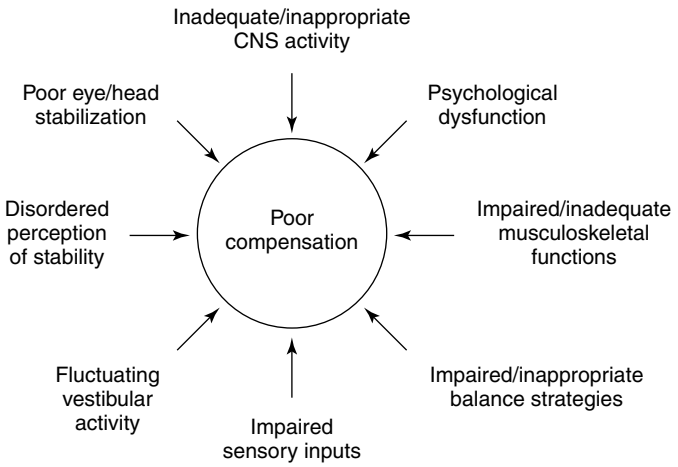

Figure 7 Factors predisposing to decompensation (After Shumway-Cook and Horak, 1990)

Chronic or recurrent vertigo, associated with poorly compensated peripheral pathology (Figure 7), is frequently accompanied by secondary symptoms of psychological distress (anxiety, depression, and phobic symptoms), malaise, fatigue, and cervical pain related to tension in neck muscles, as a result of conscious or subconscious limitation of neck movements, which are likely to precipitate an increase in vertiginous symptoms. The development of psychological symptoms in patients with disequilibrium is now well recognized (Burker *et al.*, 1995; Staab and Ruckenstein, 2003), and appropriate psychological support in the form of behavioral therapy or psychiatric care is essential for patients who manifest psychological symptoms if optimal vestibular compensation is to be achieved. This is particularly important in the elderly age-group, who are more likely to be susceptible than their younger counterparts and are therefore deeply concerned by disorders that impair their physical abilities and threaten their independence.

As early as the mid-1940s, physical exercise regimes (the Cawthorne Cooksey exercises) were introduced as a means of expediting recovery from peripheral vestibular disorders. These exercises are a graduated series of exercises aimed at encouraging head and eye movements, which provokes dizziness in a systematic manner and facilitates vestibular compensation. The exercises are not an endurance test, and for the elderly patient it is important to modify the regime within the limits of the patient's physical abilities. The passage of time has supported the efficacy of these exercises (Norre, 1987) and successful vestibular rehabilitation improves activities of daily living and reduces fall risk. Significant improvement has been shown in patients with peripheral vestibular dysfunction, but also in patients with central balance disorders. Moreover, there is no evidence that age is a negative prognostic factor (Whitney *et al.*, 2002).

Recent work has suggested that "customized" exercises, tailored to the individual patient, are equally effective (Herdman, 1994). Specific positional maneuvers for the management of benign positional vertigo have been described earlier and form an important element of vestibular management. A combination of canalith repositioning maneuver and vestibular rehabilitation has been shown to improve benign positional vertigo in the elderly. Although repositioning maneuver is the most effective treatment, vestibular rehabilitation can be added to improve the results in the treatment.

As noted previously, vestibular sedatives such as cinnarizine are of value in the management of acute vertigo, but have a very limited role in the management of chronic vestibular syndromes. In particular, antiemetics such as prochlorperazine should be avoided, because of the rare but irreversible syndrome of extrapyramidal dysfunction. Moreover, psychotropic drugs should be administered only for specific psychiatric indications, as such medication may interfere with compensatory mechanisms for peripheral vestibular disorders.

In the elderly, the indications for otological surgery for vestibular disorders must be carefully weighed against the general medical state of the patient and the likely extent of recovery postoperatively. Ludman's (1984) excellent review of the surgical treatment of vertigo outlines the various techniques available. As has already been noted, compensation may be prolonged or indeed incomplete as a result of dysfunction of the integrating ability of the CNS and/or other sensory modalities. The risk of a persisting imbalance after vestibular destruction must therefore be borne in mind.

KEY POINTS

- Do not attribute vertigo to "age".
- A thorough history and examination will often provide a clear direction as to diagnosis.
- Correct diagnosis allows treatment of many of the peripheral and central vestibular disorders.
- Introduce vestibular rehabilitation/gait strategy exercises in the elderly early and aggressively.
- Destructive surgical procedures should not be considered, until detailed neuro-otological investigation and medical management have been tried exhaustively.

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Smell and Taste

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INTRODUCTION

Since 1900, the percentage of Americans over the age of 65 has more than tripled (4.1% in 1900 to over 12% in 2000) and their number has increased over 11 times (from 3.1 to 34.9 million) (Facts for Features, 2004). Given the fact that the ability to perceive odors and tastes decreases markedly with age (Doty, 1995), it is not surprising that increasing numbers of elderly patients are seeking medical help for their chemosensory problem. Indeed, over half the population between the ages of 65 and 80 years, and over three-quarters beyond 80 years, have significant olfactory loss. The implications of such age-related chemosensory losses are far-reaching. Aside from being unable to appreciate fragrances, the taste of food, and the freshness of spring and the seashore, elderly persons suffering from chemosensory disorders are compromised in their ability to detect fire, leaking natural gas, toxic fumes, and spoiled food. Many become depressed, and a disproportionate number die in accidental gas poisonings (Chalke *et al.*, 1958). Others lose their lives or are severely burned in the hundreds of butane and propane gas explosions that occur each year. Clearly, it is incumbent upon both the physician and patient to be aware of this problem, and for the physician to employ the most modern means available to evaluate, counsel, and treat such patients whenever possible.

This chapter provides the gerontologist with an up-to-date overview of the nature and cause of age-related chemosensory disturbances, means for evaluating such disturbances, and approaches useful for counseling and treating the underlying dysfunction.

CHARACTERIZATION OF CHEMOSENSORY PROBLEMS

The general term for inability to smell is anosmia, and for lessened smell function, hyposmia. The corresponding terms for taste are ageusia and hypogeusia. In the older medical literature, anosmia is sometimes referred to as *olfactory anesthesia* or *anosphrasia*. In some nosological schemes, anosmia and hyposmia are classified under the general term dysosmia (distorted smell function), whereas ageusia and hypogeusia are classified under the term dysgeusia (distorted taste function). In this scheme, dysosmia includes forms of dysfunction in addition to anosmia, such as distorted smell sensations (parosmia, cacosmia) and smell hallucinations (phantosmia). Dysgeusia similarly includes both ageusia and distortions in taste function, such as sweet, salty, or sour sensations in the absence of appropriate stimulation. Today, however, it is more common that anosmia, ageusia, dysosmia, and dysgeusia are classified separately from one another, with the first two terms signifying losses, and the second two distortions of smell and taste sensations, respectively.

ANATOMY OF THE OLFACTORY SYSTEM

To be sensed, odorants must enter the nose and reach specialized receptors within the olfactory neuroepithelium, a patch of tissue a few square centimeters in size that lines the upper recesses of the nasal vault, including the cribriform plate and sectors of the nasal septum, middle turbinate, and superior turbinate (Menco and Morrison, 2003) (Figure 1). When activated, the odorant receptors open or close (e.g., via second-messenger systems) membrane channels on the cilia, resulting in a flux of ions and an alteration of the cell's resting potential that ultimately leads to an axonal action potential (Moon and Ronnett, 2003).

Odorant receptor genes, whose discovery by Buck and Axel in 1991 led to the Nobel Prize for Medicine or Physiology in 2004 (Buck and Axel, 1991), represent the largest of all mammalian gene families, comprising nearly 3% of the more than 30 000 genes in the mouse and human genomes. Interestingly, only one type of receptor is expressed

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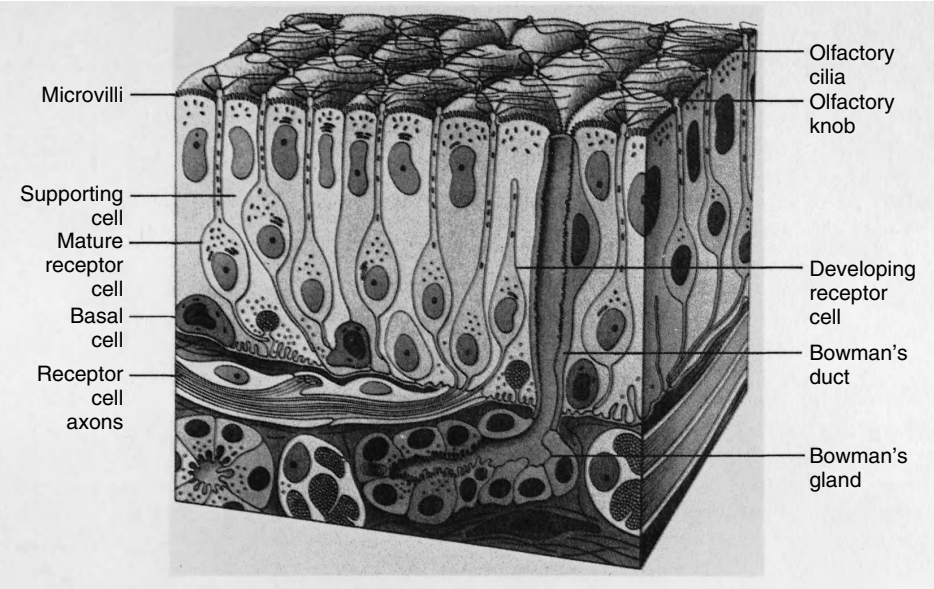

Figure 1 Schematic of the cellular organization of the human olfactory neuroepithelium. Not pictured are the microvillar cells, which are small goblet-shaped cells interspersed among the other cell types at the surface of the epithelium in a ratio to the mature receptor cells of 1 : 10 (Reprinted from Gray's Anatomy, Warwick R and Williams PL, Copyright 1973, with permission from Elsevier)

on the surface of the cilia of a given receptor cell, and odorants typically bind to more than one type of receptor. The olfactory receptor cells number from 6–10 million in the adult human and are insulated from one another at the epithelial surface by sustentacular cells (Menco and Morrison, 2003). A blanket of mucus, which contains a number of enzymes (e.g. cytochrome P-450), covers the olfactory neuroepithelium and deactivates or filters materials that are absorbed into the mucus, including some odorants (Ding and Dahl, 2003). This mucus also aids in protecting the epithelium from desiccation, heat, and xenobiotic insult, and serves as a solvent and carrier for odorant binding proteins – proteins that facilitate the transport of some lipophilic molecules to the receptors through aqueous phases of the mucus.

The unmyelinated axons of the bipolar olfactory receptor cells collect into 15–20 fascicles (fila olfactoria) that collectively make up the olfactory nerve (cranial nerve (CN) I). These axons course through the cribriform plate and synapse within spherical masses of neuropile within the olfactory bulb termed *glomeruli*. Second-order connections with the dendrites of mitral and tufted cells are made within these structures. The latter cells extend processes that project to higher centers, including the anterior olfactory nucleus, the entorhinal cortex, the prepiriform cortex, the olfactory tubercle, and the corticomedial nucleus of the amygdala. In turn, a number of these areas have extensive connections between hippocampus, mediodorsal thalamus, hypothalamus, and other brain regions (Doty and Bromley, 2000).

Ultimately, the perception of smell is the result of a complex series of electrochemical events extending from the surface of the olfactory epithelium to cortical brain structures. The pattern of neuronal activity set up by a given stimulus results in its intensity, duration, and quality. While only certain populations of receptor cells respond to a specific odorant, considerable overlap is present among odorants, and most odorants stimulate a broad range of receptor cells. The pattern of the projection of receptor cells suggests that the coding of odor quality relies on the activation of spatially overlapping projections of the olfactory receptor cells to various loci among and within the glomeruli.

In addition to the sensory innervation of the olfactory nerve, free nerve endings of the trigeminal nerve (CN V) are distributed throughout the nasal mucosa. The ophthalmic and maxillary divisions of CN V carry information regarding irritation, temperature, and pungency. Sensations mediated by non-CN I nerves are those of the "common chemical sense" and do not encode the qualitative perception of "odor" *per se* (Doty and Cometto-Muñz, 2003).

ANATOMY OF THE GUSTATORY SYSTEM

Taste receptor cells are located within taste buds on the tongue, soft palate, uvula, epiglottis, rostral esophagus, and mucous membranes of the laryngeal cartilages. Most lingual taste buds are found imbedded in the surface of protuberances termed *papillae*. Fungiform papillae are prevalent on the anterior tongue, circumvallate papillae within the chevron of the posterior tongue, and foliate papillae within the lateral margins of the medial tongue separating the anterior and posterior sectors (Shepherd, 1994) (Figure 2).

The sense of taste is supplied by three CNs: the facial nerve (CN VII), the glossopharyngeal nerve (CN IX), and vagus nerve (CN X). As shown in Figure 2, the taste buds

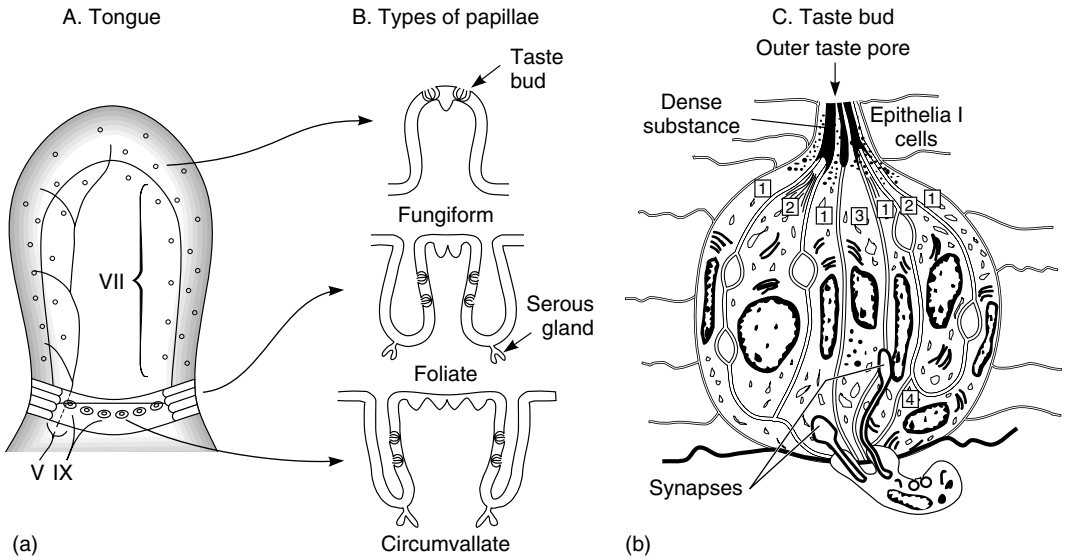

Figure 2 (a and b) Schematic of the distribution of taste buds on the human tongue. Taste buds of the fungiform and foliate papillae are innervated by CN VII. Those of the circumvallate papillae are innervated by CN IX. CN V carries nontaste somatosensory sensations. See text for details. (c) Schematic of fine structure of taste bud. (1) and (2) are presumably supporting cells that secrete materials into the lumen of the bud. (3) is a sensory receptor cell; and (4) a basal cell from which other cell types arise (Reproduced from Murray RG, 1973. Copyright Murray RG)

on the fungiform papillae are supplied by the chorda tympani branch of CN VII, whereas the taste buds on the other types of papillae are supplied by the lingual branch of CN IX. Taste buds located on the soft palate send their projections centrally via the greater superficial petrosal branch of CN VII and those on the epiglottis, esophagus, and larynx transmit taste information by way of the superior laryngeal branch of CN X. As in the case of olfaction, trigeminal (CN V) free nerve endings, distributed throughout the oral cavity, mediate somatosensory sensations (e.g. pungency, burning, sharpness). All branches of the gustatory nerves enter the brainstem and terminate in the rostral part of the nucleus of the solitary tract. The subsequent projections are not thoroughly understood in humans; however, connections are made with the ventral posteromedial thalamus and insular cortex. In rodents, fibers from the pons also travel to areas involved in feeding and autonomic regulation, including the lateral hypothalamus, central amygdala, and stria terminalis (Pritchard, 1991).

CLINICAL TESTS OF OLFACTORY AND GUSTATORY FUNCTION

The physician of the past assessed the ability to smell by asking a patient to sniff vials containing one or two odorants such as coffee or tobacco, and to report whether or not an odor is perceived. The analogous taste test was to sprinkle grains of sugar or salt onto the tongue, and ask about the corresponding sensations. Unfortunately, such procedures are akin to testing vision by shining a flashlight into the eye, or audition by sounding a bullhorn next to the ear. This problem is not corrected, in the case of olfaction, by having the patient attempt to identify the presented odorants, since without cuing, even normal subjects have difficulty identifying most odorants. In the case of taste, nonsolubilized tastants are often not recognized by patients whose mouths are dry, or who have little time to dissolve the tastants into saliva.

During the last 25 years, remarkable progress has been made in the development of reliable, valid, and clinically practical olfactory tests. Physicians and insurance carriers are now aware, more than ever, that objective chemosensory assessment is essential for (1) establishing the validity of a patient's complaint, (2) characterizing the specific nature of a chemosensory problem, (3) accurately monitoring medical or surgical interventions, (4) detecting malingering, (5) counseling patients to help cope with their problem, and (6) assigning disability compensation. Importantly, accurate assessment decreases the costs of continuing treatment seeking on the part of patients, who are usually assumed as having a problem even in the absence of objective data.

Several commercially available tests of olfactory function are now available, including tests of odor detection and identification (for review, see Doty, 2001). The most widely used of these tests (the University of Pennsylvania Smell Identification Test or UPSIT: commercially termed *the Smell Identification Test*™, Sensonics. Inc., Haddon Hts, NJ) was developed at our center and evaluates the ability of patients to identify, from sets of four descriptors, each of 40 "scratch and sniff" odorants (Doty, 1995; Figure 3). The number of items correctly identified out of 40 items serves as the test score. This measure is compared with norms based upon data from a large number of individuals sampled from the community at large and a percentile rank is determined, depending upon the age and gender of the patient. This test, which correlates strongly with traditional threshold tests, is amenable to self-administration and provides a

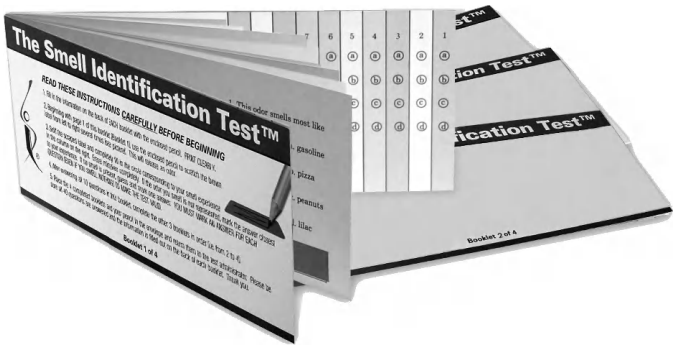

Figure 3 The 40-odorant, self-administered, University of Pennsylvania Smell Identification Test (UPSIT). Each page contains a microencapsulated odorant that is released by means of a pencil tip. Answers are marked on the columns on the last page of each booklet. Copyright 2004, Sensonics, Inc., Haddon Heights, NJ 08035

means for detecting malingering. Unfortunately, taste tests with similar reliability, validity, and practicality to that of the UPSIT do not exist, although electrogustometry can provide quantitative assessments of taste function that are correlated with the number of underlying taste elements (Miller *et al.*, 2002).

Traditionally, physicians have assumed that if a patient presenting with the complaint of anosmia fails to report the presence of an irritating vapor via CN V, he or she is malingering. However, this test is not foolproof, as even the most ardent malingerer rarely denies not perceiving a strong irritating substance, particularly one which leads to reflexive mucous secretion or eye watering. Furthermore, trigeminal thresholds to chemicals can be quite variable among individuals. Thus, a more valid means for detecting malingering is to determine the percentage of responses to stimuli that are correct in a forced-choice situation where chance responding can be calculated. When significantly fewer correct responses than expected on the basis of chance responding are demonstrated, malingering is suspected (Doty, 1995).

AGE-RELATED CHANGES IN OLFACTORY FUNCTION

It is not known to what extent age-related changes in olfactory function represent the process of aging *per se*, or alterations in the chemosensory systems brought about by factors correlated with age (i.e. cumulative viral insults, repeated exposures to environmental agents and air pollutants, alterations in trophic factors, the early progression of neurodegenerative disease pathology, etc.). Whatever the cause, however, the elderly evidence marked olfactory loss, as discussed in the beginning of this chapter. Such loss appears to occur in all cultures and is found using any one of a wide range of nominally distinct olfactory tests (e.g. odor threshold, detection, discrimination, and memory tests). However, large individual differences are present.

The age-related decline in olfactory function is exemplified by scores on the UPSIT (Doty, 1995). As can be seen in Figure 4, considerable average decline occurs in the ability to identify odors in persons after the age of 60. In general, olfactory identification ability peaks, for both men and women, during the third to fifth decades of life and significantly declines in the seventh decade. Women outperform men at all ages, with the gender gap increasing in later years.

AGE-RELATED CHANGES IN GUSTATORY FUNCTION

Taste function, like olfactory function, also declines over the life span. Older persons show decreased ability to discern sweet, sour, bitter and salty tasting agents, including a number of amino acids at both threshold and suprathreshold levels. Functionally, however, such a decrease has much less impact on the individual than olfactory loss, since whole-mouth tests often show only moderate declines in age-related function (Weiffenbach *et al.*, 1986). This is due, in part, to the fact that the taste buds in different regions of the mouth are innervated by several different sets of CNs. Such nerves are less susceptible to insult than the fine olfactory filaments. In the case of head trauma, for example, total ageusia, as measured by whole-mouth testing, is rare (<0.5%), compared to total anosmia (Deems *et al.*, 1991). Nevertheless, studies that have tested well-defined localized regions of the tongue to brief presentations of stimuli report marked age-related dysfunction (Matsuda and Doty, 1995) (Figure 5). Such losses may be particularly significant for foodstuffs that minimally leach chemicals during mastication.

It is important for the clinician to be aware that complaints of loss of "taste" usually reflect the loss of flavor sensations derived from retronasal stimulation of the olfactory receptors (Deems *et al.*, 1991; Burdach and Doty, 1987). Thus, other than basic sweet, sour, salty, and bitter sensations (or possibly metallic or "Umami" sensations), or temperature or textural sensations (sharpness, pungency, burning, etc.), the rich experiences attributed to "taste" are actually due to molecules that enter the nose from the oral cavity via the nasal pharynx. Among the hundreds of "tastes" which are really due to stimulation of CN I are banana, chocolate, strawberry, pizza sauce, vanilla, root beer, cola, licorice, steak sauce, steak, fried chicken, apples, and lemon.

CAUSES OF SMELL DYSFUNCTION IN THE ELDERLY

The olfactory receptors are rather directly exposed to the outside environment, making them susceptible to insult from bacteria, viruses, toxic agents, and other nosogenic stimuli. For this reason, it is not surprising that environmentally induced damage to the olfactory epithelium appears to be the most common cause of age-related decrements in the ability to smell. Indeed, cumulative destruction of the olfactory

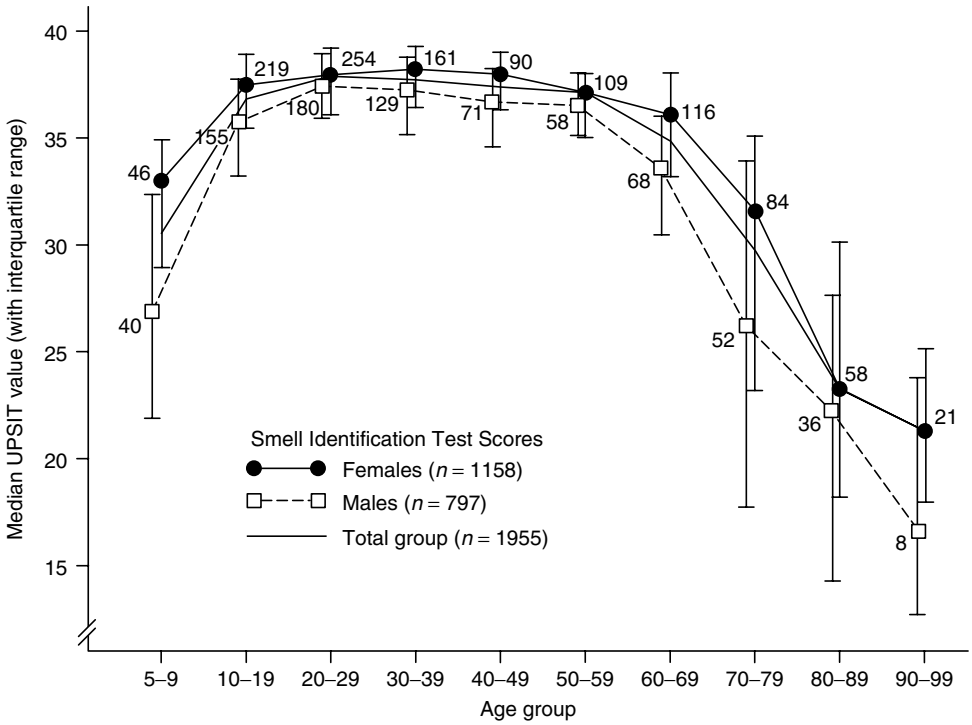

Figure 4 Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of age in a large heterogeneous group of subjects. Numbers by data points indicate sample sizes (Reprinted with permission from Doty RL *et al.*, Smell identification ability: changes with age. *Science*, **226**:1441–1443. Copyright 1984 AAAS.)

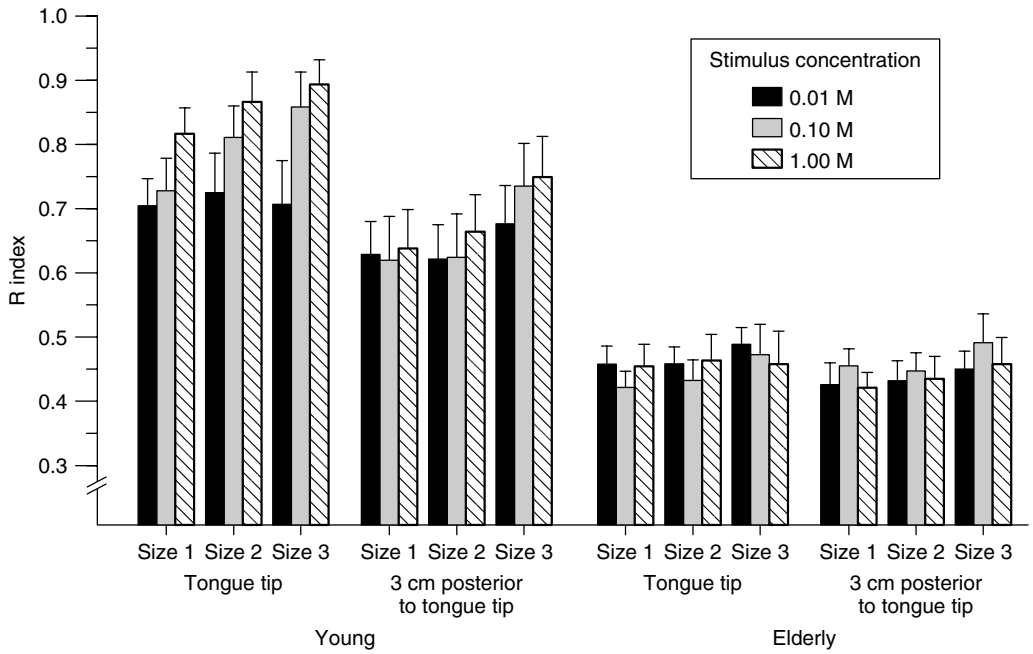

Figure 5 Mean (±SEM) sensitivity values (R index) obtained from 12 young and 12 elderly subjects for sodium chloride stimuli presented to the tongue tip and to a medial tongue region 3 cm posterior to the tongue tip for three stimulation areas (12.5. 25, 50 mm^2) and three stimulus concentrations. Note that the sensitivity of the elderly subjects was approximately chance and that the sensitivity did not increase as either a function of the stimulus area or concentration. Note also that, unlike the case with the young subjects, the tongue tip of the elderly subjects was no more sensitive than the tongue region 3 cm posterior to the tongue tip (Reproduced from Matsuda T, Doty RL. Regional taste sensitivity to NaCl:relationship to subject age, tongue locus and area of stimulation. Chem Senses 1995; **20**: 283–90, by permission of Oxford University Press)

epithelium occurs over the course of one's life with metaplasia from respiratory-like epithelium appearing as islands within the membrane (Nakashima *et al.*, 1984). However, age-related functional or structural changes may also directly damage the epithelium or predispose it to damage from environmental insults, such as from influenza. Potential changes include reduced protein synthesis or metabolic insufficiency (as in hypothyroidism), changes in the vascular elasticity of the epithelium, altered airway patency, decreased intramucosal blood flow, loss of neurotrophic factors, occlusion of cribriform plate foramina through which the olfactory nerve axons project, increased viscosity of the nasal mucus, atrophy of secretory glands and lymphatics, and, potentially, decreases in enzyme systems that deactivate xenobiotic materials within the olfactory mucosa (Doty, 1994).

The vast majority of elderly patients complaining of a smell deficit can be classified into one of six proximal etiologic categories: (1) nasal/paranasal sinus disease; (2) prior upper respiratory infection (URI); (3) head trauma; (4) Alzheimer's disease (AD); (5) Parkinson's disease (PD); or (6) idiopathic.

Nasal/Paranasal Sinus Disease

Inflammation of the nasal cavity and sinuses (e.g. chronic sinusitis, allergic rhinitis, bacterial rhinitis, viral rhinitis) reduces upper airway patency, thereby restricting odorant access to the olfactory neuroepithelium. Additionally, structural abnormalities such as marked sepal deviation (particularly with adhesions to the turbinates), polyps, and neoplasms can lead to decreased olfactory sensitivity. Even individuals with a moderate degree of ostiomeatal disease, without intranasal polyps, may complain of olfactory loss (Murphy *et al.*, 2003). The loss of smell can be quite severe in patients with nasal sinus disease, with most being anosmic or profoundly hyposmic. These patients are more likely to describe a gradual onset of olfactory loss than those patients whose loss is due to prior URIs. Fluctuations in smell sensitivity are also characteristic of nasal sinus disease. For example, nasal decongestion from exercise, hot showers, or medications may temporarily improve the sense of smell. Administration of corticosteroids (particularly systemic) typically improves smell function in this group of patients and can be used to diagnose olfactory loss due to nasal sinus disease when function is still present. Unfortunately, sustained corticosteroid treatment is not medically indicated in most cases and chronic nasal sinus disease can lead to damage to the olfactory mucosa (Kern *et al.*, 2004). Once such damage occurs, olfactory function does not improve by administration of an anti-inflammatory agent. It is encouraging, however, that olfactory dysfunction arising from nasal sinus disease is often amenable to treatment (Doty and Mishra, 2001). Management of allergies, sinusitis, and structural abnormalities through medication or endoscopic surgery can alleviate smell loss in a number of these patients.

Prior Upper Respiratory Infections

URIs are the most common cause of permanently decreased olfaction in persons older than 50 years (Deems *et al.*, 1991). The diagnosis of viral-induced olfactory dysfunction is based upon a history of a viral illness prior to the onset of olfactory loss in combination with the absence of other etiologic factors. Patients will often describe an olfactory deficit during a "cold" that was more severe than usual. After recuperation from the illness, however, the sense of smell does not return. These patients are more likely to experience a nonfluctuating hyposmia in comparison to the fluctuating anosmia of patients with nasal sinus disease.

Whether viral-induced smell loss is reflective of the age-related resistance to viral insult or a culmination of repeated insults to the olfactory neuroepithelium (or both) is unknown. Olfactory biopsies in individuals with olfactory dysfunction secondary to upper respiratory infections demonstrate a decrease in the number of olfactory receptor cells, extensive scarring, and islands of metaplasia from respiratory-like epithelia (Menco and Morrison, 2003). These characteristics are frequently evidenced in the olfactory epithelia of elderly individuals, suggesting the possibility that cumulative viral insults over time may be one reason for their overall loss, even if a precipitating event cannot be identified or differs from a viral infection.

Currently, no treatment is available for viral-induced chronic anosmia or hyposmia. Nevertheless, some authors have reported spontaneous remission in at least a few such cases, although such remission is relatively minor and noticeable only after 2 or 3 years (Duncan and Seiden, 1995).

Head Trauma

Most studies have reported incidence rates of smell loss following head trauma between 5 and 15%, although such estimates are not available from random samples of head injury patients at large (Doty *et al.*, 1997). Injuries that involve rapid acceleration/deceleration of the brain are most commonly associated with smell loss. Such coup/contrecoup movements lead to shearing or tearing of the olfactory nerve filaments at the level of the cribriform plate. Interestingly, occipital blows are more likely to produce smell loss than frontal blows, presumably because less soft tissue is available for absorbing the impact. It is not presently known whether equivalent head injuries in young and older persons produce equivalent degrees of damage to the olfactory pathways, although it would seem reasonable to expect the elderly to be more susceptible to such loss.

Smell loss in head trauma patients tends to be severe, as most are anosmic rather than hyposmic under objective testing. Unfortunately, such individuals rarely regain olfactory function and scar tissue at the level of the cribriform plate often precludes entry of axons from regenerating olfactory neurons through the cribriform plate into the central nervous system.

Alzheimer's Disease (*see* Chapter 93, Clinical Aspects of Alzheimer's Disease)

Most individuals with even mild AD demonstrate decreased olfactory function relative to age-matched controls. Physiological changes associated with normal aging may be responsible, in part, for some of the AD-related olfactory dysfunction. However, even relatively young and early-stage AD patients with mild dementia score markedly lower on olfactory tests than do age-matched controls. Thus, on the 40-item UPSIT, 50% of the items, on average, cannot be identified by early-stage AD patients. In a picture identification test analogous to the odor identification test (except that pictures, rather than odors, need to be identified), only 5% of the items are similarly misidentified by the same AD patients.

It now appears that olfactory dysfunction – particularly in conjunction with other risk factors – may be a predictor of the subsequent development of AD in older persons (Devanand *et al.*, 2000; Bacon *et al.*, 1998; Graves *et al.*, 1999). In one study, for example, a standardized 12-item odor identification test was administered to 1604 nondemented community-dwelling senior citizens aged 65 years and older (Graves *et al.*, 1999). The olfactory test scores were found to be a better predictor of cognitive decline over the following 2 years than scores on a global cognitive test. Persons who were anosmic and possessed at least one APOE-4 allele exhibited 4.9 times the risk of having cognitive decline than normosmic persons not possessing this allele. This was in contrast to a 1.23 times greater risk for cognitive decline in normosmic individuals possessing at least one such allele. A sex difference was noted. Thus, women who were anosmic and possessed at least one APOE-4 allele were 9.71 times more likely to experience cognitive decline than their normosmic nonallele possessing counterparts. The corresponding figure for men was 3.18. Women and men who were normosmic and possessed at least one allele were only 1.9 and 0.67 times more likely, respectively, than their normosmic nonallele possessing counterparts.

Although the olfactory system-related neuropathology of AD may involve the neuroepithelium, most likely central structures are the most heavily involved (Esiri and Wilcock, 1984; Hyman *et al.*, 1991; Kovacs *et al.*, 1999; Smutzer *et al.*, 2003; Davies *et al.*, 1993; Tsuboi *et al.*, 2003). There is evidence that AD pathology begins in olfactory regions within the medial temporal lobe, most notably, layer II of the entorhinal cortex (Brouillet *et al.*, 1994; Gomez-Isla *et al.*, 1996), and progresses from there to neocortical regions, although involvement of the olfactory bulbs early in the disease process has also been demonstrated (Kovacs *et al.*, 2001; Braak and Braak, 1998). A 40% decrease in the cross-sectional area of the olfactory tract and a 52% loss of myelinated axons has been reported in AD. Neurofibrillary tangle formation occurs earlier than amyloid deposition within the olfactory bulb of AD patients, and the presence of more than 10 neurofibrillary tangles per olfactory bulb section is associated with a 93.3% AD diagnostic accuracy rate (Kovacs *et al.*, 1999).

Parkinson's Disease

Idiopathic PD is another age-related neurodegenerative disorder characterized by olfactory dysfunction (Doty, 2003). As in AD, patients with PD evidence olfactory deficits on a wide variety of olfactory tests. Importantly, the proportion of early-stage PD patients with olfactory dysfunction appears to be equal to or greater than the proportion of early-stage PD patients exhibiting a number of the cardinal signs of PD (e.g. tremor) (Doty *et al.*, 1988).

The following important observations have been made: (1) PD-related smell loss is bilateral and present very early in the disease process; (2) the magnitude of olfactory dysfunction is unrelated to disease stage, severity of motor dysfunction or use of antiparkinsonian medications; (3) the olfactory loss is stable over time, even when other elements of the disease progress; (4) olfactory evoked potentials are abnormal in PD patients, demonstrating a prolonged latency, or in most cases, an absent response; and (5) among the major motor disorders, the olfactory loss of PD is relatively specific (Doty *et al.*, 1988; Doty, 2003). Thus, decreased ability to smell is absent, or present infrequently or only to a minor degree, in progressive supranuclear palsy (a condition that shares a number of signs with PD), essential tremor, multiple system atrophy, amyotrophic lateral sclerosis, multiple sclerosis, and parkinsonism induced by intravenous administration of the proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Doty *et al.*, 1993; Wenning *et al.*, 1995; Sajjadian *et al.*, 1994; Doty *et al.*, 1992).

While the basis for the olfactory deficit in idiopathic PD is unknown, it appears to be indistinguishable from that observed in AD, suggesting the possibility that these two disorders may share a common neuropathological substrate (Doty *et al.*, 1991). As with AD, both olfactory vector and degenerative hypotheses could explain the dysfunction. Tangential support for the olfactory vector hypothesis comes from evidence that (1) certain viruses (e.g. encephalitis lethargica) have been epidemiologically associated with PD, (2) a number of viruses, including ones associated with encephalitis, enter the central nervous system via the primary olfactory neurons, and (3) patients whose parkinsonism is due to the intravenous administration of MPTP have a relatively normal olfactory function (Doty, 2003). Recent data suggest the possibility that the olfactory dysfunction of AD and PD may be secondary to the damage to the anterior olfactory nucleus, a relay station within the core of the olfactory bulb. Thus, intraneuronal pathology related to the protein τ is clearly marked in the anterior olfactory nucleus of neurodegenerative diseases such as AD and PD that are associated with olfactory loss, but nearly absent in such disorders as progressive supranuclear palsy, corticobasal degeneration, and frontal temporal dementia (disorders with little or no olfactory dysfunction) (Tsuboi *et al.*, 2003; Braak *et al.*, 2003; Doty, 1991).

Idiopathic Factors

A number of individuals presenting with an olfactory complaint lack a clear etiology for their dysfunction. It is possible that subclinical manifestations of disorders that alter the sense of smell are responsible for some of these cases. For example, we have observed patients presenting to our clinic with complaints of distorted olfactory function of unknown origin who came down with influenza a week or two later. The olfactory losses of a disproportionate number of idiopathic cases occur during the influenza season; thus, some of these cases may reflect influenza that culminates in no other noticeable clinical manifestations.

CAUSES OF TASTE DYSFUNCTION IN THE ELDERLY

As discussed in detail earlier in this chapter, the subjective complaint of "taste" loss, a common complaint of the elderly is often not verified by whole-mouth taste testing. A number of such patients are undoubtedly confusing "taste" with "flavor", and upon careful testing, exhibit major olfactory, rather than major gustatory, deficits (Deems *et al.*, 1991).

As with olfactory dysfunction, a broad array of age-related changes may predispose the taste system to damage from environmental insults or other factors, including reduced protein synthesis or metabolic insufficiency, changes in epithelial vascularity, decreased blood flow, loss of neurotrophic factors, and atrophy of secretory glands and lymphatics (Doty, 1994). Common conditions seen in the elderly that may interfere with the access of the tastant to the taste bud (transport loss) include inflammatory processes of the oral cavity, bacterial and fungal colonization of the taste pore, and xerostomia. Poor oral hygiene may also contribute to taste dysfunction.

Viral infections, medications, and radiation therapy to the oral cavity and pharynx represent the most common causes of sensory gustatory loss. The chorda tympani is particularly susceptible to viral or bacterial insult as it courses through the middle ear. In turn, the middle ear is connected to the eustachian tube and nasopharynx which provide a portal of entry for infectious agents. Thus, it is not surprising that taste loss or distortion has been associated with upper respiratory and middle ear infections. Numerous drugs have been suggested to alter the ability to taste, including antihypertensives and antilipidemics (Doty *et al.*, 2003), and drugs affecting cell turnover, such as antineoplastic, antithyroid, and antirheumatic agents (Doty and Bromley, 2004).

Neural gustatory loss results from head trauma, neoplasms, and a variety of dental and otologic operations that may damage the facial nerve or glossopharyngeal nerve. Injury in this patient population can be to the taste nerves or to more central structures.

In addition to the aforementioned causes of altered taste perception in the elderly, several other conditions are important. Diabetics often experience a loss in taste perception, especially for glucose. This loss can be progressive and eventually extend to other taste stimuli (Settle, 1991). Burning mouth syndrome is a poorly characterized disorder in which patients describe an intraoral burning sensation that commonly occurs in combination with dysgeusia (Ship *et al.*, 1995). This problem is prevalent in postmenopausal women. Although no clear etiologic factor has been identified, hormone replacement and tricyclic antidepressant are effective in alleviating the oral sensations in some cases. The limited data suggest that neurodegenerative disorders such as AD do not influence the ability to taste to any major degree.

EVALUATING AND MANAGING ELDERLY PATIENTS WITH CHEMOSENSORY DYSFUNCTION

In general, a thorough medical history will identify the proximal cause of most smell and taste problems. During this history, the clinician should question the patient as to whether there is loss (e.g. anosmia) or a decrease (e.g. hyposmia) in function and whether the symptoms are unchanging, progressive, or fluctuant. The degree to which the loss or distortion is localized to one nostril or the other, or to one section of the tongue or the other, is useful in establishing whether a given nerve is involved. Antecedent events (i.e. prior URI, head trauma, medications, surgery) leading up to the dysfunction as well as the duration of symptoms are important pieces of information to be gathered from the history. For example, fluctuating olfactory deficits suggest interference with the transport of the odorant to the olfactory neuroepithelium (e.g. nasal sinus disease) rather than a sensorineural disorder.

After obtaining a thorough medical history, it is critical to evaluate the patient objectively, so as to characterize the nature of the dysfunction. In most cases, olfactory dysfunction is the problem. Thus, even when the patient reports that smell is all right and only taste is problematic, quantitative olfactory testing should be performed. If unilateral dysfunction is suspected, the olfactory test can be administered to each half of the nose separately while occluding the contralateral naris using a piece of Microfoam^{TM} tape (3M Corporation, Minneapolis, MN). Contemporaneously, a thorough upper airway examination, ideally using endoscopic procedures, should be performed along with appropriate imaging of the sinuses and higher brain structures. If nasal or intracranial disease is found, appropriate medical or surgical treatment should be initiated, and olfactory testing should be repeated some time after the completion of the treatment regimen to ascertain whether improvement has occurred. Obviously, the basic diseases associated with aging should be ruled out by the physician to preclude their possible association with the chemosensory dysfunction. Importantly, a review of the medications taken by the elderly should be undertaken, particularly if dysgeusia is the presenting symptom.

If the medical tests prove negative, it is likely that the dysfunction is due to neural damage for which no treatment is available (e.g. damage to the olfactory receptors proper). In this case, it is still prudent to assess the chemosensory function quantitatively and obtain a percentile score for the patient. While an older person may evidence, in an absolute sense, considerable olfactory loss, it is still important to characterize this person relative to his or her peer group. Thus, an 85-year-old man may have olfactory loss indicative of marked hyposmia; however, he may still be at the 75th percentile of his normative group, indicating that he is outperforming three-quarters of his peers. Simply telling him this fact would be highly therapeutic, as elderly persons expect some degree of decline in their function, but appreciate it when their decline is still not as great as that seen in most of their peers. This simple strategy is very therapeutic and ensures that at least half the patients complaining of chemosensory function loss can receive meaningful psychological benefit.

In cases where borderline dysfunction is present in menopausal women, the astute clinician can explore whether hormone or vitamin replacement therapy may be indicated in an attempt to return function. This is particularly the case in burning mouth syndrome, where such treatments have been found effective in some cases (Grushka and Sessle, 1991). Although zinc therapy has been suggested in the literature, double-blind studies indicate that zinc is no more effective than a placebo in helping patients with chemosensory disorders (unless, of course, frank zinc deficiency is present) (Henkin *et al.*, 1976). One study reporting effectiveness of the antioxidant α-lipoic acid had no controls and the number reporting resolution was of the same magnitude as would be expected from spontaneous resolution (Hummel *et al.*, 2002). Some cases of taste dysfunction may represent age-related xerostomia, and, therefore, this condition should be addressed and, if present, treated as well as possible.

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KEY POINTS

- Taste and smell are critical for determining the flavor of foods and beverages and for protection from leaking natural gas, fire, toxic agents, and spoiled beverages and foodstuffs.
- Smell dysfunction is the norm, not the exception, for persons over the age of 65.
- It is important for the physician and patient to have an accurate understanding of a patient's abilities to taste and smell, and easy-to-administer quantitative tests of smell function are widely available.
- Smell loss is among the very earliest signs of Alzheimer's disease and idiopathic Parkinson's disease.
- The most common cause of *permanent* smell loss in the elderly is an upper respiratory infection.

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PART III

Medicine in Old Age

Section 9

Bone and Joint Health

Age-related Changes in Calcium Homeostasis and Bone Loss

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INTRODUCTION

Serum calcium (Ca) must be maintained within narrow limits for the proper functioning of nerve, muscle, and bone. In general, the diurnal variation of serum Ca is plus or minus 3%. The major organs involved in Ca homeostasis are the intestine, bone, and kidney. The intestine absorbs Ca from the diet, the bone serves as a large reserve for Ca, and the kidney reabsorbs filtered Ca. These organs work together so that Ca loss is balanced by Ca intake.

Serum Ca does not change with age, but the mechanism by which it is maintained changes markedly with age. This fact has important implications for bone mass in older adults. This review will first describe the changes that take place with age in regard to Ca metabolism. It will then describe age-related changes in the levels and actions of the major calcium-regulating hormones, vitamin D, and parathyroid hormone (PTH). The implication of these changes for the maintenance of bone mass with age and possible causes for bone loss will be discussed. Finally, the efficacy of Ca and vitamin D supplementation will be examined. In general, the results of clinical studies will form the basis of this review. However, animal studies will be cited where relevant, particularly in the discussion of mechanisms.

DESCRIPTION OF CALCIUM METABOLISM

A typical daily Ca balance for a young adult is shown in Table 1. If 1000 mg of Ca is taken in the diet during the day, then the intestine will absorb about 300 mg. This assumes a 30% absorption efficiency in a young person. About 700 mg will be unabsorbed and lost in the feces, along with about 200 mg secreted into the intestine. Thus, the net Ca loss via the intestine is 900 mg. The kidney filters large amounts of Ca, but it reabsorbs about 98–99%. A typical daily loss of Ca in the urine is about 100 mg. Thus, under normal circumstances, the loss of Ca in the feces and urine (900 + 100 mg) is just balanced by the intake of dietary Ca (1000 mg). Serum Ca levels are buffered by a constant exchange of the Ca in bone with the Ca in the extracellular fluid. This exchange has been estimated to be about 250 mg. Normally, the amount of Ca deposited in the bone equals the amount reabsorbed, so that there is no net gain or loss of bone mineral.

A number of changes take place in Ca metabolism with age, even though serum Ca levels themselves do not change with age (Table 2). First, the amount of Ca in the diet tends to decline with age. Second, there is a decline in the efficiency of Ca absorption with age. Third, with regard to bone, Ca resorption tends to exceed Ca deposition, so that the net loss of Ca from bone increases with age. On the other hand, there is no evidence that the amount of Ca secreted into the intestine or that the amount of Ca excreted in the urine changes with age. The net effect of the decreased absorption of dietary Ca and the increased loss of Ca from bone is for Ca balance to become more negative with age. These age-related changes in Ca balance are also summarized in Table 1 (right column). The mechanisms responsible for these changes in Ca balance will be described in greater detail in the rest of the chapter.

REGULATION OF CALCIUM METABOLISM

The regulation of Ca homeostasis by intestine, bone, and kidney is coordinated by vitamin D and PTH (Holick, 2003) (Figure 1). When serum Ca falls below 10 mg/100 ml, this decrease is sensed by the parathyroid glands, which secrete

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Table 1 Daily calcium balance in young adults

Parameter	Calcium (mg day^{-1})		Age changes
Dietary Ca		+1000	Decreases
Intestine			
Ca unabsorbed	−700		Increases
Ca secreted	−200		Unchanged
NET		−900	
Kidney			
Ca excreted	−100		Unchanged
NET		−100	
Bone			
Ca deposited	+250		Ca deposited less than Ca reabsorbed
Ca reabsorbed	−250		
NET		0	
Balance		0	Becomes negative

Table 2 Age-related changes in calcium metabolism

- Decreased amount of Ca in diet.
- Decreased efficiency of intestinal Ca absorption.
- Resorption of Ca from bone greater than deposition.
- RESULT: Net Ca balance becomes negative.

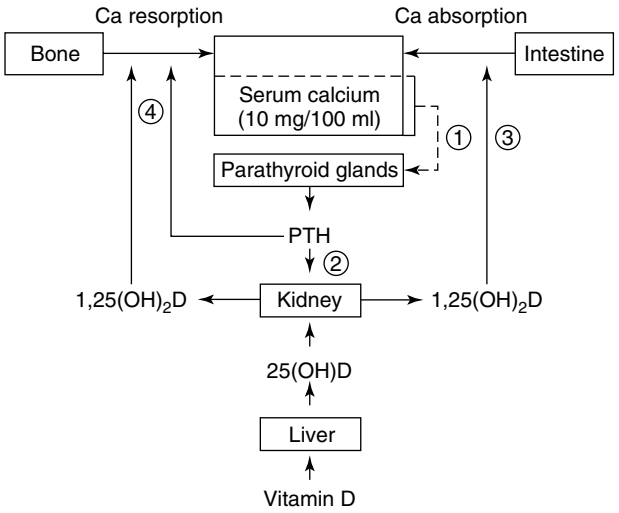

Figure 1 Regulation of serum calcium by vitamin D and PTH. A decrease in serum Ca is detected by the parathyroid glands, which respond by secreting PTH (step 1). PTH acts on the kidney to increase the conversion of 25(OH)D to 1,25(OH)$_2$D, the active metabolite of vitamin D (step 2). 1,25(OH)$_2$D acts on the intestine to increase absorption of dietary Ca (step 3). 1,25(OH)$_2$D and PTH act together on bone to increase resorption of Ca from bone (step 4). These actions normalize serum Ca and reduce PTH secretion by the parathyroid glands

PTH in proportion to the fall in serum Ca (Figure 1, step 1). PTH acts on the kidney to increase the synthesis of the active form of vitamin D_3, 1,25-dihydroxyvitamin D_3 (1,25(OH)$_2$D) (Figure 1, step 2). Vitamin D_3 by itself has very little biological activity. The biologically active form is produced by first hydroxylating vitamin D_3 in the liver to form 25-hydroxyvitamin D_3 (25(OH)D), and 25(OH)D is then hydroxylated in the kidney to produce 1,25(OH)$_2$D. The 1,25(OH)$_2$D then acts on the intestine to stimulate Ca absorption (Figure 1, step 3). In addition, PTH and 1,25(OH)$_2$D work in concert to stimulate Ca resorption from bone (Figure 1, step 4). The increased Ca absorption by the intestine and increased Ca resorption from bone tend to increase serum Ca levels. As serum Ca rises toward normal levels, PTH secretion by the parathyroid glands decreases.

AGE-RELATED CHANGES IN CALCIUM METABOLISM

In general, serum Ca does not change with age. Most clinical studies have reported that total serum Ca does not change with age (Fujisawa *et al.*, 1984; Insogna *et al.*, 1981; Tsai *et al.*, 1984), although some have reported a slight decline in serum ionized Ca (Wiske *et al.*, 1979). This maintenance of serum Ca is all the more remarkable since dietary intake of Ca tends to decline with age.

Changes in Intestinal Ca Absorption

There have been a number of clinical studies on the effect of age on intestinal Ca absorption (Gallagher *et al.*, 1979; Bullamore *et al.*, 1970; Ebeling *et al.*, 1992; Kinyamu *et al.*, 1997). Many of these studies have found a gradual decrease in Ca absorption with age (Gallagher *et al.*, 1979). The decrease in Ca absorption tended to parallel the decrease in serum 1,25(OH)$_2$D levels with age. One study (Bullamore *et al.*, 1970) found no decrease until after 60 years. One study, which found no age-related decrease in Ca absorption, reported an increase in serum 1,25(OH)$_2$D levels with age (Ebeling *et al.*, 1992). This suggested an age-related decrease in intestinal responsiveness to 1,25(OH)$_2$D.

Changes in Bone Ca Deposition and Resorption

There is a progressive bone loss with age in both men and women. This bone loss results from the rate of resorption of Ca from bone exceeding the rate of Ca deposition during remodeling (Riggs and Melton, 1986). One possibility is that the activity of osteoblasts, the cells involved in bone formation, decreases with age relative to the activity of osteoclasts, the cells involved in bone resorption. In support of this, it has been reported that the osteoblasts of older individuals fail to completely refill the resorption cavities created by osteoclasts (Eriksen *et al.*, 1985). In addition, bone turnover (rate of formation and deposition) tends to increase with age (Eastell *et al.*, 1988). Thus, any discrepancy between bone formation relative to bone resorption tends to be magnified in older individuals who have rapid bone turnover.

Changes in Ca Balance

Ca balance is Ca ingested minus Ca excreted in the feces and urine. It must be zero or slightly positive to avoid chronic loss of bone mineral. Ca balance studies are difficult to perform because they generally require measuring the difference between two large numbers – Ca ingested in the diet and Ca excreted in the feces. However, when examined as a group, balance studies suggest that Ca balance decreases (becomes more negative) with age. Heaney (Heaney *et al.*, 1982) tabulated a number of balance studies, and they found that the mean Ca requirement was 668 mg day^{-1} for young and adult subjects and 1040 mg day^{-1} for elderly subjects.

AGE-RELATED CHANGES IN CALCIUM-REGULATING HORMONES

Changes in Serum 1,25$(OH)_2$D

Most clinical studies have found a decline in serum 1,25$(OH)_2$D levels with age. Studies which have focused on older adults have reported a decrease in serum 1,25$(OH)_2$D between the ages of 50 and 65 (Fujisawa *et al.*, 1984; Gallagher *et al.*, 1979). This decrease in serum 1,25$(OH)_2$D levels could be due to several factors. These include decreased intake and absorption of dietary vitamin D, decreased synthesis of vitamin D in the skin (MacLaughlin and Holick, 1985), and decreased production of 1,25$(OH)_2$D by the kidney (Tsai *et al.*, 1984) (Table 3). In some of these studies, there was a decrease in serum 1,25$(OH)_2$D levels with age despite constant levels of 25(OH)D (Tsai *et al.*, 1984; Gallagher *et al.*, 1979). This suggests that there is a progressive decrease in the capacity of the kidney to hydroxylate 25(OH)D and form 1,25$(OH)_2$D with age. One study found no age-related change in serum 1,25$(OH)_2$D levels in men whose glomerular filtration rate was not reduced (Halloran *et al.*, 1990). This suggests that decreased renal function may contribute to decreased serum 1,25$(OH)_2$D levels.

Changes in Serum PTH

Numerous clinical studies have documented increases in serum immunoreactive PTH with age (Insogna *et al.*, 1981; Wiske *et al.*, 1979; Gallagher *et al.*, 1980; Forero *et al.*, 1987). The increased amount of PTH appears to be biologically active, since there is a concurrent increase in urinary cAMP and a decrease in tubular reabsorption of phosphorus with age (Insogna *et al.*, 1981; Forero *et al.*, 1987). These are both well-known actions of PTH in the kidney. It has been suggested that the age-related increase in serum immunoreactive PTH is due to decreased renal function. However, PTH levels increase with age even when decreased renal function is taken into account (Gallagher *et al.*, 1980). The increase in serum immunoreactive PTH appears to be due to increased PTH secretion by the parathyroid gland with age.

AGE-RELATED CHANGES IN THE REGULATION OF CALCIUM METABOLISM

There are a number of changes in the mechanism by which serum Ca is maintained throughout the lifespan (Table 4). Taken together, these changes tend to put older individuals at risk for age-related bone loss. In the following sections, these changes and their genesis will be discussed.

Decreased Renal 1,25$(OH)_2$D Production in Response to PTH

In the young, PTH stimulates renal 1,25$(OH)_2$D production (Figure 1, step 2). However, with age, serum 1,25$(OH)_2$D levels decline despite a progressive increase in serum PTH levels (see previous text). Refractoriness to PTH is also suggested by a study that found that maintenance of normal 1,25$(OH)_2$D production in elderly men required increased levels of serum PTH (Halloran *et al.*, 1990). The effect of age on renal responsiveness to PTH has been tested directly in several clinical studies. Two of these studies showed that the capacity of PTH to increase serum 1,25$(OH)_2$D declines with age (Tsai *et al.*, 1984; Kinyamu *et al.*, 1996). The third study found that the action of PTH was delayed with age, but that comparable levels were eventually achieved (Halloran *et al.*, 1996).

With regard to mechanisms, in the rat, the capacity of PTH to stimulate 1,25$(OH)_2$D production also declines with age (Armbrecht *et al.*, 1987). However, the capacity of PTH to stimulate second messenger signals does not change with age (Friedlander *et al.*, 1994). Likewise, the capacity of PTH to stimulate transcription of the gene for the enzyme that makes the 1,25$(OH)_2$D, the renal 1alpha-hydroxylase, does not change with age (Armbrecht *et al.*, 2003). This suggests that there are age-related changes distal to the PTH receptor. However, an age-related decrease in PTH receptor number has also been reported (Hanai *et al.*, 1990).

Table 3 Age-related changes in vitamin D metabolism

- Decreased intake and absorption of dietary vitamin D.
- Decreased vitamin D production by the skin.
- Decreased 1,25$(OH)_2$D production by the kidney.
- RESULT: Decreased serum 1,25$(OH)_2$D levels.

Table 4 Age-related changes in Ca metabolism regulation

- Decreased renal 1,25$(OH)_2$D production in response to PTH.
- Decreased intestinal Ca absorption in response to 1,25$(OH)_2$D.
- Decreased sensitivity of the parathyroid glands to serum Ca.
- Decreased bone deposition relative to resorption.

Decreased Intestinal Ca Absorption in Response to 1,25(OH)$_2$D

In the young, 1,25(OH)$_2$D stimulates intestinal absorption of Ca (Figure 1, step 3). There are several clinical studies suggesting that intestinal responsiveness to 1,25(OH)$_2$D declines with age. In one study, increased levels of serum 1,25(OH)$_2$D were required to maintain Ca absorption in older individuals (Ebeling *et al.*, 1992). In a second study, serum 1,25(OH)$_2$D levels were manipulated over a wide range in young and elderly women (Pattanaungkul *et al.*, 2000). It was found that there was a relative resistance to 1,25(OH)$_2$D in elderly women with regard to Ca absorption.

The mechanisms responsible for this decreased intestinal responsiveness to 1,25(OH)$_2$D are still under investigation. In humans, some studies have found a correlation between decreased intestinal responsiveness and a decrease in intestinal vitamin D receptors (VDR) (Ebeling *et al.*, 1992). A decreased number of receptors could contribute to the decreased intestinal responsiveness to 1,25(OH)$_2$D with age. However, this has not been seen in all studies (Kinyamu *et al.*, 1997). In the rat, there is also an age-related decline in the capacity of 1,25(OH)$_2$D to stimulate intestinal Ca absorption (Wood *et al.*, 1998; Armbrecht *et al.*, 1999). This is correlated with the decreased capacity of 1,25(OH)$_2$D to stimulate key proteins involved in the intestinal transport of Ca (Armbrecht *et al.*, 1999; Armbrecht *et al.*, 1998). As in human studies, there is lack of agreement as to whether there is a decline in rat intestinal VDR with age. Some studies report a decline (Horst *et al.*, 1990) while others do not (Wood *et al.*, 1998).

Decreased Sensitivity of the Parathyroid Glands to Serum Ca

In the young, PTH secretion by the parathyroid glands is regulated by Ca levels in the blood (Figure 1, step 1). Numerous clinical studies have reported that serum PTH levels increase with age (see previous text), and one study correlated this with age-related bone loss (Ledger *et al.*, 1995). This rise in serum PTH is seen even when age-related changes in renal clearance are taken into account (Gallagher *et al.*, 1980), suggesting that there is an increase in PTH secretion by the parathyroid glands with age. Several studies have found that basal and stimulated PTH secretion was higher in older women compared to that in younger women (Ledger *et al.*, 1994; Portale *et al.*, 1997). However, the set point, which is the serum Ca concentration that inhibits half of the PTH secretion, did not change with age (Ledger *et al.*, 1994).

Since the rat also show studies in an age-related increase in serum PTH levels, it has been studied with regard to possible mechanisms. Perfusion studies have found that secretion of PTH increases with age in the rat (Uden *et al.*, 1992; Fox, 1991). One study attributed this to an increase in the set point with age (Uden *et al.*, 1992), but another did not (Fox, 1991). In molecular terms, the parathyroid gland senses external Ca levels via a Ca-sensing receptor. However, the expression of the Ca-sensing receptor in the parathyroid gland of the rat actually increases with age (Autry *et al.*, 1997).

PRIMARY VERSUS SECONDARY CHANGES IN Ca METABOLISM

Owing to the high degree of integration of the Ca regulating system, it is difficult to determine which age-related change (or changes) is primary and which changes are compensatory in response to the primary event(s). Two age-related changes that are often cited as explanations of age-related bone loss are (1) decreased stimulation of renal 1,25(OH)$_2$D production by PTH (Figure 1, step 2) and (2) decreased stimulation of intestinal Ca transport by 1,25(OH)$_2$D (Figure 1, step 3). Decreased production of 1,25(OH)$_2$D by the kidney would result in the observed decrease in serum 1,25(OH)$_2$D levels and in decreased intestinal Ca absorption with age. This would lead to a slight drop in serum Ca which would then result in increased secretion of PTH by the parathyroid glands.

On the other hand, decreased stimulation of the intestine by 1,25(OH)$_2$D could also explain the observed changes. Decreased Ca absorption would result in a slight drop in serum Ca, which would result in the observed increase in serum PTH with age. However, this model would predict a subsequent rise in serum 1,25(OH)$_2$D to overcome the intestinal resistance, unless there were also renal refractoriness to the action of PTH.

CHANGES IN Ca METABOLISM AND AGE-RELATED BONE LOSS (*see* Chapter 110, Epidemiology of Osteoporosis; Chapter 111, Osteoporosis and its Consequences: a Major Threat to the Quality of Life in the Elderly)

Postmenopausal Bone Loss

Bone mass declines with age in both men and women. There is a decline in skeletal mass that begins about the fourth or fifth decade and continues throughout life in both men and women. In women, there is an additional loss of bone during the first 5 years after menopause, which is superimposed on the age-related decline (Gallagher *et al.*, 1987). This has led to the concept that there are two types of bone loss – postmenopausal and age-related osteoporosis (Table 5) (Riggs and Melton, 1986). Postmenopausal (Type I) osteoporosis occurs earlier (51–75 years) and is seen in women. This type of osteoporosis is related to the loss of estrogen at menopause. The bone loss seen in postmenopausal osteoporosis is mainly trabecular, and it results in vertebral crush fractures and fractures of the distal radius. In postmenopausal osteoporosis, the primary event is excessive

Table 5 The two types of osteoporosis

	Postmenopausal (Type I)	Age-related (Type II)
Age (years)	51–75	70+
Sex	Female	Female/male
Fracture sites	Vertebrae (crush)	Vertebrae (wedge)
	Distal radius	Hip
Ca absorption	Decreased	Decreased
Serum $1,25(OH)_2D$	Decreased	Decreased
Serum PTH	Decreased	Increased

Source: Adapted with permission from Riggs BL, Melton LJ, III, Involutional osteoporosis, *New England Journal of Medicine*, Copyright 1986, Massachusetts Medical Society. All rights reserved.

resorption of bone due to the loss of the protective effect of estrogen at menopause. The excess Ca released from bone suppresses PTH secretion by the parathyroid glands, which reduces serum PTH levels (Figure 1). Decreased PTH levels then result in decreased renal production of $1,25(OH)_2D$ and decreased absorption of dietary Ca.

Age-related Bone Loss

Age-related (Type II) osteoporosis (sometimes referred to as *senile osteoporosis*) occurs later (after 70 years) and is found in men as well as in women (Table 5). The bone loss is cortical as well as trabecular, and it results in vertebral wedge fractures and hip fractures. Major contributors to age-related bone loss are the age-related changes in Ca metabolism described previously (Table 4). A decreased capacity of PTH to stimulate $1,25(OH)_2D$ production may lead to a decline in serum $1,25(OH)_2D$. A decreased action of $1,25(OH)_2D$ on the intestine tends to increase serum PTH levels. This rise in serum PTH is reinforced by the fact that the sensitivity of the parathyroid glands to Ca declines with age. The age-related rise in serum PTH levels results in a greater resorption of Ca from bone relative to deposition. It has also been proposed that a decline in estrogen plays a role in age-related bone loss – even in men (Riggs *et al.*, 1998). Possible mechanisms for this include the loss of estrogen action on the intestine and kidney, although these actions have not been well characterized.

Mechanisms of Age-related Bone Loss

Age-related bone loss is the culmination of multiple factors both extrinsic and intrinsic to bone (Seeman, 2003). The extrinsic factors include age-related changes in systemic hormones such as $1,25(OH)_2D$ and PTH (discussed above), estrogen, and growth hormone. Recent studies in rats have shown that at certain doses, $1,25(OH)_2D$ blocks the effect of PTH on bone resorption (Suda *et al.*, 2003). Thus, a decline in serum $1,25(OH)_2D$ levels may make the effect of PTH on bone even more pronounced in older animals. This may explain why chronic PTH administration increased the percent of bone-forming surface to a greater degree in aged rats than in young rats (Hock *et al.*, 1995). It has also been proposed that a decline in estrogen plays a role in age-related bone loss in both men and women (Riggs *et al.*, 1998). Finally, growth hormone and the insulin-like growth factors have been implicated in age-related bone loss (Geusens and Boonen, 2002).

In addition to hormonal changes, there are intrinsic changes within the bone itself that contribute to bone loss. There is increasing evidence that the responsiveness of bone cells to certain hormones and cytokines changes with age. Human osteoblast-like cells isolated from donors of different ages show a decreased responsiveness to insulin-like growth factor I (d'Avis *et al.*, 1997) and estrogen (Ankrom *et al.*, 1998). The response of osteoblastic cells to $1,25(OH)_2D$ has also been reported to decline with donor age (Martinez *et al.*, 2001). In osteoblast-like cells isolated from human trabecular bone, responsiveness to several growth factors declined as the age of the donor increased (Pfeilschifter *et al.*, 1993). In addition to changes in function, there also may be age-related changes that favor the production of osteoclasts over osteoblasts from bone marrow cells (Manolagas, 1998).

In general, the action of osteoblasts and osteoclasts is tightly coupled, but in age-related (and postmenopausal) osteoporosis, there is a loss of this coupling. Recently, the molecular basis of this coupling has been elucidated in the form of the RANK/RANKL/OPG regulatory system (see review by Boyle *et al.*, 2003). In mice, expression of RANKL (receptor activator of NF-kappaB ligand) and OPG (osteoprotegerin) correlates with age-related bone loss (Cao *et al.*, 2003). In humans, bone levels of RANKL increase with age (Fazzalari *et al.*, 2001), and this could mediate age-related bone loss. The RANK/RANKL/OPG system is regulated by many factors, including PTH and $1,25(OH)_2D$ (Suda *et al.*, 2003). It is also modulated by numerous hormones, growth factors, and cytokines. Changes in the local production and action of these factors, along with PTH and $1,25(OH)_2D$, may modulate the RANK/RANKL/OPG system and play an important role in age-related bone loss (see review by Troen, 2003).

DIETARY Ca AND VITAMIN D SUPPLEMENTATION (*see* Chapter 29, Vitamins and Minerals in the Elderly)

The roles of vitamin D supplementation (Lips, 2001) and Ca supplementation (Heaney, 2001) in reducing age-related bone loss have recently been reviewed. Since alterations in Ca and vitamin D metabolism contribute to age-related osteoporosis, Ca and vitamin D supplementation would be expected to be effective. This is in contrast to postmenopausal osteoporosis where there is an excess of Ca due to excessive resorption of mineral from bone. In a study by Dawson-Hughes *et al.*, (1990), Ca supplements had no effect on bone loss in the spine of women within 5 years of menopause. However, Ca supplementation retarded bone loss in women who were more than 5 years past menopause. Vitamin D and Ca supplementation together have been shown to reduce bone

loss in both men and women over the age of 65 (Dawson-Hughes *et al.*, 1997). Significantly, in addition to reducing bone loss, vitamin D and Ca supplementation have been shown to reduce hip and other nonvertebral fractures (Chapuy *et al.*, 1992). Vitamin D and Ca supplementation have also been shown to reduce the seasonal variation in bone loss that is seen in more northern climates (Meier *et al.*, 2004). Finally, antiresorptive drug therapies are more effective in the presence of adequate dietary Ca (Nieves *et al.*, 1998).

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KEY POINTS

- Intestinal absorption of dietary Ca declines with age.
- Serum PTH increases with age while serum 1,25 $(OH)_2D$ stays the same or declines.
- Resorption of Ca from bone gradually exceeds deposition with age.
- These changes contribute to age-related bone loss after the age of 70.
- Age-related bone loss can be reduced by dietary Ca and/or vitamin D.

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Paget's Disease of Bone

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INTRODUCTION

Paget's disease of the bone, also known as *Osteitis deformans* is a common chronic focal disorder of the skeleton characterized by an abnormal rate of bone turnover and disorganized osteoid formation. The disorder was first described by Sir James Paget in 1877 (Paget, 1877). He described six cases of slowly progressive deforming bone disorder, which he termed *Osteitis deformans*. He considered the disease to be a chronic inflammation of the bone. The disease is characterized by accelerated skeletal remodeling due to abnormal osteoclasts, which can involve a single bone (monostotic) or multiple bones (polyostotic). This leads to bony hypertrophy, expansion of the bone cortex and resultant abnormal bone structure responsible for bone pain, deformity, and skeletal fragility. Complications of this disease can involve bones (deformity, fracture, and neoplastic degeneration), joints (osteoarthritis), the nervous system, and the vascular system (Delmas and Meunier, 1997). The abnormal bone has increased metabolic activity and blood flow, which in itself may contribute to pain, and can also increase neurological complications as a part of vascular steal syndrome. The disease usually affects people older than 50 years and has characteristic geographic distribution.

EPIDEMIOLOGY

The epidemiology of Paget's disease is unusual because of its distinctive geographic distribution throughout the world. It is commonly seen in the United Kingdom, Australia, United States, New Zealand, and central Europe. It is less common in Switzerland, Scandinavia, southern Europe, and Ireland, and is conspicuously rare in countries like India, Japan, China, the Middle East, and black Africa (Barker, 1984; Collins, 1956). Both environmental and genetic factors have been thought to play a role and have been studied for more than 20 years. There is still no definite answer to the disorder's etiology (Collins, 1956).

Since the disorder mostly affects older individuals, the disease is rarely seen before the age of 40; however, the prevalence doubles each decade from the age of 50 onwards (Kanis, 1998) to reach 10% in the ninth decade. The incidence of disease is difficult to estimate because most of the patients remain asymptomatic. A study from the Netherlands reports that 1 in 43 asymptomatic people over the age of 50 have Paget's disease, while 1 in 5 people over the age of 50 with an elevated alkaline phosphatase level have Paget's disease. In the United Kingdom, prevalence is 2.5% in men and 1.6% in women aged 55 years and older. However, there is also a marked variation in the prevalence of the disease in Great Britain itself, with rates ranging from 8.3% in parts of northwest England to 4.6% in southern areas. In the United States, it occurs in 1.5–3.0% of people over 60 years and the prevalence is slightly higher in northeast than in south (Ankrom and Shapiro, 1998). The disorder affects men and women equally (Polednak, 1987). Also, recent epidemiologic studies suggest a decline in the prevalence and the severity of the disorder in New Zealand and the United Kingdom (Ankrom and Shapiro, 1998; Polednak, 1987; Cundy *et al.*, 1997; Kanis, 1991; Cooper *et al.*, 1999; Baker *et al.*, 1997, 1980).

ETIOLOGY

The etiology of Paget's disease remains unknown (Delmas and Meunier, 1997). Several familial and pathologic studies suggest genetic susceptibility (Barry, 1969). Viral infections play a pathogenetic role. Several Paramyxoviruses (measles virus, respiratory syncytial virus, and canine distemper virus) have been thought to play a role in the etiology of Paget's disease but this hypothesis still remains controversial (Rebel *et al.*, 1974; Mills and Singer, 1976; Basle *et al.*, 1986; Gordon *et al.*, 1991, 1992; Ralston *et al.*, 1991; Birch *et al.*,

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1994). These observations were based upon findings of intranuclear inclusion of nucleocapsid-like structures and antigens in the osteoclast nuclei and cytoplasm. In addition, Paramyxovirus transcripts also have been identified in the osteoclast precursor cells (Basle *et al.*, 1986; Gordon *et al.*, 1991, 1992; Ralston *et al.*, 1991; Birch *et al.*, 1994; Reddy *et al.*, 1995, 1996). However, attempts to isolate or culture the viruses from pagetic cells remain unsuccessful. Hence, the role of Paramyxovirus in the etiology of Paget's disease remains controversial. Some of the studies have also found elevated levels of Interleukin-6 (IL-6, a peptide produced by bone cells) in the marrow, plasma, and blood from patients with Paget's disease, which increases differentiation of monocyte/macrophage cells to osteoclasts. IL-6 has been shown to promote osteoclast formation when added to the marrow cells (Roodrnan *et al.*, 1992); however, elevated productions of cytokines have not been confirmed by all reports and hence still remains a subject of interest. It has also been postulated that viral infection upregulates the IL-6 gene and the IL-6 receptors in Paget's disease (Hoyland *et al.*, 1994). However, elevated levels of cytokines have not been consistently shown in all the studies. It still remains unknown what triggers the initial lesions.

Paget's disease also appears to have a significant genetic component, as approximately 15–30% of patients have a positive family history of the disorder (McKusick, 1972; Sins *et al.*, 1991; Morales-Piga *et al.*, 1995). An autosomal pattern of transmission has also been described. In families with apparent autosomal dominant inheritance of Paget's disease, four susceptibility loci have been identified, one on chromosome 18, one on chromosome 6 and two on chromosome 5 (Haslam *et al.*, 1998; Good *et al.*, 2001; Laurin *et al.*, 2001). Patients with a positive family history have an earlier onset of the disease and a greater prevalence of bone deformity than those with a negative family history. Various histocompatibility antigens (HLA) have also been associated with Paget's disease; however, these results have not been replicated (Tilyard *et al.*, 1982; Foldes *et al.*, 1991; Singer *et al.*, 1985, 1996).

PATHOPHYSIOLOGY

The disease is characterized by the formation of abnormal bone. In the early stages, there is increase resorption of the bone at localized areas caused by recruitment of large and numerous osteoclasts. These osteoclasts are large and may have up to 100 nuclei. These areas of localized resorption on radiographs are seen as advancing lytic wedge or "blade of grass" lesion in the long bones or as a resorptive wave or "osteoporosis circumscripta" in the skull. This phase of resorption is followed by a compensatory increase in bone formation with recruitment of osteoblasts in the areas of bone resorption. The osteoblasts form new osteoid tissue at a rapid rate and this is deposited in a disorganized, woven, or mosaic pattern that replaces the normal lamellar pattern seen in bone remodeling units. This result in the formation of a woven pattern of bone that is of poor quality and can bow and fracture easily (Meunier *et al.*, 1980). Different stages of the disease processes can be seen at the same time in different areas of bone. Furthermore, the bone marrow becomes infiltrated with an excess of fibrous connective tissue and blood vessels, leading to hypervascularity. Over time, the remodeling activity at a pagetic site decreases and leaves sclerotic or mosaic bone.

CLINICAL PRESENTATION

Most patients with Paget's disease are asymptomatic. It is commonly accepted that approximately 5% of the patients have symptoms but the estimates vary considerably. Most of the patients at the time of diagnosis are usually more than 45 years old. In the majority of cases, the diagnosis is made incidentally when the routine chemistry shows an elevated serum alkaline phosphatase level or an incidental lesion is noted on the X rays of the pelvis or spine, obtained for a different reason. Symptoms depend on the bone(s) and the part of the bone involved as well as the activity of the bone remodeling. Bone pain and deformity remain the two most common clinical manifestations of the disease. Most of the patients have one or several bones affected by Paget's disease. The areas commonly involved include the pelvis, vertebrae, skull, femur, and tibia. However, any bone may be affected. The bones of upper extremity, clavicle, and scapula are not commonly involved.

Bone deformity remains a hallmark of the disease. It is usually manifested as an increase in size and/or abnormal shape of bone. Progressive painless bowing of the weight-bearing, lower-extremity long bones is a feature. Deformity is most commonly seen in the femur, tibia, humerus, and ulna. The bowing seen in the femur and tibia are often associated with fissure (incomplete) fractures seen on the convex surface of the bowed bone. The most serious fractures involve the femoral shaft or subtrochanteric area. The femoral fractures may have a higher rate of nonunion, between 10 and 40%. Bone deformity can cause joint destruction and lead to osteoarthritis in joints proximate to bones with Pagetic lesions. There can be an increase in the skin temperature over the affected long bone, especially tibia. This is a sign of increased vascularity of the surrounding soft tissue and the bone, which is characteristic of active Paget's disease. Other bones in which deformity can occur are the skull, jaws, and the clavicles.

Bone pain is another well-recognized feature of Paget's disease that often appears late, rather than early, in the course of disease. Pain is usually described as dull but may be the sharp shooting type as well. It is often present at rest and worsen by weight bearing, especially if the disease involves the weight-bearing bones. Periarticular bone pain sometimes can be the presenting feature and is an important diagnostic problem because Paget's disease commonly affects bones around major weight-bearing joints as well as the spine. Acute pain may develop at times because of the consequence

of pathologic fractures. It is thought that the pain arises because of periosteal stretching caused by bone enlargement, hyperemia, and often because of microfractures. The pain may be due to the pagetic lesion itself or from its complications caused by the abnormal bone, such as degenerative arthritis, nerve impingement, and rarely due to osteosarcoma. These complications have a striking impact on the overall quality of life for many patients (Gold *et al.*, 1996).

Neurological symptoms may arise due to the involvement of the axial skeleton, depending upon the site of involvement. The symptoms may be progressive and often overlooked in elders. The involvement of skull may cause nonspecific headaches, conductive hearing loss due to the involvement of the temporal bone, or the ossicles of the inner ear itself, which is a disabling complication (Sparrow and Duvall, 1967). Other cranial nerves including the optic, trigeminal, and facial nerves may also be involved, rarely resulting in visual loss, tic douloureux, and facial palsy. Enlargement of the skull may cause frontal bossing (enlargement of the vault) and the resultant change is the hat size. Deformity of the base of the skull can cause brainstem compression and sometimes obstructive hydrocephalus. Involvement of the spine can cause symptoms due to radiculopathy, spinal stenosis, and ischemia of the spinal cord due to "vascular steal" syndrome, resulting in ischemic myelitis. The symptoms associated with spinal stenosis are much less common despite the high prevalence of the pagetic involvement of the vertebrae. Patients may develop paraplegia or quadriplegia depending upon the extent of the disease.

A variety of cardiac disorders can be associated with Paget's disease and are usually seen if there is an involvement of more than one-third of the skeleton. Patients can develop calcific aortic stenosis (Hultgren, 1998), conduction abnormalities, and congestive heart failure. Cardiac output increases with increasing extent of the disease (Haworth, 1953) because of an increased vascularity of the bone and surrounding tissue; however, documented occurrences of the high output failure is uncommon.

A much higher incidence of bone tumors is seen in patients with Paget's disease compared to age-matched individuals. The most common tumor associated with Paget's disease is Osteosarcoma which is seen in less than 1% of patients (Haibach *et al.*, 1985; Hadjipavlou *et al.*, 1992). It is more commonly seen in the polyostotic form of Paget's. The prevalence of sarcoma gradually increases with age and the mean age at the time of diagnosis is usually 68 years. These are commonly found in the femur, pelvis, humerus, skull, and facial bones. The prognosis associated with sarcoma remains very poor and most of the patients die within 12 months of diagnosis. Other types of tumors associated with Paget's disease are chondrosarcomas, fibrosarcomas, and tumors of mixed histological characters. When malignant neoplasms occur, they tend to be very aggressive and may be fatal unless the neoplasm is completely removed (usually requiring limb amputation). Giant cell tumors of the bone are seen in a much smaller percentage of patients and are usually benign (Singer and Mills, 1993).

Other fibrosing or inflammatory disorders that are also sometimes seen with Paget's disease are Dupuytren's contracture, Peyronie's disease, and Hashimoto thyroiditis. It is not known whether these are caused by the release of cytokines from the areas of increased bone turnover or are just associated with Paget's disease.

Generally, levels of serum, calcium, and phosphorus do not change in Paget's disease; however, hypercalcemia can sometimes be seen due to prolonged immobilization or fractures. Nephrolithiasis can occur but is unusual. Occasionally, hyperuricemia and gout may be seen.

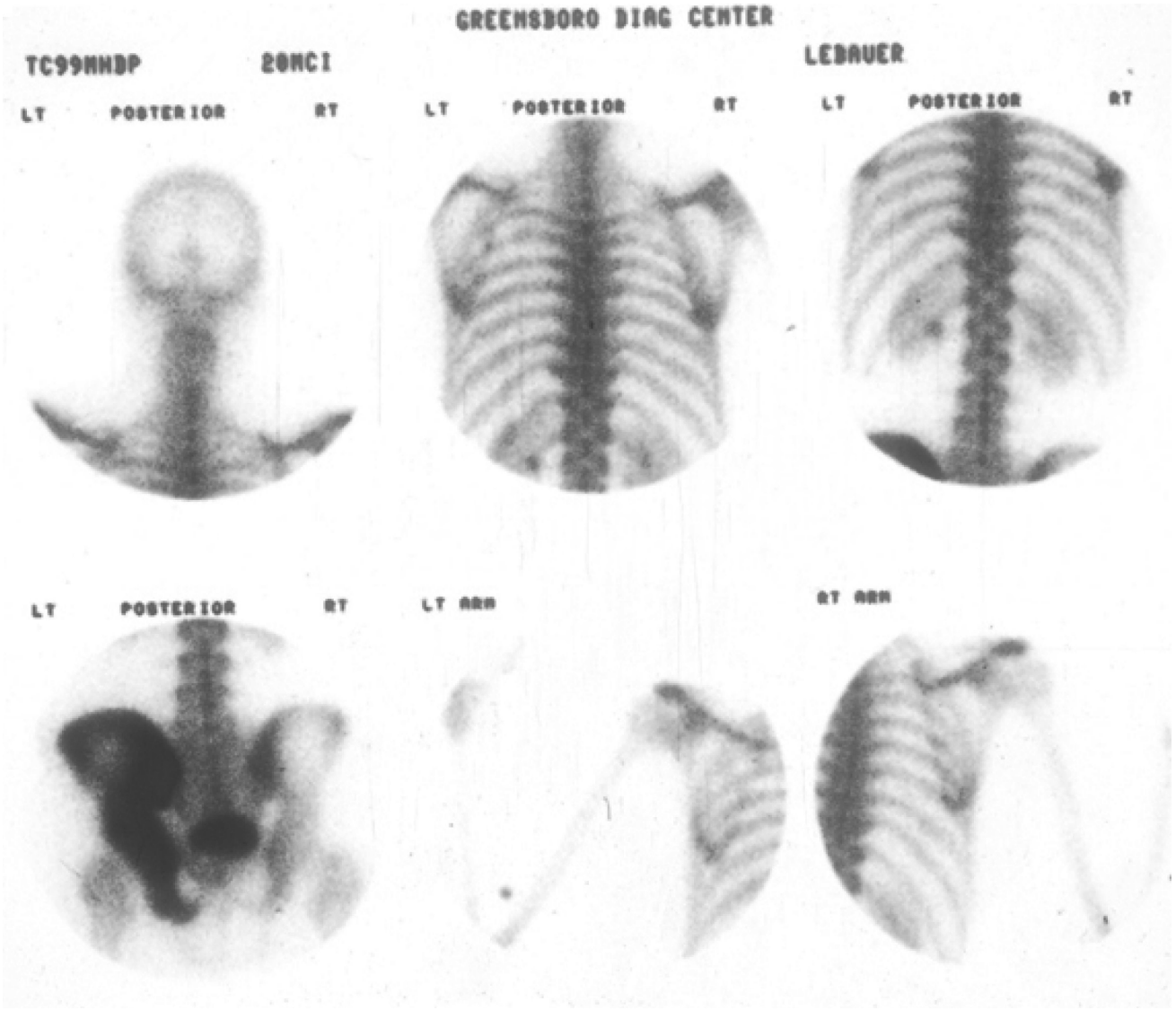
DIAGNOSTIC EVALUATION

As most of the patients with Paget's disease remain asymptomatic, the diagnosis is usually made on the basis of the radiological and biochemical abnormalities that are detected incidentally. A thorough history and physical examination remains the key to the diagnosis.

Radiology and Radionuclide Bone Scanning

The most sensitive means of detecting Paget's disease in the skeleton is by means of radionuclide bone scan. All patients with Paget's disease should have a total body bone scan using technetium-labeled bisphosphonate tracer (Fogelman *et al.*, 1981) to define the disease activity and its distribution. (Figure 1) The agent after administration is preferentially concentrated in areas of increased blood flow and high levels of bone formation, common characteristic of Paget's disease. These rapidly remodeling areas appear as hot spots. Even though there are characteristic patterns of tracer uptake, plain X rays are required to confirm the diagnosis of Paget's disease. In approximately 15–30% of the patients, the bone scan may pick up lesions not seen on the X rays. Rarely, a sclerotic lesion in an untreated patient exhibits no tracer uptake presumably because disease activity is negligible or "burned out". Generally, the bone scans are not used for follow-up of patients but primarily to establish the disease activity and extent of the skeletal involvement. However, in patients with localized disease, monostotic form, and normal biochemical indices, serial quantitative bone scans may be used to determine the objective response to the therapy.

The diagnosis of Paget's disease is primarily made by radiographic examination of the skeleton (Resnick, 1995). Plain radiographs are useful for diagnosis as well as detection of complications associated with the disease process (Figures 2, 3 and 4). In the early stages the disease is characterized by lytic areas that may be seen as V-shaped "cutting cone" lesions that are first seen at one end, gradually progressing toward the other end. The V-shaped lesion can grow at a speed of up to 1 cm $year^{-1}$. In the skull, the lytic areas are seen as osteoporosis circumscripta (well-defined lucent areas), which commonly involves the frontal, parietal, and occipital bones. In the later stages, the scleroticchanges also



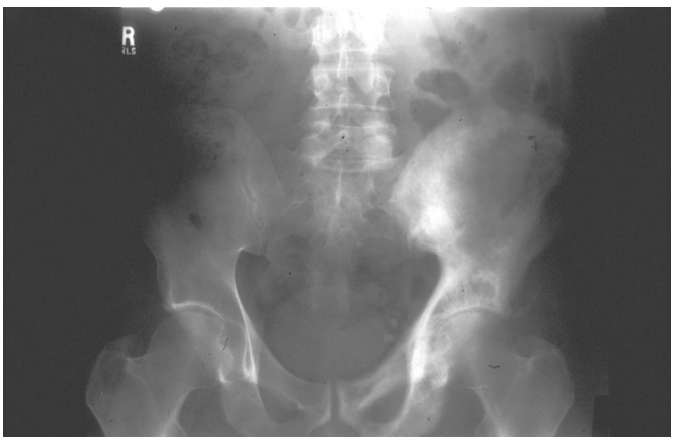


Figure 1 and 2 This 57-year-old man had an elevated alkaline phosphatase of 257 IU (normal 30–135) found on an annual physical examination. He had no symptoms and had a normal physical examination. Total body bone scan and pelvic radiographs confirmed Paget's disease of the bone on the left Ileum

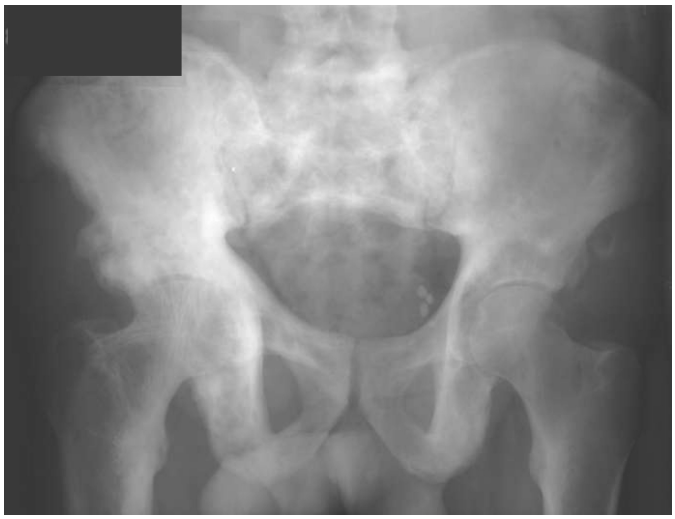


Figure 3 This 45-year-old man has polyostotic Paget's disease involving his pelvis, sacrum, and right femur. He has developed osteoarthritis in the right hip

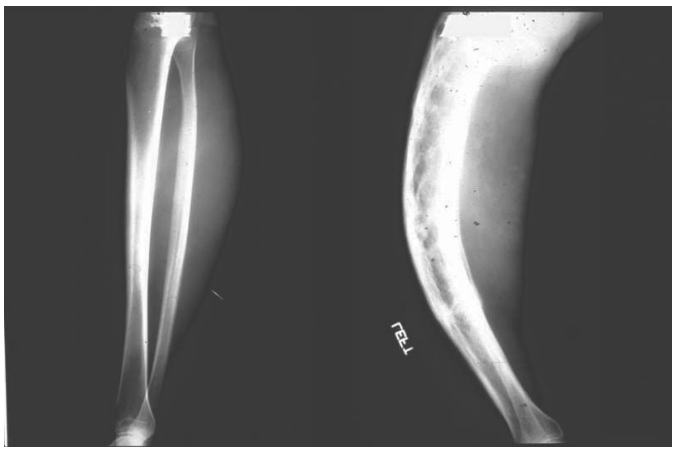


Figure 4 This 82-year-old lady had untreated Paget's disease of the bone in the left tibia. Notice the bowing compared to a normal tibia. Also the affected tibia is larger in size, has thickened cortices, evidence of thickened trabeculae and loss of trabeculae

appear along with the lytic changes resulting in thickening of the cortex and loss of distinction at the corticomedullary junction. Plain X rays can reveal both osteolytic and sclerotic changes in the same bone if taken at this stage. In the last and final stages of the disease, the sclerotic phase predominates, which is characterized by thickening and increase of bone size and marked sclerosis. The radiographs have a definite advantage over the bone scan as they can help decide if the process is predominantly osteolytic, osteoblastic, or mixed.

In selected patients, computerized tomography or magnetic resonance imaging may be helpful to define the atypical lesions, especially when sarcomatous changes are suspected. It may also be helpful in assessing back pain due to spinal stenosis, hydrocephalous, or brain stem compression from basilar skull invagination. Magnetic resonance imaging is also of value in detecting a soft tissue component of a tumor arising in a pagetic bone lesion.

If there is uncertainty about the diagnosis, a bone biopsy is a definite means of establishing the diagnosis. This is occasionally useful to differentiate from the metastatic osteoblastic lesions or osteosarcoma. However, biopsy specimen should be avoided in the weight-bearing bone because of the risk of fracture or of complications.

BIOCHEMICAL MARKERS IN PAGET'S DISEASE

A number of biochemical markers have been designed, which can predict the disease activity. These include the markers of bone formation and markers of bone resorption, which in turn reflect the activity of osteoblasts and osteoclasts.

Markers of Bone Formation

The most useful and standard biochemical index of Paget's disease activity is the measurement of the total serum alkaline phosphatase level, which has a sensitivity of 74% (Alvarez *et al.*, 1995). The enzyme is found on the plasma membrane of osteoblasts and its levels are elevated in more than 90% of affected patients. Its serum level provides a clinically useful index of osteoblastic activity in the absence of significant liver disease or pregnancy. The levels, however, may be normal in up to 15% of symptomatic patients as well as in some patients with monostotic form of Paget's disease. The enzyme can be used both in diagnosis and in monitoring of therapy. With the institution of treatment of Paget's disease, alkaline phosphatase levels fall more slowly than bone resorption parameters, but within 4–8 weeks, a clear response is usually noted. The levels correlate well with the extent of skeletal involvement as established by the radionuclide bone scan; however, the lesions in the skull may produce much higher levels of serum alkaline phosphatase. Serum alkaline phosphatase activity changes from day to day and hence to be clinically significant, the levels should increase or decrease by 25%. The specificity of the assay is limited because serum alkaline phosphatase includes isoenzymes derived from the liver, kidney, placenta, intestine, and spleen, as well as certain tumors.

Recently, assays for the bone-specific alkaline phosphatase have been developed. However, this test is more expensive, less readily available, and there are no convincing data to indicate that there is an advantage of this test over the cheaper, standard alkaline phosphatase assays in the average patient. This test may be of value in patients with monostotic Paget's disease, patients with liver disease, and in patients with Paget's disease without any elevation of total plasma alkaline phosphatase activity. Approximately 60% of patients with normal total alkaline phosphatase have increased bone-specific alkaline phosphatase.

Serum osteocalcin, another product of osteoblast may be increased in patients with Paget's disease, but its levels do not

correlate well with disease activity (Calvo *et al.*, 1996). It has a sensitivity of approximately 35%. It is not recommended as a standard means of evaluating Paget's disease. The carboxy-terminal propeptide of type 1 procollagen in the serum of patients with Paget's disease may be evaluated, but it has not been proven to be a particularly useful clinical index of the disease. It is elevated in approximately 45% of patients with active Paget's disease.

Markers of Bone Resorption

A variety of biochemical tests reflecting bone matrix resorption provide good indices of disease activity including measurement of 24-hour or second morning void urinary hydroxyproline/creatinine as an index of bone collagen absorption. Other specific tests of bone collagen resorption include urinary and serum deoxypyridinoline, *N*-telopeptide, and *C*-telopeptide, and are not affected by dietary intake. Of all the markers, urinary excretion of pyridinium cross-link pyridinoline is a good measure of bone resorption than hydroxyproline, because pyridinoline molecules and the related *N*- and *C*-telopeptide of collagen are more specific components of bone matrix than is hydroxyproline. Markers of bone resorption change within a day or 1 week after the initiation of the therapy, whereas it may take 1–2 months before the alkaline phosphatase levels show a response to therapy.

Generally, the serum and urinary calcium and phosphorus levels remain normal during the course of disease unless the patient has a large amount of skeletal disease. Urinary calcium levels can be elevated in patients with active disease in multiple skeletal sites.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Paget's disease consists of the conditions that can cause elevated alkaline phosphatase or the radiological lesions that are similar to Paget's disease (Table 1). With a careful analysis of the history, physical examination, biochemical studies and judicious use of radiological studies, in the vast majority of the patients, the diagnosis is not difficult to make. Rarely a bone biopsy is needed to confirm the diagnosis.

Table 1 Differential diagnosis of Paget's disease of bone

Osteoarthritis
Osteoporosis
Metastatic malignancy with osteoblastic lesions (Prostate, breast, lymphoma)
Metastatic malignancy with osteolytic lesions (Multiple myeloma, breast, lung)
Primary malignancy of bone
Ricketts/osteomalacia
Congenital syphilis
Other osteoblastic skeletal lesions
Other osteolytic lesions

Source: Lyles K., PIER, *Amer. College of Physicians,* 2002.

DIAGNOSTIC RECOMMENDATIONS

The minimum evaluation of a patient with Paget's disease should include X rays of the affected bones and at least one parameter of bone metabolic activity. In patients with lytic lesions in the weight-bearing bones, serial radiography should be performed to document healing. In most patients, changes in the total alkaline phosphatase activity are adequate to determine changes in the overall disease activity, but the total serum alkaline phosphatase level in any patient is a reflection of both the total bone surface affected by Paget's disease and the total activity of the disease at those sites. Consequently, serum alkaline phosphatase can be normal in patients with a small focus of symptomatic Paget's disease. A bone scan is valuable in defining the full extent of the diseases and identify still asymptomatic lesions located in "at risk" areas.

TREATMENT OF PAGET'S DISEASE

All patients with Paget's disease do not require treatment, as the disease may be localized and may not cause any symptoms. Thus, it is important to do a careful assessment of symptoms and physical and radiological findings before a decision is made to treat the patient. None of the treatments currently available cure the disease. The specific goals of the treatment are to alleviate pain, prevent complications and stop the resorptive process, and restore normal bone remodeling. Treatment reduces the extension of lytic fronts and progression of deformity and restores the normal pattern of bone deposition (Meunier and Vignot, 1995). In general, treatment is initiated in patients with metabolically active Paget's disease, causing persistent pain, fractures, and headaches. Involvements of weight-bearing long bones and presence of disease in proximity to major weight-bearing joints, as well as involvement of the axial skeleton are also some of the indications to initiate therapy. Treatment is also indicated in patients who are planning to undergo elective surgery on a pagetic site such as hip replacement, in an attempt to reduce the hypervascularity of the pagetic lesion and hence the intraoperative blood loss. Treatment is also offered in patients who have high output cardiac failure, hypercalcemia due to immobility and severe hypercalciuria, with or without renal stones. Treatment with alendronate and risedronate is associated with the reduction of elevated indices of bone turnover from active Paget's disease to the normal range in the majority of patients (Harinck *et al.*, 1987; Cantrill *et al.*, 1986; Reid *et al.*, 1996; Sins *et al.*, 1996).

Nonpharmacological Measures

Patients with bowing deformity of a limb, gait alterations, chronic back pain, or difficulties from spinal stenosis may be helped by walking aids such as canes, shoe lifts, or other orthotics devices. An external fixation device (Ilizarov) has been useful in patients with Paget's disease involving the tibia, which allows an osteotomy to be performed, and then a gradual change in external pressure is used to straighten the bowed tibia. It can also be used to heal a nonunion fracture seen in Paget's disease. Physical therapy may well be indicated to improve muscle strength and preserve function.

Pharmacological Measures

Treatment of Paget's disease has undergone significant improvement in the last three decades as more potent therapeutic agents continue to be available. Because the primary defect appears to be related to resorptive process, the treatment focuses on decreasing osteoclast-mediated bone resorption.

BISPHOSPHONATES

Bisphosphonates are analogs of inorganic pyrophosphates and are currently considered the drugs of choice for the treatment of Paget's disease. The main action of bisphosphonates is to induce marked and prolonged inhibition of bone resorption by decreasing osteoclastic activity (Felisch *et al.*, 1969; Zimolo *et al.*, 1995). Bisphosphonates are made of a phosphorus–carbon–phosphorus chain in which the hydrogen atoms can be replaced by various groups. They can be nitrogen containing such as pamidronate, alendronate, and risedronate or non-nitrogen containing such as etidronate, clodronate, and tiludronate. Currently, only four of them are registered in the United States for the treatment of Paget's disease; these include pamidronate, alendronate, tiludronate, and risedronate. Bisphosphonates bind to the hydroxyapatite crystal within the bone and decrease bone resorption by disrupting osteoclast recruitment and cellular activity. In addition, they also decrease the number of osteoclasts by perturbing cellular metabolism and inducing their apoptosis. These effects may last for several months in contrast to calcitonin which has short-lived effects (Felisch, 1993). The potency depends upon the structure of the attached side chain. In the order of increasing potency, these include etidronate, tiludronate, pamidronate, alendronate, and risedronate. Bisphosphonates, in general, are poorly absorbed from the gastrointestinal tract, and have to be taken in an empty stomach, and are not metabolized *in vivo*; approximately half of the orally administered dose is cleared by the kidney, and they are rapidly taken up by the bones. Patients should concurrently receive 1000 mg of oral calcium and 800 units of Vitamin D supplement in order to reduce the chances of hypocalcemia and secondary hyperparathyroidism, which can occur with bisphosphonate therapy. Approximately 20% of patients treated with bisphosphonates may experience exacerbation of pain in their pagetic lesions that can be well managed with acetaminophen, but sometimes short-term use of narcotic-based analgesics may be needed.

Etidronate was the first bisphosphonate to be used for the treatment of Paget's disease. It can be administered in doses of $5\,mg\,kg^{-1}$ (average dose of 200–400 mg) daily, and is usually given for a period of 6 months. Treatment with etidronate shows moderate improvement in disease activity and lowers the alkaline phosphatase by 40–70% (Altman *et al.*, 1973). Higher doses are associated with gastrointestinal upset and focal osteomalacia. Approximately 25% of patients treated with etidronate develop resistance to etidronate with repeated courses (Siris *et al.*, 1981). Etidronate is contraindicated in presence of renal failure, preexistent osteomalacia, or known lytic lesions

Tiludronate is administered by the oral route as 200 mg twice daily for 3 months and is slightly more potent than etidronate. It has to be taken 2 hours before or after eating food with 6–8 oz of water. It is fairly well tolerated in the usual dose. It may also improve pagetic bone pain. Unlike etidronate, tiludronate does pose problems with mineralization deficits at the therapeutic doses. Approximately a third of the patients do achieve normal indices with the first course of etidronate or tiludronate, and the majority will have a 50% decrease in serum alkaline phosphatase (Canfield *et al.*, 1977; MdChmg *et al.*, 1995; Roux *et al.*, 1995). Patients who have gastrointestinal side effects with newer bisphosphonates, etidronate and possibly tiludronate may be an option to consider.

Pamidronate is administered by the intravenous route only and is more potent than etidronate. The dosing and the number of infusions depend upon the individual patient. Mild diseases can be successfully treated with one or two 60-mg infusions; however, more severe diseases may require several infusions of 60–90 mg given on a weekly or twice weekly basis. Once the required numbers of infusions are provided, the serum alkaline phosphatase should be measured in 2–3 months. Treatment results in the reduction of plasma alkaline phosphatase activity by 50–80%. If values after the treatment stabilize at a near normal level, retreatment is appropriate once the nadir level rises by 25%. The biochemical response may last 12–18 months posttreatment. One-third of the patients may experience mild flu-like episodes after the first dose, consisting of fever, myalgias, headache, and malaise. Uveitis, episcleritis, and ototoxicity have also been reported.

Alendronate administered orally as 40 mg is given daily for 6 months. Administration of alendronate can result in the reduction of the biochemical markers of turnover into the normal range in more than 50% of patients (Reid *et al.*, 1996; Sins *et al.*, 1996). The biochemical markers may remain stable for up to 6–18 months or longer before retreatment is considered. Gastrointestinal disturbances can occur in up to 17% of the patients and may result in discontinuation of the medication.

Risedronate has also been approved for the treatment of Paget's disease in the United States as a 30-mg tablet administered orally, once daily for 2 months. In an open label, multicenter study at the aforementioned dose, risedronate showed a 60–70% reduction in alkaline phosphatase levels (Sins *et al.*, 1998; Miller *et al.*, 1999). Another randomized double-blind controlled trial with etidronate showed that 73% of the patients had normalization of alkaline phosphatase, whereas only one out of seven in the etidronate group did normalize their alkaline phosphatase activity. The gastrointestinal side effects with risedronate appear to be less compared to alendronate and this may be better tolerated.

Both alendronate and risedronate are taken as a single daily dose with a 40-mg dose of alendronate or a 30-mg tablet of risedronate on rising after an overnight fast, with 6–8 oz of plain water and nothing by mouth (except more water) for the next 30 minutes. The patient may not lie down to avoid esophagitis, which is seen more in patients on alendronate than on risedronate.

Secondary resistance to bisphosphonates has been reported (Trdmbetti *et al.*, 1999). The exact biochemical mechanism of bisphosphonate resistance is unknown. It has been proposed that in patients treated with bisphosphonate therapy a certain group of osteoclasts gradually become resistant to apoptotic effect of the drug. Continued therapy with bisphosphonate may induce a series of enzymes that confer resistance to a subset of osteoclasts or their precursor cells. However, more studies are needed to provide further insights into osteoclasts biology and the action of bisphosphonates to better understand the true mechanism of resistance. It has also been shown that patients who become resistant to one type of bisphosphonate may respond well to another bisphosphonate (Trdmbetti *et al.*, 1999; Gutteridge *et al.*, 1999).

OTHER BISPHOSPHONATES

Several other newer bisphosphonates have been used in the treatment of Paget's disease and are currently under development and trials. These include neridronate, olpadronate, ibandronate, and zoledronate. The preliminary studies with zoledronic acid appear to have encouraging results and this could become a potential therapy for the treatment for Paget's disease; however, it is currently not approved by the US Food and drug administration (FDA) for the treatment of Paget's disease.

Calcitonin

Calcitonin is a 32-amino acid hormone secreted by the C-cells of the thyroid gland. It was the mainstay of treatment for Paget's disease in the 1970s and 1980s and now its use has been largely replaced by more potent bisphosphonates. Salmon calcitonin is available for use daily at doses of 100 units by subcutaneous route, which after 1 to 2 months can be changed to 3 times a week. Nasal formulation of calcitonin is available, but its use in Paget's disease is not approved in the United States, as only 40% of the drug is bioavailable after nasal administration. Calcitonin does inhibit osteoclast activity and rapidly decreases bone resorption. It reduces elevated indices of bone turnover by 50%, decreases symptoms of bone pain (by centrally mediated analgesic effects), reduces warmth over affected bone areas, and also promotes healing of lytic lesions. Today, its use probably is limited to those patients who are not able to tolerate bisphosphonates. The major drawbacks are its weaker activity, high cost and shorter duration of action, adverse side effect profile, and resistance that develops in approximately 20% of patients (Singer *et al.*, 1972). Patients also develop neutralizing antibodies, but it is not known if these play a role in its resistance. Downregulation of calcitonin receptors may lead to secondary hyperparathyroidism. Side effects include nausea, vomiting, polyuria, hypercalciuria, and facial or palmer flushing that is seen in approximately 20–30%. This may require the drug to be started at a dose of 25 units, with a gradual increase in dose every few days to the full 100 units. The suppression of disease activity does not persist long after the withdrawal of calcitonin treatment, which is the limiting factor to the use of such a treatment. Secondary resistance to salmon calcitonin can occur necessitating a change to bisphosphonate therapy.

Plicamycin

Formerly called *mithramycin*, plicamycin is a cytotoxic agent that inhibits the synthesis of ribonucleic acid. It was used in the management of hypercalcemia of malignancy (for which it is FDA approved) and as an early experimental agent in Paget's disease. At doses of 10 to 25 $mg\,kg^{-1}$ body weight daily for 10 days or 15–25 $mg\,kg^{-1}$ weekly, it may decrease bone pain and induce remission that may last several months. It is rarely indicated at this time because of its associated dose-dependent toxicity to the liver, bone marrow, skin, and kidney and the availability of potent newer bisphosphonates, which are relatively much safer to use.

Gallium Nitrate

Gallium nitrate has been approved for the treatment of hypercalcemia of malignancy. It inhibits bone resorption by inhibiting the adenosine triphosphate (ATP)-dependent proton pump of the osteoclasts. It has been proven to be effective in the treatment of Paget's disease; however, side effects such as renal failure preclude its use, and hence it is not currently approved by the FDA in the United States.

MONITORING OF THERAPY AND FOLLOW-UP

The ultimate goal of treatment of Paget's disease is to relieve the symptoms and prevent associated complications. The

effect of treatment is usually evident in 3 to 6 months and if the patient has not responded by then, a second course of therapy should be offered. If the patient fails to respond to the second course of therapy, a different bisphosphonate should be tried. The frequency and extent of follow-up depends upon the severity of the disease. The disease activity can be efficiently monitored by the serial measurement of alkaline phosphatase levels every 3 to 6 months. In patients with monostotic form of Paget's disease, measurement of bone-specific alkaline phosphatase and sometimes urinary excretion of pyridinoline and related peptides may be necessary. Patients should also be monitored for bone pain, articular function, and any new neurological signs or symptoms every 3 to 6 months. Treatment regimen should be aimed at normalizing biochemical markers. The markers reach a nadir level several months after the completion of therapy and then the level needs to be followed every 6 months. Retreatment should be considered if the level of alkaline phosphatase rises by more than 20–30% above the nadir level. Routine radiographic follow-up of all the involved sites is not necessary; however, the involvement of the base of the skull and the weight-bearing bones requires imaging every 6 to 12 months.

ANALGESIC AGENTS

Patients with Paget's disease often experience bone pain related to the pagetic process. Pain can be successfully controlled with the use of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDS), or the newer cox-2 inhibitors in addition to anti-osteoclastic agents. Care should be taken to monitor for renal, gastrointestinal, and hepatic toxicity, as many of the patients are elderly. Judicious use of narcotic analgesics may also be needed if the pain is not well controlled with the above regimen and is not contraindicated.

SURGERY

Orthopedic interventions may be required in several situations in patients with Paget's disease (Singer *et al.*, 1972). Pathological fractures and bony deformities are well-known complications of Paget's disease. Surgery may provide significant relief of pain and can improve mobility. Total hip or knee arthroplasty may be indicated for patients with severe arthritic pain, refractory to medical therapy. Complete pathological fracture of long bones may require internal fixation for early mobilization. Control of Paget's disease activity in these patients is recommended to minimize the chance of loosening of the prosthesis. Corrective proximal tibial osteotomies are sometime needed to realign the knee and decrease mechanical pain, especially if medical therapy is unsuccessful in managing severe pain symptoms. Spinal stenosis, focal nerve compression (in the spine or cranium), and resultant radiculopathies caused by pagetic and nonpagetic changes in vertebrae, skull, or facet joints, may require orthopedic or neurosurgical interventions. Prolonged treatment with bisphosphonates or calcitonin sometimes reverses the signs of nerve compression and hence should be tried to improve the symptoms before surgery is undertaken (Walpine and Singer, 1979; Ravichandran, 1979). In any case of surgical intervention, pretreatment with bisphosphonate or calcitonin is needed for several months prior to elective surgery to reduce hypervascularity and to significantly reduce the risk of excessive operative blood loss. In emergent situations, patient can receive intravenous pamidronate or calcitonin.

KEY POINTS

- The disease is unusual before the age of 40 with increasing prevalence after the age of 50.
- Pathophysiology is that of increased osteoclastic activity coupled with increased bone formation.
- Many patients with this disorder have no symptoms.
- In the last 30 years, there has been development of effective therapies.

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Epidemiology of Osteoporosis

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INTRODUCTION

Osteoporosis is a condition of structural deterioration of skeletal tissue and low bone mass. Osteoporosis is associated with increased risk of fracture (Woolf and Pfleger, 2003; Klibanski *et al.*, 2001). Skeletal tissue may be readily divided into two types, cortical and trabecular. Cortical bone has a characteristic formation, layer wrapped around layer of bone. It occurs on the outermost portion of the skeleton and is only minimally reactive to metabolic stimuli. Trabecular bone, on the other hand, is the sponge-like inner portion of the bone. It is lined with osteoclasts (bone reabsorbing cells) and osteoblasts (bone forming cells) with pockets of marrow or fat distributed throughout. Trabecular bone is also much more metabolically active. Certain diseases, including Paget's and the osteomalacic phase of vitamin D Resistant Ricketts may result in the loss of the clear demarcation between these two types of bone, but it is otherwise generally maintained.

Skeletal mass peaks in the late second or early third decade of life and remains stable for 15–20 years after that. Peak bone mass has an obvious genetic component (Albagha and Ralston, 2003; Pocock *et al.*, 1987). Men have greater bone mass than women. Short individuals have less bone mass than tall individuals. Further, African or African-American individuals have greater mean bone mass than Caucasian individuals of the same gender and similar built (Melton, 2003). Finally certain genetic diseases, for example, cystic fibrosis (Conway *et al.*, 2000) or lactose intolerance (Kudlacek *et al.*, 2002) may prevent afflicted individuals from attaining their maximum (peak) bone mass.

Peak skeletal bone mass is also effected by behavior. Individuals who do not take or absorb adequate calcium or vitamin D intake, smoke or abuse alcohol as they are obtaining their peak bone mass will generally have lower peak skeletal mass, then might otherwise be expected.

In about the fifth decade of life, skeletal mass begins to decrease at a rate of about 4% per decade. Without intervention, this rate continues throughout the remaining life span. In women, this rate accelerates as menopause supervenes and then slowly returns to normal, so that women may lose as much as 5–15% of their previous bone mass in the 5 years surrounding menopause.

In the United States, 10 million Americans (8 million women and 2 million men) are estimated to have osteoporosis and an additional 34 million are estimated to have low bone mass (osteopenia) with an increased risk for developing osteoporosis. (US Department of Health and Human Services, 2004) One in two women over the age of 50 and one in four men of the age of 50 will have a fracture in their remaining life span because of differences in longevity in women, compared to men. Four out of five individuals with osteoporosis are women. Despite differences of bone mass related to gender and ethnicity, osteoporosis fractures occur in both genders and all ethnicities. Morbidity and mortality may be different in men versus women and Caucasians versus African-Americans. Thus, Caucasian women have the lowest mortality after hip fracture, with African-American women and Caucasian men having about twice and African-American men about three times the risk of death after hip fracture than men in the United States and who are over 50.

There is general widespread agreement about the cut points of bone density measurement for osteoporosis and osteopenia in Caucasian women. Osteopenia in Caucasian women is a bone mass between one and two and a half standard deviation below mean bone mass of young women. Osteoporosis in Caucasian women is a bone mass more than the two and a half standard deviations below mean bone mass of young women. This formal agreement of cut points does not exist at this time for women of other ethnicities or men of any ethnicity. Most reports have generally extended the same cut points in Caucasian women to other ethnicities and/or in men; comparing bone mass in older individuals to a mean young bone mass (Table 1). Using this methodology, 20% of Caucasian women, 20% of Asian women, 10% of Hispanic women and 5% of African-American women are estimated to have osteoporosis in the United States. Over the age of 50, 52% of Caucasian and Asian women, and 49% of Hispanic and 35% African-American women are estimated

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Table 1 Risk for osteoporosis or osteopenia by gender and ethnicity over the age of 50

	Osteoporosis (%)	Osteopenia (%)
Women		
Caucasian/Asian	20	52
African-American	05	35
Hispanic	10	49
Men		
Caucasian/Asian	07	35
African-American	04	19
Hispanic	03	23

to have osteopenia with its concomitant increased risk for developing osteoporosis. It must be noted that the definition of osteoporosis includes a deterioration of skeletal integrity, which is generally poorly quantified. Attempts to quantify structural deterioration in trabecular bone are ongoing. These studies demonstrate loss of "struts" of trabecular bone but do not (cannot) quantify deterioration of skeletal integrity. Thus, the best (only) measure of osteoporosis at this time is bone mass (Klibanski *et al.*, 2001).

In the United States, in men over the age of 50, 7% of Caucasian men, 7% of Asian men, 3% of Hispanic men and 4% of African-American men are estimated to have osteoporosis. For osteopenia, the estimate for men over the age of 50 are 35% of Caucasian men, 35% of Asian men, 23% of Hispanic men, and 19% of African-American men.

The presence of certain risk factors can dramatically increase the risk for osteoporosis. These include medications like glucocorticoids and antiseizure medications (Lukert and Raisz, 1990), thin athletic build, early or surgical menopause in women without estrogen replacement, secondary amenorrhea (related to anorexia nervosa, excessive exercise, but not pregnancy), low testosterone in men, smoking, alcohol abuse or heavy use, low calcium intake and/or inadequate vitamin D intake.

The primary risk associated with osteoporosis is fracture. Essentially the incidence of all fractures increases with age (Table 2). Since trabecular bone is more metabolically active then cortical bone, the incidence of fractures of bone thought to be mostly trabecular (distal radius, vertebrae) increase earlier than those bones throughout cortical (femur). Fractures of either distal radius or vertebra are not easily studied, since some Colles fractures are seen in the office and a major portion of (perhaps two-thirds) of vertebral fracture are silent. On the other hand, hip fractures generally require hospitalization and are much easier to track. It is estimated that osteoporosis is responsible for about 1.5 million fractures each year. Of these approximately 300 000 are femoral fractures costing about 18 billion dollars in 2002 in direct expense for hospitals and nursing homes. The indirect cost to the families of the patients in the time lot to care for individuals transitioning back to independent living or to those unable to completely return to previous function is not known but estimated to be as much as twice the figure for direct cost.

Generally, after a hip fracture, most individuals perceive that they return to their previous ambulatory status in one year. Some, however, do not. These are reported to be those with marginal ambulatory status or dementia prior to fracture. Within the first year after fracture, however, many require ambulatory assistance. Thus, 6 months after fracture, 85% may require ambulatory assistance (walker, cane, or wheelchair). About one-quarter of those who were ambulatory prior to hip fracture require long-term placement no matter what their ambulatory status.

Table 2 Risk for future fragility fractures in individuals over the age of 50

	Men	Women
Overall risk of fracture	1 in 4	1 in 2
Risk of femur fracture	1 in 6	1 in 3
Risk of mortality	1 in 11	1 in 11
Placement	1 in 30	1 in 10

Other fractures have significant sequelae also. In particular, vertebral fractures often have significant sequelae. Kyphoscoliosis accounts for most of these. Permanent deformities related to collapsed vertebra (e) are associated with arthritic pain. Loss of vertebral height can compromise lung function, altering ventilation perfusion ratios throughout the lung fields, cause localized areas of emphysema and change pulmonary clearance of pathogens. Loss of vertebral height in the abdomen causes abdominal protrusion and discomfort. It has been associated with constipation. Generally compression fractures are associated with loss of body image, self-esteem, and more frequent pain (Ettinger *et al.*, 1988). Fractures of the distal forearm cause long-term osteoarthritis and deformities with some loss of function (Warwick *et al.*, 1993).

Present guidelines for assessing risk of osteoporosis using a direct measure of bone mass have been published by the National Osteoporosis Foundation and others. These recommendations include a bone mass measurement in all women of the age of 65. Secondly, a bone mass measurement is recommended for all postmenopausal women with a risk factor for osteoporosis in addition to being Caucasian or Asian (Table 3). These include their aesthenic habitus, primary relative with osteoporotic fracture, smoking, excessive alcohol use, early or surgical menopause and chronic use of medications (glucocoticoids or antiseizure) associated with osteoporosis. A series of other lifestyle differences also effects bone mass, but the epidemiologic effect is probably small. Vegetarians have a small increase in bone mass compared to similar individuals who eat meat. Soda (carbonated beverages) may decrease bone mass slightly (Wyshak *et al.*, 1989). Caffeine intake may have an adverse effect on bone mass (Lloyd *et al.*, 1997) and vitamin B12 levels are associated with low bone mass (Tucker *et al.*, 2005).

MEASUREMENT OF BONE MINERAL DENSITY

A series of machines provide localized measurement of bone mineral density measures, which may be used to estimate

Table 3 Risk factors for osteoporosis

Major		Moderate		Small	
Gender	Female	Habitus	Slender	Vegetarian	Lower
Ethnicity	Caucasian	Vitamin D/Calcium	Low	Caffeine intake	Higher
Age	Older	Smoke		Soda	Higher
		Heavy or abuse of alcohol			
		Medication			
		Glucocorticoid	Higher		
		Antiseizure	Higher		
		Thiazide	Lower		
		Premature or early menopause			

hip or spine bone density. The extrapolation is not exact, however, and these machines are most useful in determining who does not need further follow-up. Screening machines are much more widely available. These technologies include peripheral dual energy absorptiometry (pDXA) which measures distal forearms, calcaneus or metacarpals, single energy X-ray absorptionmetry (SXA) which measures distal forearm, calcaneus, quantitative ultrasound (QUS) which uses ultrasound to measure vibration at the calcaneus, tibia, and patella, peripheral quantitative tomography (pQCT) which measures the distal forearm, radiologic absorptiometry which compares metacarpal bone thickness to a standard; and single photon densitometry (SPA) which is not in general use and measures distal forearm. Individuals who screen positively and are to be treated or individuals with osteoporotic fractures who are to be treated should have basal quantitative computerized tomography (QCT) or DXA measurements of spine and/or hip prior to treatment. Individuals who screen positively should also be screened for primary hyperparathyroidism, hyperthyroidism, and tumors including multiple myeloma since therapies for any of these conditions may be significantly different from therapy for primary osteoporosis. Endogenous glucorticoid excess also causes osteoporosis and appropriate individuals should be screened for this. Secondary causes may be easy or difficult to deal with. Poor calcium intake is relatively easy to deal with, but glucorticoid therapy or antiseizure therapy, for example, are generally more difficult to treat. Definitive measurements of the hip or spine bone density may be performed by DXA (dual energy X-ray absorptiometry) which is generally performed at a center. It has relatively low radiation exposure and is widely accepted. Secondly, QCT is also generally performed at a center, is usually more expensive than DXA, and has more radiation exposure. It is widely accepted but much less frequently available than DXA. Thirdly, dual photon absorptiometry (DPA) has little radiation exposure. It is a precursor of DXA and is not generally available.

MANAGEMENT STRATEGIES

The cornerstone of treatment for osteoporosis is adequate calcium and vitamin D intake. Most studies of calcium intake indicate improvement in bone mass and/or decrease in fractures (Dawson-Hughes *et al.*, 1997). This is particularly true in older institutionalized women, but has not always been as easy to demonstrate in the younger, free-living senior. In the study of older institutionalized women 800 IU of vitamin D and 1200 mg of calcium significantly reduced fractures (Chapuy *et al.*, 1992). In the United States, the inclusion of vitamin A (10 000 IU/tablet) makes the use of the multiple vitamins problematic for vitamin D therapy. This dose of vitamin A has been associated with increased risk of fracture, presumably related to vitamin A toxicity (Michaelsson *et al.*, 2003).

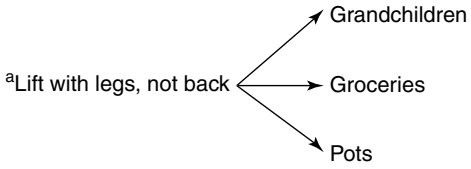
A number of therapies in addition to vitamin D and calcium supplementation have been demonstrated to provide additional benefit. Bisphosphonates decrease bone reabsorption without apparently decreasing bone formation (except etidronate) and further decrease incidence of compression fractures, hip fractures, and all fractures (Black *et al.*, 1998; Harris *et al.*, 1999). These medications include alendronate and risidronate. Others are likely to be available shortly. Their major drawback is poor absorbability. They must be taken orally on an empty stomach. Because of gastrointestinal side effects, the patients must remain upright after taking the medication. Even in the best circumstances, about one-quarter of the patients still have gastrointestinal side effects which require withdrawal of the medication. Other bisphosphonates may be given intravenously to minimize this side effect. Biophosphonates improve bone density and reduce fracture incidence, but appear to require about 6 months of therapy, before onset of effect. At this time, alendronate is approved for primary osteoporosis in men and women. Alendronate and risidronate are approved for steroid-induced osteopenia in men and women.

Calcitonin has been used to improve bone density and decrease compression fracture incidence (Body, 2002). It is administered via a nasal inhaler and is approved for primary osteoporosis.

A parathyroid hormone derivative (amino acid residue 1–34) is also available in an injectable form for treatment of osteoporosis.

Selective estrogen receptor modulators (e.g. raloxifen) are demonstrated to decrease fracture risk (Delmas *et al.*, 1997). Estrogen has long been used to treat osteoporosis in postmenopausal women. The recent results from the Women's Health Initiative have cast the future of this therapy into grave doubt. The use of testosterone in older

Table 4 Control risk of trauma



[a]Wear Safe Shoes.
Use lights and hand rails on stairs; remove low furniture and loose rugs.

(hypogonadal) men has been demonstrated to increase bone density, but not as yet to decrease fracture incidence. It has similar effects in women.

Lastly, there are a series of nonpharmacologic recommendations for all patients (Table 4). First, adequate weight-bearing exercise improves bone mass as long as the exercise is maintained. Secondly, falls or other fractures frequently are associated with fractures. Patients should be advised to review their surroundings to minimize the risk for falls. Thus, they should remove loose throw rugs, low furniture, and wires. They should ensure adequate lighting, particularly at night, and get up slowly from bed. Use of rails or grab bars on stairs and bathrooms will decrease the risk of falling. Restricting pet access from the bedroom decreases the risk of patients falling over them when they get up at night. Outdoor activity should be restricted as much as possible when ice or snow is present. Wearing high heels is a risk for falling. Lastly, patients should be taught to lift groceries, grandchildren, and so forth with their legs and not their backs. (i.e. bend knees and not back to pick up things.)

KEY POINTS

- Osteoporosis or low bone mass is one of the most common diseases of aging.
- Osteoporosis is defined as a bone mass more than two and a half standard deviations below that of young women.
- Males over the age of 50 have a 1 in 4 risk of fracture and females a 1 in 2 risk.

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Osteoporosis and its Consequences: a Major Threat to the Quality of Life in the Elderly

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INTRODUCTION

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk (World Health Organization, 2003). The diagnosis of the disease relies on the quantitative assessment of bone mineral mass/density, which represents so far one major determinant of bone strength and thereby of fracture risk. Thus, the diagnosis of osteoporosis is not based on the demonstration of fracture, which constitutes a complication, or the clinical expression of the disease, but on parameters capable of reliably predicting the risk of fracture. Indications to treatment are based on the evaluation of fracture risk, which also integrates other factors than osteoporosis diagnosis.

EPIDEMIOLOGY

Bone mass decreases and the risk of osteoporotic fracture increases as people age. Fractures of the vertebrae, proximal femur, distal forearm, and proximal humerus are considered to be typical of osteoporotic origin when they occur following a low-energy trauma (*see* **Chapter 110, Epidemiology of Osteoporosis**).

Hip fracture is the best studied osteoporotic fracture, because it cannot remain unrecognized, being nearly always treated in hospitals and thereby more precisely recorded. Most, if not all, hip fractures associated with osteoporosis result from a fall from standing height. The age-related increase in fracture risk depends on the progressive decrease in bone mass, and on the rising risk of falling. However, only a minority of falls in the elderly (less than 2%) result in hip fracture (Cummings and Melton, 2002; (*see* **Chapter 112, Gait, Balance, and Falls**)).

Vertebral fracture risk is less clearly studied than hip fracture. Only a fraction of all X-ray-determined vertebral fractures comes to clinical attention and diagnosis. Furthermore, even if the criteria used to define vertebral fracture may vary, deformities of vertebral body on conventional X-ray examination remain largely underrecognized, or not mentioned in the radiologist's report (Gehlbach *et al.*, 2000).

The incidence of osteoporotic fractures increases exponentially with age. After the age of 80, one-third and one-fourth of women and men respectively experience a fracture over a 5-year period (Center *et al.*, 1999) (Figure 1). At the age of 50, the lifetime risk of sustaining an osteoporotic fracture is close to 50% and more than 20% for women and men, respectively (Johnell and Kanis, 2005).

Osteoporosis and osteoporotic fractures have so far been a predominantly women's disease. Indeed, the women-to-men ratio for hip fracture risk is between 3 and 5. Several reasons can explain the lower age-adjusted incidence in men: a higher bone mass and larger bone size at the end of the growth period, the absence of accelerated bone loss occurring at the time of sex hormone deprivation, that is, after menopause, and a shorter life expectancy. In the framework of the progressive aging of the population, there is a particularly marked increase of life expectancy in men. Thus, fracture-related problems will become major public health issues for both genders in many countries.

The incidence of osteoporotic fractures varies from region to region, and may be related to population age distribution, genetic background, or lifestyle conditions. For instance, it appears that hip fracture incidence is higher in urban

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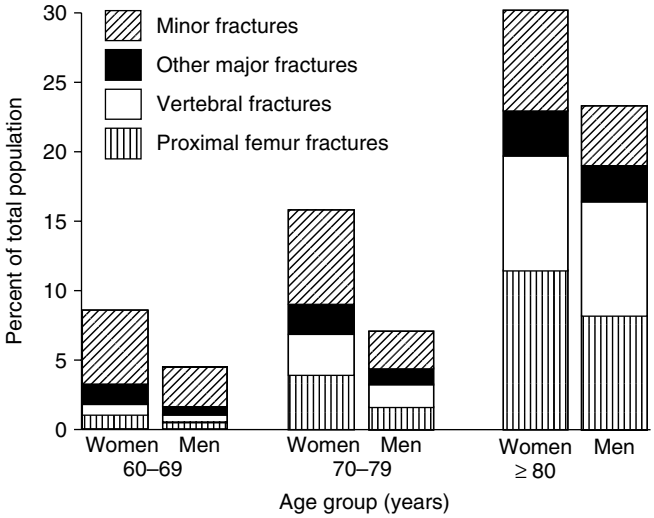

Figure 1 Fracture risk according to age and gender. In the Dubbo osteoporosis epidemiology study, fracture risk was recorded during a five-year cohort prospective follow-up. The results are presented per class of age and for each gender (Reprinted from Center *et al.*, 1999 with permission from Elsevier (The Lancet, 1999, Vol 353, pp 878–882))

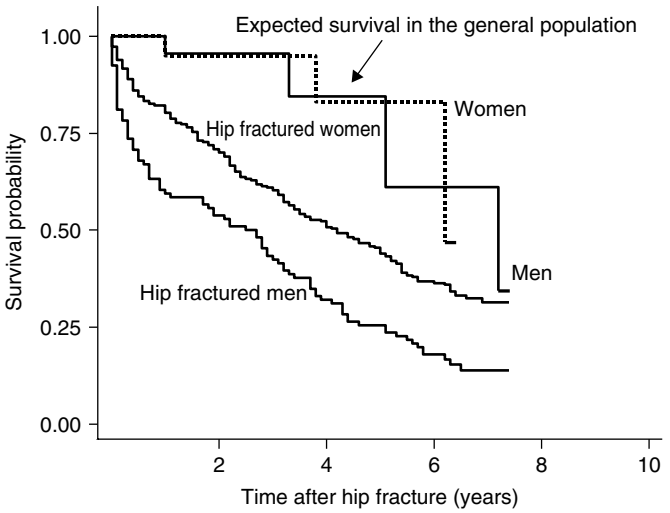

Figure 2 Survival estimate for age-matched men and women with hip fracture, and the expected survival in the general population (Reproduced from Trombetti A *et al.*, Survival and potential years of life lost after hip fracture in men and age-matched women, Osteoporosis International, 13, pp 731–737, Copyright 2002, with kind permission of Springer Science and Business Media)

Table 1 Age-standardized mortality ratio

Fracture	Women	Men
Proximal femur	2.2	3.2
Vertebral	1.7	2.4
Other major	1.9	2.2
Other minor	0.8	1.5

The mortality after major types of osteoporotic fracture was obtained in a 5-year prospective cohort study.
Source: Adapted from Center *et al.*, 1999.

than in rural areas in a given population (Chevalley *et al.*, 2002a). Up to 40% of hip fractures concern patients living in nursing homes (Schurch *et al.*, 1996). This is probably related to their advanced age and to a high prevalence of comorbidities requiring long-term care (*see* **Chapter 133, Frailty**). Moreover, this population is at high risk of repeated falls.

Among the complications of osteoporosis, increased mortality has been clearly demonstrated after hip or vertebral fracture (Table 1) (Center *et al.*, 1999). There is no increased mortality after forearm fracture. During the first year after hip fracture, mortality rate of the patients is around 25%, whereas, mortality rate in the nonfractured population of the same age remains around 5%. Hip fracture is thereby associated with a 20% increase in mortality (Schurch *et al.*, 1996). Mortality is nearly twice as high in men as in women, because of a higher prevalence of comorbidities (Trombetti *et al.*, 2002). Mortality is higher in the general male population, with a life expectancy approximately 7 years shorter. Given the reduction of life expectancy as a consequence of hip fracture, the proportion of the years of life lost is significantly higher in men than in women (70 vs. 59%) (Figure 2) (Trombetti *et al.*, 2002). Thus, among the complications of osteoporosis, hip fracture represents the most dramatic expression of the disease, in terms of morbidity, mortality, and medical costs. For vertebral fracture, reduced survival cannot be attributed directly to the fracture, but to underlying cardiovascular or pulmonary diseases that might become decompensated because of the fracture event. By the prolonged handicaps they cause, fractures are a major threat for the quality of life of the elderly and represent a significant reason of increased health costs. By one year after hip fracture, close to 20% of the patients still require rehabilitation in hospital. The burden is expected to worsen, since the number of hip fractures, for instance, is likely to quadruple worldwide during the first half of the twenty-first century. This will markedly increase the demand for health care, with treatment and consequences of osteoporotic fractures potentially compromising the economy and social equilibrium in many countries where the proportion of the elderly population is exploding.

DIAGNOSIS

Dual-energy Absorptiometry

There are many techniques available to assess bone mass, measure bone mineral content, or areal bone mineral density (BMD), which is the amount of bone mineral per projected bone scanned area. Dual X-ray absorptiometry (DXA) techniques are now validated for this measurement not only at the two skeletal sites particularly at risk of osteoporotic fracture, such as lumbar spine and proximal femur but also at the peripheral skeleton such as the forearm. For the diagnosis of

osteoporosis, hip and/or spine are mainly to be considered (Cummings *et al.*, 2002; Kanis, 2002). Areal BMD accounts for more than two-thirds of the variance of bone strength as determined *in vitro* on isolated skeletal pieces (Ammann *et al.*, 1996). There is an inverse relationship between incidence of osteoporotic fracture and DXA-provided BMD values. Long-term longitudinal studies have demonstrated that a decrease of 1 SD in lumbar spine BMD (in anteroposterior view) is associated with a more than 2.5-fold increase in fracture risk, comparable with a 10–17-year increase in years after menopause (Marshall *et al.*, 1996). Areal BMD integrates the size of the bone and its thickness, as well as its true volumetric density.

With the progressive development of degenerative joint diseases, spine BMD values could be largely overestimated, particularly in the elderly. Lumbar spine BMD measurements in lateral view could theoretically offer an advantage over conventional anteroposterior projection by avoiding osteophytes and posterior elements osteoarthritis. However, measurement of lateral spine is not routinely advocated because of the superposition of ribs and/or pelvis, reducing the number of vertebrae analyzable, and because of the lower accuracy and precision of this measurement. Indeed, lateral BMD, at least with present technology, does not appear to be of clinical advantage, since the error of the measurement is more than double the annual bone loss after menopause. Thus, it does not seem to be superior in diagnostic sensitivity, except possibly for corticosteroid-induced bone loss. Above the age of 65, osteoarthritis makes the measurement of lumbar spine BMD highly unreliable for diagnostic purposes.

Femoral neck BMD appears to be a better predictor of fracture of the proximal femur. This is based on long-term prospective longitudinal studies with fracture as an outcome. Since this measurement seems to be influenced by osteoarthritis to a much lower extent than the measurement of the spine, it would be the most suitable one for the diagnosis of osteoporosis in the elderly. However, proximal femur measurements are influenced by a variety of factors likely to impair accuracy and decrease the precision of the measurement. The size of the region of interest as well as its location along the hip axis and the degree of leg rotation can affect proximal femur BMD measurement. The potential for error in terms of both accuracy and precision of dual X-ray absorptiometry measurements of lumbar spine and proximal femur emphasizes the need for strictly controlled conditions of measurements.

A World Health Organization (WHO) panel has proposed the limit of -2.5 standard deviations below the mean values recorded in young healthy individuals of the same gender as the diagnostic criterion for osteoporosis (T-Score; T-Score = [measured BMD – young adult BMD]/young adult SD). The fracture rate in this reference population is very low. This approach is very similar to the measurement of blood pressure for the diagnosis of hypertension. This constitutes a diagnosis threshold, which should not be automatically translated into a therapeutic threshold. Indeed, other factors such as age, concomitant risk factors, bone turnover, or treatment cost/benefits, should be included into the treatment decision. The prevalence of subjects with bone mass values below this limit increases with age, reaching approximately 50% at the age of 80. Indeed, this prevalence corresponds to the lifetime risk of any skeletal fracture in a 50-year old woman (Johnell and Kanis, 2005) (Table 2). However, it should be remembered that there is no BMD threshold value for the risk of osteoporotic fracture, but the relationship is characterized by a continuous increasing gradient of risk with the decrease of BMD. Z-score compares a patient's value with the mean BMD of age- and gender-matched healthy subjects (Z-score = [measured BMD – age-matched mean BMD]/age-matched SD).

Table 2 Lifetime risk of fragility fracture in the Swedish population at the age of 50

	Women (%)	Men (%)
Proximal femur	23	11
Distal forearm	21	5
Vertebral (clinical)	15	8
Proximal humerus	13	5
Any site	46	22

Source: Adapted from Johnell and Kanis, 2005.

Other Skeletal Determinants of Osteoporotic Fractures

Macro- and Microarchitecture

In the proximal femur, the hip axis length has been shown to be a BMD-independent predictor of fracture risk. The bending strength of bones is influenced not only by the amount of bone within the bone, but also by its geometrical distribution. In cortical bone, mechanical strength is influenced by the histological structure, that is, primary versus osteonal bone, the orientation of the collagen fibers, the number and orientation of the cement lines, and the presence of microdamage or microcracks. In trabecular bone, mechanical strength is affected by the microstructural arrangement of trabeculae, which includes their orientation, their degree of connection, the mean trabecular thickness, and the trabecular interspace. Other important determinants of bone strength for both cortical and trabecular bone include the cross-linking between collagen fibers, the degree of mineralization of the matrix, as well as the crystal characteristics. Macro- and microarchitectural components of bone strength can explain, at least in part, clinical observations in which variations in bone mineral mass were not closely correlated to changes in fracture rate.

Bone Remodeling and Bone Fragility

The degree of bone remodeling, as assessed by the measurement of biochemical markers of bone resorption, has been shown to be a BMD-independent predictor of osteoporotic hip fractures (Delmas *et al.*, 2000). This observation suggests that increased bone resorption also increases skeletal fragility

Table 3 Biochemical markers of bone turnover

Bone formation markers (serum)	Bone resorption markers (serum and urine)
Osteocalcin	Hydroxyproline
Bone specific alkaline phosphatase	Deoxypyridinoline
Procollagen type 1 *N*-propeptide (P1NP)	Bone sialoprotein
Procollagen type 1 *C*-propeptide (P1CP)	Tartrate resistant acid phosphatase
	Peptide-bound pyridinoline cross-links (CTX, NTX)

To avoid the variations due to circadian rhythm and food intake, serum, and/or urine samples have to be collected in fasting state (Delmas *et al.*, 2000).

by an increase in bone loss, leading to a DXA detectable decrease in bone mineral mass and a deterioration of microarchitecture due to an increased trabecular plate perforation. The potential use of biochemical markers of bone turnover includes the prediction of bone loss (the higher the bone turnover, the greater the postmenopausal bone loss), the prediction of fracture risk, and the monitoring of therapy with anticatabolic agents (prediction of response and improvement of compliance) (Table 3).

Extraskeletal Determinants of Osteoporotic Fractures

A fracture represents a structural failure of the bone whereby the forces applied to the bone exceed its load-bearing capacity (Figure 3). Therefore, besides the size, geometry, and material property of the bone tissue, the direction and magnitude of the applied load will determine whether a bone will fracture. Almost all fractures, even those qualified as "low-trauma" fractures, occur as the result of some injury. Usually this is the result of a fall, or the application of a specific loading event in some cases of vertebral fractures, as bending forward to lift a heavy object with the arms extended.

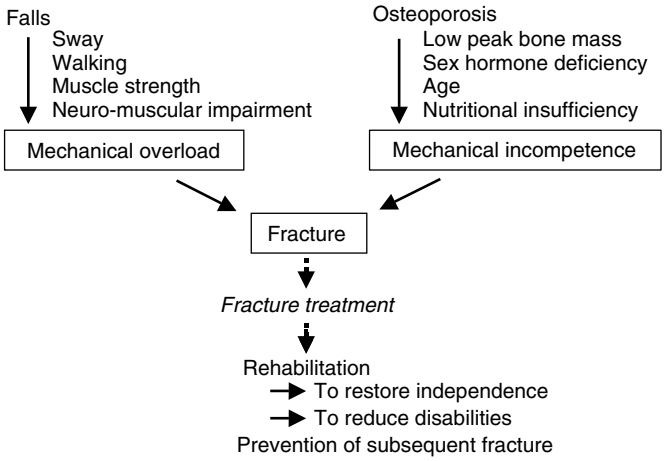

Figure 3 Pathogenesis and management of osteoporotic fracture. Fracture results from mechanical load and incompetence. Once fracture has occurred, the main goal is to prevent a subsequent one

Table 4 Risk factors associated with falls

1. Impaired mobility, disability
2. Impaired gait and balance
3. Neuromuscular or musculoskeletal disorders
4. Age
5. Impaired vision
6. Neurological, heart disorders
7. History of falls
8. Medication
9. Cognitive impairment

Source: Adapted from Myers *et al.*, 1996.

Risk Factors for Falls

The risk of falling increases with age (*see* **Chapter 112, Gait, Balance, and Falls**). Most falls in the elderly are due to intrinsic and extrinsic, or environmental factors (Table 4). Among the intrinsic factors, the risk of falling increases with the number of disabilities. Impairment of gait, mobility, and balance are the most consistently identified risk factors for falls and fall-related injuries. The ability to maintain postural control and avoid environmental obstacles depends on proprioceptive, vestibular, and visual input translated into appropriate motor responses. Thus, the risk of falling increases with reduced visual acuity or diminished sensory perception of the lower extremities. Chronic illnesses such as various neurological disorders, heart diseases, stroke, urinary incontinence, depression, and impaired cognitive functions increase the risk of falling. Medications such as hypnotics, antidepressants, or sedatives are associated with falls. Environmental factors include potential hazards that can be found in the home, such as slippery floors, unstable furniture, or insufficient lighting. The orientation of falls influences the consequences of falling. Indeed, the points of impact of a fall determine the type and extent of injury. When falling, the elderly tend to land on their hip. In contrast, middle-aged adults tend to fall forward with the main impact on their wrist. Several reflexes and postural responses are initiated during a fall, which can prevent or reduce the injury. The effectiveness of reflex actions depends on speed of execution and strength of the muscle initiating the protective movement. The impact of falls can be absorbed by surrounding soft tissue. The apparent protective effect of higher body weight may be due, at least in part, to the local shock-absorbing capacity of muscle and fat.

PATHOPHYSIOLOGY OF BONE LOSS

The onset of substantial bone loss occurs around the age of 50 and 65 years in women and men, respectively. In contrast with bone mineral accrual during adolescence, bone size varies little throughout life, other than the continuous and slight expansion of bone outer dimensions, which is mainly found in men, and which affects both the axial and the peripheral skeleton. This periosteal expansion is less than the increase in bone marrow space, which results from

a continuous endosteal resorption. Under these conditions, bone cortex becomes thinner. This phenomenon, together with an increment in cortical porosity and a destruction of trabeculae through thinning and perforation, account for age-dependent bone loss. Thus, this modeling process could be interpreted as a response to bone loss, in an attempt to compensate for a reduction in mechanical resistance (Seeman, 2002).

Hormonal Causes of Bone Mass Loss

Sex Hormone Deficiency

Female sex hormones appear to be mandatory not only to the maximal acquisition of bone mass in both males and females, but also to the maintenance of bone mass by controlling bone remodeling during the reproductive life in females and in aging men (Riggs *et al.*, 2002; Seeman, 2002). Other pathological conditions associated with premature estrogen deficiency, such as anorexia nervosa, secondary amenorrhea due to strenuous exercise, or the use of inhibitors of gonadotropin secretion, support the concept of a causal link between estrogen deficiency and accelerated bone loss. By increasing bone turnover and uncoupling bone formation from resorption, estrogen deficiency appears to be the main cause of osteoporosis observed in women after the fifth decade, and possibly also in men, and thus is directly implicated in the age-related increase in the incidence of fragility fractures. It is now clearly established that bone loss does not attenuate with age, but continues throughout the whole life, at least in the peripheral skeletal sites.

Increased bone turnover, with an imbalance between bone formation and resorption as a consequence of estrogen deficiency, involves the production and action of a variety of cytokines released in the bone marrow environment. There is evidence that Tumor Necrosis Factor-alpha (TNF-alpha), Interleukin-1, Interleukin-6, and Receptor Activator Nuclear Kappa-b Ligand (RANKL), cytokines that stimulate bone resorption *in vitro* and *in vivo*, may affect the initial step leading to bone loss induced by estrogen deficiency. A critical role for TNF-alpha in bone loss induced by estrogen deficiency has been demonstrated in a model of transgenic mice in which the activity of TNF-alpha is permanently prevented by the constitutive presence of high levels of circulating soluble TNF-alpha-receptor 1 (Ammann *et al.*, 1997). In this model, the decrease in bone mass and the increase in bone turnover observed after ovariectomy in control mice were not observed in transgenic mice, which appeared to be fully protected.

Other Endocrine Causes of Bone Loss

Apart from gonadal deficiency, which is an important cause of osteoporosis in both genders, a number of other endocrine diseases can also lead to bone loss. The effect of primary hyperparathyroidism on bone is to increase the activation frequency of bone remodeling. This increase in bone turnover is associated with a reduction in cancellous bone volume as observed by histomorphometric technique. Osteodensitometry indicates a decrease in BMD at both axial and appendicular sites. An excess of thyroid hormones also increases the rate of bone remodeling. Thus, bone loss can occur in hyperthyroidism and in patients under long-term thyroid replacement therapy at doses suppressing thyroid stimulating hormone (TSH). The major net effect of glucocorticoid excess is the reduction of bone formation. In addition, there is some evidence that the administration of glucocorticoids in pharmacological excess decreases the intestinal absorption of calcium and perhaps the tubular reabsorption of calcium (Pennisi *et al.*, 2006). These latter two effects would lead to a negative calcium balance and consecutive increased bone resorption.

Nutritional Causes of Bone Mass Loss

Calcium Intake, Vitamin D, and Osteoporosis

Calcium contributes to the preservation of the bony tissue during adulthood, particularly in the elderly. Without an appropriate supply of vitamin D, from cutaneous and/or exogenous source, the bioavailability and metabolism of calcium is disturbed (Heaney, 2000). This results in accelerated bone loss.

In the elderly, several alterations contribute toward a negative calcium balance (*see* **Chapter 108, Age-related Changes in Calcium Homeostasis and Bone Loss**). Indeed, with aging there is a decrease in the calcium intake because of reduction in dairy products consumption, in the intestinal absorption of calcium, in the absorptive capacity of the intestinal epithelium to adapt to a low-calcium intake, in the exposure to sunlight and the capacity of the skin to produce vitamin D, and in the renal reabsorption of calcium, as well as in the tubular calcium reabsorptive capacity to respond to the stimulatory effect of parathyroid hormone (PTH). Furthermore, the mild renal insufficiency regularly observed in the elderly can contribute to a state of chronic hyperparathyroidism that favors negative bone mineral balance and thereby osteoporosis. Increasing calcium intake is certainly an important strategy that appears to be relatively easier to implement as compared to other possible preventive measures.

Protein Malnutrition

Nutritional deficiencies play a significant role in osteoporosis in the elderly. Indeed, undernutrition is often observed in the elderly, and it appears to be more severe in patients with hip fracture than in the general aging population. A low protein intake could be particularly detrimental for both the acquisition of bone mass during childhood and adolescence, and for the conservation of bone integrity with aging (Rizzoli and Bonjour, 1999; Rizzoli *et al.*, 2001a). Protein undernutrition can favor the occurrence of hip fracture by increasing the propensity to fall as a result of

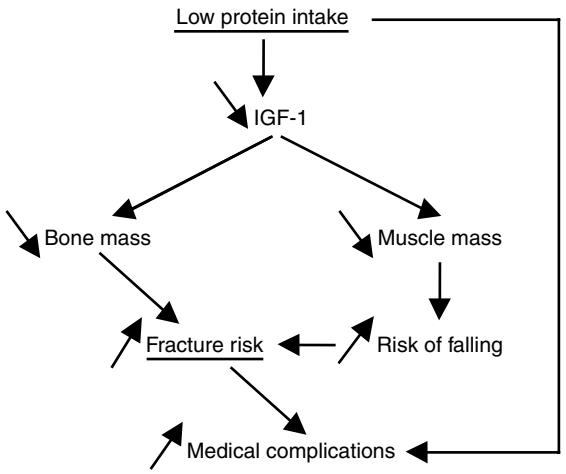

Figure 4 Protein undernutrition in the elderly. Possible role of IGF-I in bone mass, muscle mass, risk of fracture, and outcome after hip fracture

muscle weakness and impairment in movement coordination, by affecting protective mechanisms such as reaction time and muscle strength, thus reducing the energy required to fracture an osteoporotic proximal femur, and/or by decreasing bone mass (Rizzoli and Bonjour, 2004) (Figure 4). Furthermore, a reduction in the protective layer of soft tissue padding decreases the force required to fracture an osteoporotic hip.

Protein and Osteoporotic Fracture

Various studies have found a relationship between the level of protein intake and calcium phosphate or bone metabolism, and have come to the conclusion that either a deficient or an excessive protein supply could negatively affect the balance of calcium (Rizzoli and Bonjour, 2004). An indirect argument in favor of a potential deleterious effect of high protein intake on bone is that hip fracture appears to be more frequent in countries with high protein intake of animal origin. But, as expected, the countries with the highest incidence of hip fracture are those with the longest life expectancy. In a prospective study carried out on more than 40 000 women in Iowa, a higher protein intake was associated with a reduced risk of hip fracture. The association was particularly evident with protein of animal rather than vegetal origin (Munger *et al.*, 1999).

Protein and Bone Mass

Regarding the relation with bone mineral mass, there is a positive correlation with spontaneous protein intake in premenopausal women (Rizzoli *et al.*, 2001b). In a survey carried out in hospitalized elderly patients, low protein intake was associated with reduced femoral neck areal BMD and poor physical performances (Geinoz *et al.*, 1993). The group with high protein intakes and a greater BMD, particularly at the femoral neck level, had also a better improvement of bicipital and quadricipital muscle strength and performance, as indicated by the increased capacity to walk and climb stairs, after four weeks of hospitalization. In a longitudinal follow-up in the frame of the Framingham study, the rate of bone mineral loss was inversely correlated to dietary protein intake (Hannan *et al.*, 2000). Increasing protein intake has a favorable effect on BMD in the elderly receiving calcium and vitamin D supplements (Dawson-Hughes and Harris, 2002). Taken altogether, these results indicate that a sufficient protein intake is mandatory for bone health, particularly in the elderly. Thus, whereas a gradual decline in calorie intake with age can be considered as an adequate adjustment to the progressive reduction in energy expenditure, the parallel reduction in protein intake may be detrimental for maintaining the integrity and function of several organs or systems, including skeletal muscles and bone (Figure 4).

Relation with IGF-I

In association with the progressive age-dependent decrease in both protein intake and bone mass, several reports have documented a decrement in insulin-like growth factor-I (IGF-I) plasma levels. Experimental and clinical studies suggest that dietary proteins, by influencing both the production and action of growth factors, particularly the Growth Hormone (GH)–Insulin-like Growth Factor (IGF) system, could influence bone homeostasis. The hepatic production and plasma level of IGF-I are under the influence of dietary proteins. Protein restriction has been shown to reduce IGF-I plasma levels by inducing a resistance to the action of GH at the hepatic level. Decreased serum IGF-I has been found in states of undernutrition such as marasmus, anorexia nervosa, celiac disease, or HIV-infected patients. In addition, protein restriction could render the target organs less sensitive to IGF-I. When IGF-I is given to rats maintained under a low protein diet, at doses even higher than those normalizing its plasma levels, it failed to restore bone formation (Bourrin *et al.*, 2000). In addition, GH treatment was even associated with a decreased bone strength under conditions of a low protein diet (Ammann *et al.*, 2002).

Protein Replenishment and Osteoporosis

A state of undernutrition on admission, which is consistently documented in elderly patients with hip fracture, followed by an inadequate food intake during hospital stay can adversely influence their clinical outcome (Delmi *et al.*, 1990). Intervention studies using supplementary feeding by nasogastric tube or parenteral nutrition, or even a simple oral dietary preparation that normalizes protein intake, can improve the clinical outcome after a hip fracture. The latter way of correcting the deficient food intake has obvious practical and psychological advantages over nasogastric tube feeding or parenteral nutrition. An oral protein supplement, which brought the intake from low to a level still below Recommended Dietary Allowances (RDA) (i.e. $0.8\,g\,kg^{-1}$ body weight), avoiding thus the risk of an excess of dietary protein, improved the clinical course in the rehabilitation hospitals by significantly lowering the rate of complications,

Table 5 Protein supplements in elderly persons with hip fracture

	Changes from baseline (%)		
	Placebo	*Protein*	*p*
Prealbumin	$+56 \pm 9$	$+86 \pm 14$	0.07
IGF-I	$+34 \pm 7$	$+86 \pm 15$	0.01
IgM	$+40 \pm 6$	$+66 \pm 9$	0.02
Proximal femur BMD	-4.7 ± 0.8	-2.3 ± 0.7	0.03
Median length of stay in rehabilitation hospital (in days)	54	33	0.02

The results are taken from Schürch *et al.*, 1998.

such as bedsore, severe anemia, intercurrent lung, or renal infections. The duration of hospital stay of elderly patients with hip fracture is not only determined by their present medical condition, but also by domestic and social factors. The total length of stay in the orthopedic ward and rehabilitation hospitals was significantly shorter by 25% in the case of supplemented patients than in controls (Delmi *et al.*, 1990; Schurch *et al.*, 1998; Tkatch *et al.*, 1992). Normalization of protein intake, independent of energy, calcium, and vitamin D intake, was in fact responsible for this more favorable outcome (Tkatch *et al.*, 1992). Finally, this normalization of protein intake was found to increase IGF-I, and even IgM concentrations (Table 5) (Schurch *et al.*, 1998). Thus, the lower incidence of medical complications with the correction of protein intake insufficiency is also compatible with the hypothesis of IGF-I improving the immune status, as this growth factor can stimulate the proliferation of immunocompetent cells and modulate immunoglobulins secretion (Auernhammer and Strasburger, 1995).

Besides the production and action of the growth hormone–IGF-I system, protein undernutrition can be associated with alterations of cytokines secretion, such as interferon gamma, TNF-alpha, or transforming growth factor beta. TNF-alpha and Interleukin-6 generally increase with age. In a situation of cachexia, such as in chronic heart failure, an inverse correlation between BMD and TNF-alpha levels has been found, further implicating a possible role of uncontrolled cytokines production in bone loss. Increased TNF-alpha can be a crucial factor in the sex hormone deficiency-induced bone loss, but it also plays a role in the target organ resistance to insulin, and possibly to IGF-I. The modulation by nutritional intakes of cytokines production and action, and the strong implication of various cytokines in the regulation of bone remodeling suggest a possible role of certain cytokines in the nutrition-bone link.

Vitamin K and Osteoporosis

A low level of vitamin K_1 and K_2 has been reported in patients sustaining hip fracture (Booth *et al.*, 2003). Vitamin K is essential for the production of gamma-carboxylated glutamyl residues present in several coagulation factors and bone proteins, particularly osteocalcin. The degree of vitamin K deficiency in humans can be assessed by measuring the undercarboxylated fraction of osteocalcin. This fraction increases with age and therefore is negatively related to BMD in elderly women. Hence, undercarboxylated osteocalcin was found to be a predictor of hip fracture. Energy-protein undernutrition is usually associated with various vitamin deficiencies. To what extent vitamin K deficiency *per se* contributes to bone loss in undernourished patients sustaining hip fracture is still not known.

Other Nutrients

By interfering with both the production and action of PTH, magnesium could indirectly affect bone metabolism. However, its specific role in the maintenance of bone mass during adulthood has not been yet identified. Several trace elements are required for normal bone metabolism. Various animal and/or ecological human studies suggest that aluminum, zinc, manganese, copper, boron, silicon, and fluoride at doses lower than that used in the treatment of osteoporosis, and vitamins B_6, B_{12}, and C, could play a positive role in the normal metabolism of bone tissue. Selective intervention studies are still required to delineate their respective role in the maintenance of bone mass, particularly in the elderly.

Mechanical Causes of Bone Mass Loss

Immobilization is an important cause of bone loss (*see* **Chapter 142, Restraints and Immobility**). The effect of "disuse" on bone mass is far greater than that of adding "walking" to an already ambulatory subject. Enforced immobilization in healthy volunteers results in a decrease in bone mineral mass. Motor deficit due to neurological disorders such as hemiplegia or paraplegia is a cause of bone loss. Bone mineral mass decreases during space flights despite forceful physical exercise. This observation underlines the importance of weight bearing in the maintenance of bone mass. At the tissue level, immobilization results in a negative balance, the amount of bone resorbed being greater than that formed. At the cellular level, immobilization results in an increased osteoclastic resorption associated with a decrease in osteoblastic formation. The nature of the molecular signal(s) perceiving the reduced mechanical strain has not yet been clearly identified.

Toxic Causes of Bone Mass Loss

Excessive alcohol consumption appears to be a significant risk factor for osteoporosis particularly in men (Kanis *et al.*, 2005a). Reduced rates of bone formation have been associated with alcohol abuse. High intake of alcohol is often associated with marked dietary disturbance such as low protein intake, other changes in lifestyle, liver disease, and decrease in testosterone production. These alterations can contribute to the osteoporosis observed in heavy drinkers. Use of tobacco appears to be associated with an increased

risk of both axial and appendicular osteoporotic fractures in women and men (Kanis *et al.*, 2005b). This risk emerges with age. Smoking reduces the protective effects of obesity and of estrogen exposure. Reduced rate of bone formation and increased bone resorption might be responsible for bone loss, through a reduction in the production and acceleration in the degradation of estrogens.

PREVENTION AND TREATMENT

The ultimate goal of osteoporosis therapy is to prevent fractures, and thus pain, handicaps, and altered quality of life consecutive to fractures. The level of evidence and how convincing the results of clinical trials are, vary substantially among therapeutic strategies. To assess the quality of evidence provided by published clinical trials, evidence-based medicine offers a method to evaluate the strength of the evidence. Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence from clinical research in making decisions about the care of individuals (Guyatt, 1998). However, as in most domains of medicine, it appears that only a small percentage of the therapeutic decisions taken in the daily medical practice can be determined according to evidence-based medicine criteria. This is particularly true for the elderly, in whom trials are difficult to undertake, and the high prevalence of comorbidities impairs the interpretation of the results.

The strength of a study design is of major importance, because randomized controlled studies with homogeneous results are considered more valuable than randomized controlled studies with inconsistent results, and offer a higher level of evidence than observational studies. In the hierarchy in the level of evidence, the opinion of experts and/or the personal clinical experience are at the bottom. To attenuate the interaction with confounding variables, and the influence of subgroups selection susceptible to introducing significant bias, randomized trials should include an appropriate blinding of both the investigator and the subjects. This is the only way to avoid a preferential assignment of patients into a group, and an imbalance in the characteristics of the patients or of other factors influencing the outcome between the studied agent and the control groups.

Another important condition is that the outcome variable should be a predefined endpoint, since there is the risk in *post-hoc* analysis of trials with small sample size of detecting drug efficacy only by chance. Since the ultimate goal of osteoporosis treatment is the prevention of fracture, regulation authorities are considering fracture rate as the reliable endpoint. The type of fracture, as well as the diagnosis criteria should thus be clearly defined. Since a substantial number of vertebral fractures may not be accompanied by complaints, morphometric fractures (i.e. objectively documented on repeated X-ray examinations) may be considered as less clinically relevant than those with an overt clinical expression. Moreover, the definition of vertebral deformity can vary from one trial to the other. The conditions retained for fracture definition will thus influence the response to therapy and thus the outcome of clinical trials.

Regarding antifracture efficacy, an important criterion is that the occurrence of one event does not increase the probability of occurrence of another event. Thus, patients with fracture instead of fracture rates should be reported. In the former, a patient with fracture is censored once the event has occurred, whereas in the latter, the number of fractures *per sum* of observation times is given; thus, the same patient can be recorded several times if the individual experiences more than one event.

Attention should also be paid to the strength of the outcome. Indeed, this outcome could be of a direct and major importance for the patient (pain, disability and functional limitation in the case of fracture of long bones), or of some importance (for instance, vertebral fractures, since some could remain unrecognized), or of indirect importance, such as changes in BMD or in bone turnover. Finally, a clear trade-off between the benefits and adverse effects should be unequivocally specified. The role of costs/effectiveness analysis is also becoming an important factor to consider in relation with the limitations on health budget appearing in many countries.

Population Studied

Fracture rate exponentially increases from about the age of 60 onward. However, the incidence of fracture does not display the same kinetics at each skeletal site. For instance, the increase in the incidence of vertebral fracture mostly occurs during the sixth and seventh decades in women, whereas the mean age for hip fracture is around 82 years. Therefore, age, gender, the severity of osteoporosis, and the selective alteration of a specific skeletal site will influence the response to an antiosteoporotic therapy. A quite often misused concept is the so-called number needed to treat (NNT). This number represents the number of patients who should be treated to avoid the occurrence of one event. It corresponds to the inverse of the reduction of the absolute risk, that is, the event rate in the placebo group minus the event rate in the treated group. For the same reduction in the relative risk, this NNT is primarily determined by the event rate in the placebo group (Figure 5). Furthermore, with the same reduction in relative risk for a given agent, differences in the inclusion criteria, influencing thereby the fracture rate in the population studied, will be associated with different NNTs. This indicates that NNT cannot be used for comparing the efficacy of different drugs, unless fracture rates in the placebo groups are very similar. In the oldest old with a very high fracture rate, NNT may be much lower than in subjects in the 7th decade, as prevailing in many trials.

General Management

The general measures to apply are based on the following reasons (Table 6):

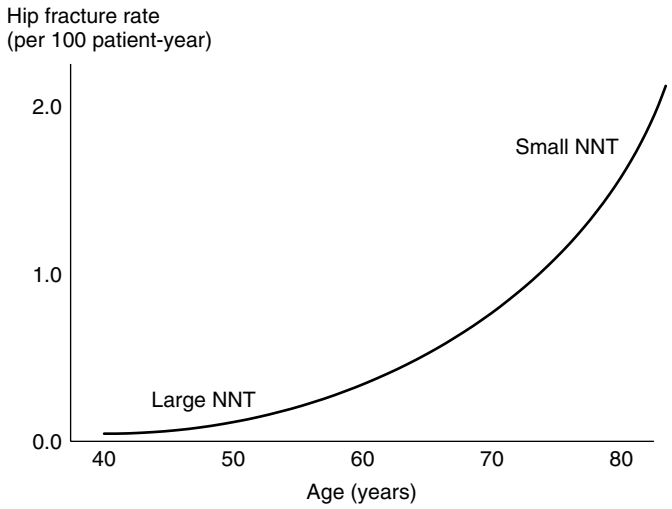

Figure 5 Number needed to treat to avoid one hip fracture in relation to age. NNT is calculated as the inverse of the absolute risk reduction observed for a given treatment. NNT is thus highly dependent on the fracture risk in the target population to be treated with a given treatment known to reduce the relative risk of fracture. The greater the fracture risk, the smaller the NNT

Table 6 General management

- Treatment of any disease causing bone loss
- Ensure dietary calcium intake of $1000\,mg\,day^{-1}$ or greater
- Ensure adequate dietary protein intake ($1\,g\,kg^{-1}$ body weight)
- Correct and prevent vitamin D insufficiency (800 IU/day)
- Promote weight-bearing physical exercise
- Reduce the risk of falling
- Reduce the consequences of falls (hip protectors)

There is a high prevalence of calcium, protein, and vitamin D insufficiency in the elderly (Heaney, 2000; Rizzoli *et al.*, 2001a). Calcium and vitamin D supplements decrease secondary hyperparathyroidism and, particularly in the elderly living in nursing homes, reduce the risk of proximal femur fracture (Chapuy *et al.*, 1992). Sufficient protein intakes are necessary not only for the homeostasis of the musculoskeletal system but also to decrease the complications occurring after an osteoporotic fracture (Rizzoli and Bonjour, 1999, 2004; Schurch *et al.*, 1998). Under these conditions, intakes of at least $1000\,mg\,day^{-1}$ of calcium, 800 IU of vitamin D, and of $1\,g\,kg^{-1}$ body weight of protein can be recommended for the general management of patients with osteoporosis. Regular physical exercise helps to maintain bone health, not only by stimulating bone formation and by retarding bone resorption, but also through a favorable influence on the muscle function (Kelley *et al.*, 2000; Wolff *et al.*, 1999). These measures, together with the correction of decreased visual acuity, the reduction in consumption of drugs that alter wakefulness and balance, and the improvement of the home environment (slippery floor, obstacles, insufficient lighting) are important steps aimed at preventing falls (Myers *et al.*, 1996; Tinetti, 2003; (*see* **Chapter 12, Physical Fitness and Exercise**, **Chapter 112, Gait, Balance, and Falls**)). However, these have not been verified in randomized controlled trials fulfilling the requirements of evidence-based medicine. Wearing hip protectors is able to significantly and specifically reduce hip fracture risk (Kannus *et al.*, 2000). This has been shown in randomized controlled trials and seems to be particularly efficient in the elderly living in nursing homes. This population is at very high risk, since close to 40% of hip fractures are occurring in this kind of setting (Schurch *et al.*, 1996).

Pharmacological Intervention

The definition of osteoporosis, according to the number of standard deviations in areal BMD as compared with values observed in young healthy individuals, is an operational definition that should be clearly distinguished from a therapeutic threshold. An improved understanding of the pathophysiology of osteoporosis has led to the development of treatments with effects on BMD, bone turnover, and/or fracture risk (Delmas, 2002; Hauselmann and Rizzoli, 2003). The agents can be classified as anticatabolic or anabolic (Riggs and Parfitt, 2005). In the first category, there are calcium, hormone replacement therapy (HRT), bisphosphonates, estrogen analogs, tibolone or calcitonin, whereas PTH belongs to the second category. The mode of action of vitamin D analogs, anabolic steroids, and recently reported strontium ranelate, is not clearly established. Particular attention should be paid to the influence of the disease on the quality of life and as to whether the treatment applied improves it (Nevitt *et al.*, 2000). It is quite likely that over the next few years the impact of any kind of treatment against osteoporosis on the quality of life will become a highly relevant issue.

Applying rigorous criteria according to the principles of evidence-based medicine, a certain level of evidence can be attributed to each of these agents, depending on whether their effect on fracture risk has been studied in several randomized controlled trials with consistent results, in at least one controlled trial, or in observational studies (Table 7). If one considers only randomized controlled double-blind trials, with vertebral fracture or hip fracture as outcome, it appears

Table 7 Evidence of antifracture efficacy from randomized controlled trials

Agent	Evidence for reduction of vertebral fracture[a]	Evidence for reduction of hip fracture[a]
Alendronate	++	+
Anabolic steroids	o	o
Etidronate	+	o
Intranasal calcitonin	+	o
PTH	++	o
Raloxifene	++	o
Risedronate	++	+
Strontium ranelate	++	+
Tibolone	o	o
Vitamin D analogs	±	o

[a]In addition to calcium and vitamin D. ++, strong evidence (several trials with homogeneous results); +, some evidence (one or two trials); o, insufficient evidence; ±, variable effects

that the bisphosphonates alendronate and risedronate administered to osteoporotic women during the sixth and seventh decades, are able to decrease the incidence of both vertebral and hip fractures (Delmas, 2002; Hauselmann and Rizzoli, 2003). Raloxifene, clodronate, ibandronate, or PTH favorably influence vertebral fracture risk. Calcium and vitamin D supplements can decrease the incidence of hip fracture in institutionalized elderly women. The new generation bisphosphonates ibandronate have demonstrated unequivocal effectiveness for reducing the risk of fractures, including those of the hip. However, a number of potential concerns regarding bone health during long-term bisphosphonates administration have been raised. In particular, some have speculated that accumulation of bisphosphonates in bone might lead to excessive suppression of bone turnover, impairing the repair of defective bone tissue and thereby increasing fracture risk. Continuous administration of earlier bisphosphonates such as etidronate has been associated with defective bone mineralization and increased fracture risk in animal studies, but this has not been reported for nitrogen-containing bisphosphonates that are largely used nowadays. Recent studies on dogs have reported that high doses of alendronate or risedronate may affect a potential indicator of bone quality (microcracks), but the significance of this finding remains uncertain, since no additional risk was associated with this observation. Furthermore, bone strength did not appear to be dependent on microcracks density (Mashiba *et al.*, 2001).

Bisphosphonates Mechanism of Action Predicts Similar Short- and Long-term Effects

On the basis of the mechanism of action, there are essentially no significant differences between short- and long-term effects of nitrogen-containing bisphosphonates administered continuously, for example, daily or weekly (Rodan *et al.*, 2004; Rizzoli, 2006). This is because bisphosphonates must be present on the bone surface in order to produce their pharmacological action. At the minimal dose that produces maximal effects, they should be repeatedly administered to achieve fully effective pharmacological levels. The bisphosphonates moiety, two phosphate groups linked by a geminal carbon, is responsible for bisphosphonates localization on the bone surface through binding to the bone mineral calcium phosphate salt, hydroxyapatite. This moiety is also responsible for the low intestinal absorption of these compounds and the lack of penetration into most of the cells in the body.

Osteoclasts attach to exposed bone mineral surfaces, initiate bone resorption, and take-up the bisphosphonate along with the other resorption products, calcium and digested matrix. Inside the osteoclasts, nitrogen-containing bisphosphonates inhibit farnesyl diphosphate synthase, an enzyme in the mevalonate to cholesterol pathway. As a consequence, there is a reduction in the level of the lipids farnesyl diphosphate and geranylgeranyl diphosphate required for prenylation of GTPases, which are crucial enzymes for cytoskeletal organization and vesicular traffic. This causes disruption of the osteoclast ruffled border and osteoclast inactivation, thus inhibiting resorption. If exposed for a sufficient duration, osteoclasts can undergo apoptosis as a result of the inhibition of prenylation (Weinstein *et al.*, 2002). The degree of bone resorption inhibition is proportional to the repeated dose, but not to the cumulative dose (Reitsma *et al.*, 1980). This is why the level of bone resorption drops into the premenopausal range within a few weeks after initiation of treatment and remains constant for as long as treatment continues. There is no detectable difference between the short term (3–6 months) and long-term (up to 10 years) pharmacological effect on bone resorption during continuous administration of the bisphosphonate alendronate (Bone *et al.*, 2004).

The administration of alendronate at a dose 7 times higher than the daily dose of 10 mg with antifracture efficacy, but once a week, has the same effects on BMD and bone turnover, and seems to be associated with a greater convenience and possibly a better profile of adverse events (Rizzoli *et al.*, 2002). Risedronate at a weekly dose of 35 mg is equivalent to the daily dose of 5 mg. Though intravenous infusion of pamidronate or ibandronate increases BMD, there is no data indicating any favorable influence on fracture rate, so this treatment cannot be recommended for fracture prevention at the present time, according to the criteria of evidence-based medicine. Phase III therapeutic trials are under way to assess whether the annual administration of the bisphosphonate zoledronate reduces the incidence of osteoporotic fractures (Reid *et al.*, 2002).

More than 150 studies have addressed the issue of the effects of calcium on bone (Heaney, 2000). There are only 4 randomized controlled trials conducted in patients with osteoporosis with fracture as the outcome (Chapuy *et al.*, 1992; Chevalley *et al.*, 1994; Dawson-Hughes *et al.*, 1997; Recker *et al.*, 1996). The reduction in the risk of vertebral fracture seen with dietary calcium alone is based on a subgroup analysis of the patients with fracture at baseline and with a low dietary calcium ($<500\,\mathrm{mg\,day^{-1}}$) (Recker *et al.*, 1996). The risk of nonvertebral fracture is decreased by calcium and vitamin D supplements (Chapuy *et al.*, 1992; Dawson-Hughes *et al.*, 1997).

It is well established that sex hormone deficiency increases bone remodeling and leads to an accelerated bone loss. HRT corrects bone remodeling, prevents bone loss, and reduces fracture risk (Writing Group for the Women's Health Initiative Investigators, 2002). Two recently published meta-analyses have shown that HRT reduces vertebral and nonvertebral fractures by 33% and 27%, respectively (Torgerson and Bell-Syer, 2001a,b). However the risk/benefit ratio of such a treatment is the subject of strong debate (Petitti, 2002; Writing Group for the Women's Health Initiative Investigators, 2002).

The Selective Estrogen Receptor Modulators (SERMs) display agonistic properties in some tissues and antagonistic properties in others. For instance, raloxifene increases BMD and decreases vertebral fracture rate in patients with postmenopausal osteoporosis (Ettinger *et al.*, 1999). Nonvertebral fractures are not significantly influenced by

this treatment. However, a *post-hoc* analysis suggests that raloxifene could also be efficacious on nonvertebral fractures in patients with severe vertebral deformities (Delmas *et al.*, 2003). One major benefit of raloxifene is undoubtedly the prevention of breast cancer.

Tibolone is transformed into various metabolites acting on either estrogen or on androgen receptors. Postmenopausal bone loss is prevented by tibolone. However, there are no available results on fracture rate at the present time.

Parathyroid hormone increases both bone formation and bone resorption. A chronic elevation of serum PTH levels is associated with a negative bone balance, with decreased BMD and increased fracture risk (Rubin *et al.*, 2002). Intermittent administration of PTH augments BMD, as well as bone strength in various animal models (Rubin *et al.*, 2002). In a large trial undertaken in patients with osteoporotic fracture, the daily injection of the aminoterminal fragment of PTH reduced the vertebral fracture incidence by 65% (Neer *et al.*, 2001).

Very recently, a "newcomer" appeared in the armentarium against osteoporosis. Strontium ranelate leads to a reduction in vertebral fracture rate (Meunier *et al.*, 2004). Hip fracture risk was decreased in patients older than 74 years and with osteoporosis. This agent appears to be well tolerated and efficacious on vertebral and nonvertebral fractures in patients older than 80 years.

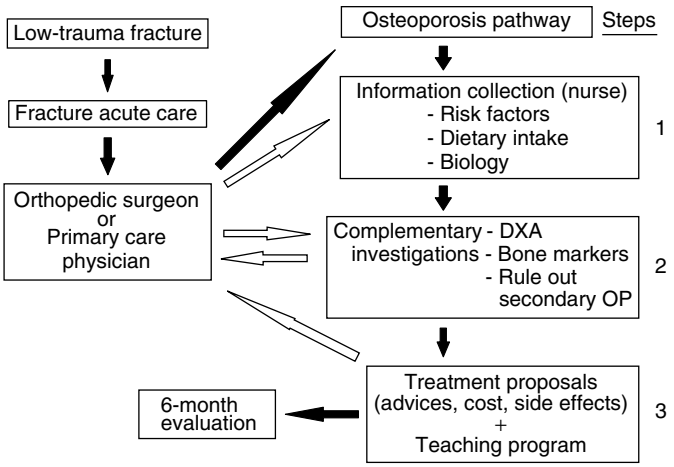

Figure 6 Course of an osteoporosis clinical pathway. The patients with a recent low-energy fracture enter this pathway in which clinical and biochemical data are completed. Then, a treatment is suggested to the medical team directly in charge of the patients. The latter is asked to attend a teaching program on osteoporosis. Filled arrows represent the patient's track after a low-trauma fracture. Open arrows represent a constant interaction between the physician in charge of the patient and the multidisciplinary team of the osteoporosis clinical pathway (Reproduced from Chevalley T *et al.*, An osteoporosis clinical pathway for the medical management of patients with low-trauma fracture, Osteoporosis International, 13, pp 450–455, Copyright 2002, with kind permission of Springer Science and Business Media)

PERSPECTIVES

The fundamental aim of the treatment of patients with osteoporosis is to rebuild bone to a normal quality and structure in order to restore a normal bone strength, reducing thereby the rate of low-trauma fracture to a level similar to that observed in young healthy people. Numerous agents are under development, such as anti-integrins, cathepsin K inhibitors, osteoprotegerin, statins, bone morphogenetic protein-like substances, or anabolic drugs. However, one of the main problems in the management of patients with osteoporosis is the identification of the patient who is at a high risk of fracture and likely to respond to the treatment. A patient with fracture has already a more than twofold risk of experiencing another one (Klotzbuecher *et al.*, 2000). This risk is as high as 20% within one year after a vertebral fracture (Lindsay *et al.*, 2001). A fracture thus constitutes the first priority to antiosteoporotic treatment. A medical pathway for the management of patients with osteoporosis provides an interaction between the medical team and the patients, as well as a teaching program on the disease (Chevalley *et al.*, 2002b) (Figure 6). It is never too late to take in charge and treat patients with osteoporosis.

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KEY POINTS

- Osteoporosis is a devastating disease for the elderly;
- Important signs like a history of low-trauma fracture are largely unrecognized;
- Patients at high risk can be detected, thanks to a pattern of various clinical risk factors;
- Nutritional aspects are highly important for the prevention of falls and osteoporosis;
- Treatment is rapidly efficacious in reducing fracture risk; thus it is never too late for treating a patient at high risk of fracture.

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Gait, Balance, and Falls

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INTRODUCTION

Falls once thought to be an inevitable consequence of aging are now known to be the result of multiple pathological and social factors. A number of risk factors have been identified, notably muscle weakness, gait and balance abnormalities, and previous falls. The more risk factors a person has, the greater their likelihood of falling. Evidence-based guidelines for the prevention of falls have been jointly published by the American and British Geriatric Societies and the American Academy of Orthopedic Surgeons (AGS/BGS/AAOS Panel on Falls Prevention, 2002) and these emphasize the importance of assessment, identification of risk factors, and multifactorial interventions. However, less than half of the older fallers report any associated contact with the health services, and out of those who are seen by a health professional, only a tiny proportion are being prescribed treatment to prevent osteoporosis. This suggests that implementing an effective falls and bone health service will present a considerable challenge. In England a start has been made with the introduction of the National Service Framework for Older People, which requires the establishment of specialized falls services working in collaboration with local primary care and social services. The high cost of falls in terms of injury, loss of confidence and functional decline, and the effectiveness of interventions justify a widespread preventative strategy.

EPIDEMIOLOGY

About one-third of people over the age of 65 living in the community fall each year, and half of these fall repeatedly. Most studies report a higher rate in women and a rising incidence with increasing age. The incidence of falls among men living at home is 368/1000 person years (py) and in women is 611/1000 py. The incidence rate in institutions is much higher, with the falls experienced by men being 2021/1000 py and women 1423/1000 py. There is a decline in fall rate among the very elderly living in institutions, suggesting that these residents are very frail and probably chair- or bed-bound, thus reducing the opportunities for falling.

Falls at home most commonly occur in the day during periods of maximal activity, usually indoors or within the immediate environs of the house. Most falls occur when walking and result from slips and trips. Falls on stairs usually occur when descending and there are many more falls on straight single flights than on U-shaped two-flight stairs.

In institutions, falls are most common in the first week after admission and are usually associated with going to or from the toilet, although falls from a chair are also common. In hospital, risk factors for falls include gait instability, agitated confusion, urinary incontinence or frequency, falls history, and the prescription of sedative drugs (Oliver *et al.*, 2004).

Serious injury following a fall is comparatively rare, with fractures occurring in about 5% of older people living at home. Accident and Emergency attendance rates following a fall per 10 000 population are 273 for those aged 60–64 years, rising to 945 in those aged 75 years and over. The percentage admitted to a hospital is 13% and 39% respectively. Recurrent fallers have a threefold increased risk of going in to institutional care compared with nonfallers.

BALANCE

Balance is a complex process that depends on the integration of vision, vestibular and peripheral sensation, central coordination, and the neuromuscular response – especially muscle strength and reaction times. When standing, any changes in orientation are perceived by proprioceptive and cutaneous sensors in the feet. Vision detects linear and angular motions of the visual field and the vestibular apparatus detects sway related linear and angular accelerations of the head. When the support surface is irregular or in motion vestibular inputs

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become essential, but when the surface is fixed and level, sensory information from the feet is predominant. An age-related decline in function can be demonstrated in all parts of this system.

An individual maintains balance by keeping the vertical projection of the center of mass (COM) on the ground (often called *the center of gravity*) within specific boundaries known as *stability limits*. These are determined by the ability to control posture without altering the base of support. During normal quiet standing, the COM is kept within the support base provided by the feet. Maintenance of this upright position is associated with body sway mainly in the anterior/posterior (AP) direction and this sway can be measured in a variety of ways: typically, as displacements of the body at waist level or, using a force platform, as the excursions of the center of pressure. Both A/P sway velocity and the area are seen to increase in normal older subjects (i.e. those who report that their balance is normal and are functionally independent). This difference is more obvious if the difficulty of the test is increased by using a moving platform or when the eyes are closed. Indeed, many experiments have shown that loss of any sensory afferents (e.g. tilting the head to reduce vestibular inputs; standing on a compliant surface or in ice cold water to reduce somatosensory inputs) increases sway.

Increases in A/P sway has been correlated with spontaneous falls, but a better predictor of falls is mediolateral sway. Falls depend on the relationship between the COM and the base of support. In older people, postural reactions controlling the COM are slowed and there appears to be particular difficulty in controlling lateral instability. Moreover, unexpected perturbations require an adjustment of the base of support through compensatory stepping, and older fallers often have problems controlling these compensatory stepping movements. Lateral falls may increase the risk of hip fractures. Experiments with a movable platform that can produce multidirectional perturbations show that the young controls react with a rapid compensatory hinging at the hips and trunk, thus keeping their COM away from the direction of tilt. They also abduct their arms uphill when tilted sideways. In older subjects, compensatory trunk movements are reduced (probably due to stiffening) and their arms are stretched in the direction of the fall (Allum *et al.*, 2002).

Peripheral sensation (proprioception and touch) is the most important afferent in the control of standing balance in healthy older people. Other factors that are highly correlated with increased sway are reduced muscle strength in the legs, poor near visual acuity, and slowed reaction time. Vision can partially compensate for loss of other sensory inputs, and with increasing age as the postural task gets harder so the reliance on vision becomes greater. Thus, patients with proprioceptive or vestibular impairments are easily upset if the visual field is faulty or misleading in any way.

There is no doubt that some individuals maintain good postural control, even into extreme old age, indicating that age-related changes alone have only a minor effect and that imbalance is largely the result of pathology. Of major importance is the slowing of central coordination due to cerebrovascular or Alzheimer's disease. In its early stages, this is often unrecognized, and the diagnosis is not made until the patient is seen in a falls clinic. Minor and even major cognitive impairment is commonly uncovered for the first time among recurrent fallers. Balance depends on cognitive processes and attention, which may be affected by anxiety and depression as well as brain pathology. The ability to recover balance demands more attention even for healthy older people when compared with young adults. Older people appear less able to weigh and select appropriate responses quickly when the environment changes suddenly. Even a modest 10% increase in the mean response time can result in a five- to sixfold increase in the number of critically slow responses with an ensuing fall.

Doing two things at once ("dual tasking") becomes more difficult in old age and this was highlighted by a report from Scandinavia, which noted that institutionalized older people who were unable to keep up a conversation while walking had a high risk of falls ("stops walking when talking"). Subsequent investigations have shown that dual tasking impairs not only gait but also static and dynamic balance. A variety of cognitive and motor secondary tasks have been examined and all show similar adverse effects on gait and balance. The difficulties increase as the tasks become more complex, and both the young and the old tend to prioritize gait performance over the secondary cognitive task (Bloem *et al.*, 2001). Interestingly, patients with Parkinson's disease (PD) are less able to prioritize and try to perform all tasks simultaneously, regardless of complexity. As a result, their gait and balance performance is poor. Dual task impairment is not a good predictor of falls in a general older population or even in patients with PD. Among people over the age of 85 it predicts falls, but no better than a simple timed walking test. It is mainly a marker of falls in cognitively impaired individuals.

Fear of falling may adversely affect postural control by causing stiffening. This may be beneficial when standing still, but reduces flexibility and the ability to respond to perturbations.

GAIT

The same changes in physiological systems that impair balance also affect gait. Follow-up for 8–10 years of healthy people in their late eighth decade shows a decline in the Tinetti gait and balance scale test (maximum score, 28) of 0.5 units per year. Even relatively fit older people with a low fall risk adopt a more conservative gait pattern: they walk more slowly due to reduced step length, although cadence (steps per minute) remains unaltered, and stance time and double support time increase. These differences are more pronounced when walking on an irregular surface. This appears to be a compensatory strategy to ensure that the head and pelvis remain stable, so that the risk of falling is reduced (Menz *et al.*, 2003). The best single predictor of falling is stride-to-stride variability in velocity, but variability in step width also predicts falling.

An exaggeration of this compensatory strategy, the senile gait disorder, is characterized by caution, a wide base, shorter and more frequent steps, hesitation, and unstable turns. It occurs in nearly a quarter of older people, the incidence rising with increasing age, and is likely to be due to underlying neuro-degenerative syndromes and stroke. These patients have a twofold increased risk of cardiovascular death compared with age matched subjects with a normal gait. Although cerebrovascular disease is a major cause of gait abnormalities several other processes may contribute.

Cerebrovascular Disease

Cerebral MRI (magnetic resonance imaging) studies show an association between impaired gait and balance and an age-related decrease in white matter volume and increased white matter signal hyperintensities, which are not age related but correlate with vascular risk factors. These white matter lesions can be found, most commonly in the periventricular region, in 95% of a largely healthy older population with no history of stroke. The pathogenesis is unclear, but it has been suggested that the underlying mechanism is an impairment of cerebrospinal fluid dynamics caused by small vessel disease and it may be progressive. Subcortical/deep white matter lesions, periventricular lesions, and brain stem lesions are associated with poor balance. These lesions have a general deleterious effect on higher motor and cognitive functions since it has been found that mental ability is strongly related to gait speed and there appears to be a concordance between motor skills and intellect in old age (Starr *et al.*, 2003). The severity of the gait and balance disturbance is likely to depend on where the white matter lesions are situated and this is further discussed in the following text.

Apraxic Gait

This is defined as the loss of ability to use the lower limbs for walking in the absence of demonstrable sensory impairment or motor weakness. It is a feature of frontal lobe disease, but there have been criticisms of the use of the word apraxia to describe the gait abnormalities in these patients on the grounds that many of them have postural disturbances as the main feature and may walk normally with no other evidence of apraxia. Over the years many different names (senile gait disorder, marche à petits pas, vascular Parkinsonism, lower-half Parkinsonism etc.) have been given to the same pattern of gait abnormality resulting in much confusion. The most helpful classification is one that divides patients into whether they have a gait abnormality characterized by ignition failure, shuffling and freezing (ignition apraxia), or have poor balance and falls (equilibrium apraxia). A combination of the gait abnormality and poor balance is a mixed gait apraxia (Liston *et al.*, 2003).

The hypothesis behind this classification reflects current thinking on the role of the basal ganglia. Symptoms of PD such as start and turn hesitation and bradykinesia result from loss of internal cues from the basal ganglia to the supplementary motor area (SMA). However, the pathway linking the sensory cortex, the premotor area, and the motor cortex is intact and this allows PD patients to walk normally (at least for a short distance) in response to visual cues. In vascular Parkinsonism, the periventricular white matter lesions disrupt the pathway from the basal ganglia to the SMA and this produces the characteristic start and turn hesitation and wide-based gait. In fact, this hesitation (or freezing) is more common in vascular Parkinsonism than in idiopathic PD. However, some patients with vascular disease do not have problems with gait ignition or turn hesitation and instead suffer mainly from disequilibrium. It is suggested that these patients have white matter lesions affecting the sensory cortex, premotor area, and motor cortex pathway. Their ability to use visual, auditory, and proprioceptive information is impaired and their balance suffers. Their walking remains reasonably normal and they would not be expected to benefit from visual or environmental cues. Thus, with ignition apraxia the lesions are in the SMA, basal ganglia or its connections and patients are able to respond to visual cues. With equilibrium apraxia, the lesions are in the premotor area or its connections and there is no response to visual or auditory cues. With mixed gait apraxia, the lesions are in the premotor area or connections and the SMA, basal ganglia or connections.

Peripheral Mechanisms

The increased risk of falling in patients with peripheral neuropathy is well recognized. Annual fall rates are nearly 50% and the risk is highest in patients with a high body mass index and relatively severe neuropathy. Two-thirds of diabetics with prior foot ulcers report falls and although having insensate feet increases the risk, comorbid conditions also contribute. Most falls occur when walking, which suggests that these patients have difficulty maintaining dynamic balance. Relatively normal walking rhythms are maintained despite an increase in gait variability, and the increased risk of falling is due to an inability to respond appropriately when faced with an unexpected obstacle or perturbation. Patients compensate by reducing their walking speed.

Muscle strength is highly related to gait. The stronger the knee extension and flexion and ankle dorsiflexion are, the higher the walking speed and the longer the step. Muscle weakness is closely correlated with arthritis and results from reflex inhibition of anterior horn cells secondary to joint pathology. Disuse atrophy and lumbar nerve root lesions also contribute. Foot problems such as calluses, hallux valgus, and retracted toes may impair stability by reducing joint mobility and displacing the COM.

Cervical Myelopathy (*see* Chapter 85, Cervical and Lumbar Spinal Canal Stenosis)

This is a common cause of gait disorder in older people and is largely caused by degenerative changes in the cervical spine

resulting from intervertebral disc decay. The first symptom is often weakness, with or without stiffness, in one leg alone. The weakness is distal and there is a tendency to drag the foot. Patients are aware that their balance is impaired and compensate by producing a protective gait pattern. Gait velocity, step length, and cadence are reduced, and step width is increased. Most patients complain of some neck stiffness and pain, although it is rarely severe. C5 and C6 nerve roots are most commonly involved and sensory symptoms and abnormal reflexes are often present in the upper limbs. In advanced cases, there is spasticity and hyper-reflexia in the legs with posterior column signs and a positive Romberg. Bladder problems consist of frequency and urgency. Urinary retention is rare.

Normal Pressure Hydrocephalus (*see* Chapter 68, Normal Pressure Hydrocephalus)

This produces the classical syndrome of dementia of insidious onset, unsteadiness of gait, and incontinence. Patients complain of a general slowing up and may describe feeling unsteady. Weakness and tiredness of the legs is commonly mentioned. Drop attacks may occur and there may be a number of vague complaints such as headaches, sleeplessness, and forgetfulness. Eventually a mixed gait apraxia develops (see preceding text) due, it is thought, to pressure on descending motor tracts as they pass close to the lateral ventricles before entering the internal capsule.

CLINICAL PRESENTATION

When people are asked why they fell, by far the commonest explanation is that they tripped or slipped. Other causes include a misplaced step, such as stepping into a hole, loss of balance, their legs giving way, or being knocked over. Many attribute their fall to hurrying too much or not looking where they were going. Although the patient's account of the circumstances of the fall is a vital part of the history, it is not a particularly helpful way of classifying falls and a more useful approach is to divide falls into intrinsic and extrinsic.

Intrinsic falls often leave the patient at a loss to explain why they fell. Remarks such as "it just happened", "down I went", or "I lost my balance" are often heard. Often they will say that they felt giddy at the time, but are usually describing a sense of unsteadiness and a fear of falling rather than true vertigo. Common causes of intrinsic falls are weakness of the leg muscles, gait and balance disorders, visual deficits, and cognitive and functional impairment. The relative risk posed by these various factors is shown in Table 1. There is likely to be synergism between multiple risk factors, since the more risk factors a person has the greater their likelihood of falling. Nearly 80% of community-living older people with four or more risk factors report falls. Urge incontinence (but not stress incontinence) carries an increased risk for women of both falls and fractures. Rushing to the toilet can be hazardous for frail-older people, and the fall may be the result of dual tasking (see preceding text) in someone with limited attentional resources who is so focused on avoiding wetting themselves that they fail to concentrate sufficiently on walking safely. An additional explanation is that falls and urinary incontinence both occur in functionally dependent patients who have multiple pathologies. They have the same predisposing risk factors and share a common multifactorial etiology.

Table 1 Results of univariate analysis of the most common risk factors for falls identified in 16 studies that examined risk factors

Risk factor	Mean Significant/Total[a]	RR-OR[b]	Range
Muscle weakness	10/11	4.4	1.5–10.3
History of falls	12/13	3.0	1.7–7.0
Gait deficit	10/12	2.9	1.3–5.6
Balance deficit	8/11	2.9	1.6–5.4
Use assistive device	8/8	2.6	1.2–4.6
Visual deficit	6/12	2.5	1.6–3.5
Arthritis	3/7	2.4	1.9–2.9
Impaired ADL	8/9	2.3	1.5–3.1
Depression	3/6	2.2	1.7–2.5
Cognitive impairment	4/11	1.8	1.0–2.3
Age > 80 years	5/8	1.7	1.1–2.5

[a]Number of studies with significant odds ratio or relative risk ratio in univariate analysis/total number of studies that included each factor. [b]Relative risk ratios (RR) calculated for prospective studies. Odds ratios (OR) calculated for retrospective studies (see AGS/BGS/AAOS Panel on Falls Prevention, 2002) (Reproduced by permission of Blackwell Publishing Ltd.)

Extrinsic falls are the result of drugs and environmental hazards. A number of hazards are recognized: trailing wires, loose mats, poor lighting, low toilet seat, lack of grab rails by the bath and toilet, shelves that are too high or too low, and stairs that are too steep, in need of repair or lack a handrail. Nearly all homes occupied by older people have at least two hazards, with the bathroom and stairs having the greatest potential for accidents. Sheltered housing designed for older people is less hazardous, but by no means as safe as one might assume. However, does any of this matter? Despite the home environment being blamed for up to a half of all falls, there is little evidence of a causal relationship between most potential hazards and falls, and no association with an increased risk of an injurious fall among most older people (Sattin *et al.*, 1998). Older, frailer people are more likely to have an intrinsic than an extrinsic fall and it is probable that people adapt to their hazardous homes. Indeed, what might appear to be a home alarmingly cluttered with furniture turns out to be a carefully placed series of handholds that aid mobility.

Drop Attacks

These were first described nearly 60 years ago as falls due to a sudden collapse or the legs giving way. There is no warning. One minute the patient is on her feet, the next she is on the ground without knowing why. Typically there is

no loss of consciousness and patients often remark on their feeling of helplessness, almost paralysis, when lying on the floor, with immediate recovery once they are helped back onto their feet. However, after any type of fall about a half of older fallers, especially if they are also frail, are unable to get up without help. Women are affected more frequently than men and most studies note a rising incidence with increasing age: from, say, 2% in the 65–74 age-group to 15% in those aged over 75. Because there is no clear definition of a drop attack, the reported incidence varies widely and one study of nearly 600 falls did not recognize a single patient with classic drop attacks.

One of the early explanations of the attacks was that they were caused by brain stem ischemia, resulting in a temporary interruption of the cerebellar descending pathways, which control the efferents from cord to muscle, leading to loss of postural tone. From this developed the view that drop attacks were the result of vertebral artery compression by cervical osteophytes, particularly during rotation and extension of the neck. There are other explanations as to why falls may occur with head movements, and vertebro-basilar insufficiency should be regarded as a rare cause of drop attacks and then also only if accompanied by other symptoms such as vertigo, diplopia, bilateral simultaneous visual loss, weakness or sensory disturbance, and crossed sensory or motor loss. Many other causes have been described such as normal pressure hydrocephalus, frontal tumors, Meniere's disease, cervical cord compression due to a disc protrusion, and even overreliance on a faulty visual framework in someone with impaired postural feedback. In many patients, these are probably best regarded as a type of intrinsic fall where there may be a single explanation, but more often there are multiple postural defects.

However, in recent years, it has become clear that cardiac syncope must be considered in these patients, now that it has been shown that carotid sinus sensitivity is a common cause of unexplained falls, dizziness, and drop attacks.

Falls Associated with Loss of Consciousness

There are only two common causes: cardiac syncope and epilepsy. Hypoglycemia, usually due to long-acting hypoglycemic drugs, rarely leads to diagnostic difficulties. Transient ischemic attacks do not usually cause loss of consciousness and then only if there are accompanying focal neurological symptoms. The causes of cardiac syncope include orthostatic hypotension (OH), vasovagal syncope, carotid sinus sensitivity, arrhythmias, and aortic stenosis. Because patients are amnesic for the event, they may deny loss of consciousness.

Although OH affects 14% of the older population, it has not been found to be as good a predictor of falls as postural dizziness. This may be because the usual method of measuring lying and standing blood pressure in the clinic is too imprecise and underestimates the true prevalence of OH. However, using a tilt table with continuous blood pressure measurement, the finding of a large drop in systolic blood pressure and an unstable pressure in the three minutes after tilting predicts a twofold increased fall rate over the ensuing year (Heitterachi *et al.*, 2002).

Epilepsy is a frequent cause of "funny turns" although falls are uncommon. The type that causes diagnostic difficulty is complex partial seizures. Clues are the stereotyped symptoms and postictal drowsiness, although a reliable witness is invaluable (*see* **Chapter 76, Epilepsy**). Patients with apparent epilepsy who do not respond to treatment should undergo tilt table testing to exclude convulsive vasovagal syncope.

Vertigo and Dizziness

Dizziness is associated with impaired balance, functional decline, and falls. It is a complaint of 30% of the older people living in the community and it is often provoked by postural change and movements of the head and neck. Dizziness in most patients is multifactorial and 85% of chronically dizzy patients have more than one diagnosis: cerebrovascular and cardiovascular disease, cervical spondylosis, anxiety, and poor vision are some of the commonest. At 1-year follow-up there is an increased incidence of falls and syncope. Indeed, 46% of older people presenting in primary care with dizziness also have syncope and falls (Lawson *et al.*, 1999).

Dizziness or a sense of imbalance on head movement is most often due to cervical spondylosis. It results from an imbalance in the flow of stimuli from damaged mechanoreceptors in the cervical spine. However, it is important to consider the possibility of benign paroxysmal positional vertigo (BPPV) in patients complaining of vertigo provoked by head movements (typically, sitting up or rolling over in bed) since this is one of the few disorders of balance for which there is a simple, safe, and effective treatment (*see* **Chapter 106, Disorders of the Vestibular System**). BPPV is often unrecognized as yet, and has a prevalence of 9% in the older population. Eighty percent of older people presenting to an Accident and Emergency department with unexplained falls have symptoms of vestibular impairment (Pothula *et al.*, 2004).

Vision (*see* Chapter 103, Disorders of the Eye)

Vision is necessary for optimal balance. On its own, visual loss is not a particularly strong risk factor for falls, but when there are other postural defects, such as impaired lower limb proprioception, there is increased reliance on vision, especially depth perception and stereopsis (i.e. perception of spatial relationships). Regular users of multifocal glasses are at increased risk of tripping and have twice the fall rate of nonusers. The blurring of the lower visual field produced by multifocal glasses impairs contrast sensitivity and depth perception at critical distances, which is required for detecting obstacles when walking. Misleading information is even more disruptive than no vision at all. Visual loss (acuity 6/18

or worse) detected by standard tests of visual acuity is associated with falls and hip fracture, but simple acuity testing is not the best way of identifying an increased fall risk. The ability to accurately judge distances and detect hazards such as curbs and uneven pavements is critical, and the visual factors that are most strongly predictive of falls are impaired depth perception, contrast sensitivity, and low-contrast visual acuity (Lord and Dayhew, 2001). Fall rates are also increased in people with good vision in one eye but only poor or moderate vision in the other.

Drugs

Drugs are often implicated in causing falls, although the results from studies are inconsistent. The best evidence for an increased falls risk is for psychotropic drugs, particularly hypnotics and antidepressants, and withdrawing the medication reduces the risk of falling. None of the studies linking psychotropic drugs and falls has been a randomized controlled trial, and observational studies have fundamental weaknesses including the possibility that the underlying condition contributes to the risk of falling. Nonetheless, a critical meta-analysis showed that there is a small but consistent association between most classes of psychotropic drugs and falls. The odds ratio for one or more falls with any psychotropic drug use is 1.73 and fall risk is increased in those taking more than one psychotropic drug or having other fall risk factors (Leipzig *et al.*, 1999). There is also a weak association between falls and digoxin, type 1A antiarrhythmics (e.g. quinidine and disopyramide), and diuretics. There is an increased risk of recurrent falls in old people taking more than three or four drugs of any type.

Dementia

Patients with dementia have twice the annual incidence of falls compared with cognitively normal older people; their risk of fall-related injuries is high and they have a threefold increase in fractures. Patients are particularly vulnerable during dual tasking and even a simple additional task impairs postural control.

Parkinson's Disease (*see* Chapter 66, Parkinson's Disease and Parkinsonism in the Elderly)

Falls are not usually an early feature of PD, but eventually up to 90% of patients become fallers. The main determinant of falling is postural instability, particularly impairment in the response to perturbations. Although the increased stiffness of the PD patient improves standing balance, the loss of flexibility increases fall risk. The tendency to walk on the ball of the foot reduces stability, and the reduced height of the foot from the ground during the swing phase increases the risk of tripping. Freezing when turning causes the patient to often overbalance.

MAIN POINTS

- Falls occur in one-third of people over 65 years; rates rise with increasing age and are higher in women.
- Impaired peripheral sensation, reduced muscle strength in the legs, poor vision, and slowed reaction times are the key factors affecting balance.
- Unrecognized cerebrovascular disease is an important cause of gait and balance problems.
- Falls associated with loss of consciousness are most commonly due to cardiac syncope.
- The visual factors that best predict falls are impaired depth perception, contrast sensitivity, and low-contrast visual acuity.

CONSEQUENCES OF FALLS

Falls in older people are a leading cause of disability, distress, admission to supervised care, and death; it is these consequences that make falls important. Approximately one in ten falls results in a serious injury such as hip fracture, other fractures, subdural hematoma, other serious soft tissue injury, or head injury. Falls are responsible for approximately 10% of visits to the emergency department and 4–6% of urgent admissions among elderly persons. Other consequences are more subtle and less apparent although equally disabling. Fear of falling is a widespread problem for many elderly people and is as common as falls themselves. Although fallers are more likely to be frightened of further falls, up to a third of nonfallers limit their activity because of the fear of falling. The fear of going out can restrict people to their homes, decrease their social contacts, and lead to further functional decline. Falls or rather the consequences of falls are commonly cited as a reason for institutionalization. Restricted activities lead to a decline in the ability to carry out activities such as dressing, bathing, shopping, or housekeeping.

Death as a result of a fall seems to be relatively uncommon, but there is good evidence that deaths due to falls are probably underreported. Death certification is well known to be inaccurate and whether a person dies from pneumonia or hypothermia is often not recognized as a complication of a fall. In addition, old people dying from falls are less likely to have an autopsy than those dying from other accidents. In summary, death-rates from injuries due to falls in the elderly are likely to be substantially more than those suggested by death-certificate data.

Standardized comparisons of hip fracture incidence per total population in different European countries and in the United States show a typical picture of an exponential increase in fractures of the proximal femur, humerus and the pelvis with advancing age, which is much more marked in women than men. Fractures of the proximal femur are most frequent followed by proximal humerus and then pelvic-fractures. There is a different pattern for distal forearm-fracture (Colle's-fracture). The incidence in women begins to

rise at an earlier age and levels-off in the sixties to seventies rather than continuing to increase as does the incidence of the other age-related fractures. A possible explanation is that distal forearm-fractures are a marker for the beginning of balance disturbance with aging, whereas the other fractures with increasing incidence rates in the very elderly are a result of ongoing deterioration of postural responses. These are associated with loss of the protective reaction of using the arms to break a fall and gait abnormalities with increased lateral instability.

Another consequence of falling is the "long lie", that is, remaining on the ground or floor for more than one hour. This consequence indicates frailty, illness, and social isolation, and is associated with increased mortality.

ASSESSMENT OF FALLERS

There are some falls that have a single cause, but the majority result from the interactions of two or more risk factors. The risk of falling consistently increases as the number of these risk factors increases. The risk of falling increases in a cohort of elderly persons living in the community, for example, from 8% among those with no risk factors to 78% among those with four or more risk factors. Many of these risk factors are interrelated as preliminary path analytical models have shown. A unidimensional classification of intrinsic versus extrinsic risk is an oversimplification. A better understanding of falls results from an appreciation of all the risk factors affecting a patient.

All risk factors are derived from the findings of population studies. In clinical practice, many medical conditions and disorders, in addition to those listed in Table 1, can play an important role in an individual's fall and may require investigation.

Although falls may result from various combinations of factors, a clinically sensible strategy can be extrapolated from the available clinical trial data augmented by observational data from well-designed studies.

The first and the most important step is to ask elderly patients on a regular basis about any falls or difficulties with balance and gait. If there is a positive answer, a more detailed assessment should be carried out. A multifactorial assessment must be the first step. It has been shown that assessments not linked to targeted interventions are ineffective in preventing falls. Thus, interventions must follow the identification of risk factors.

After history taking and asking about the circumstances of previous falls, a full general examination is required, with focus on the cardiovascular, neurological, and musculo-skeletal system. A neurological examination can reveal impaired proprioception, impaired cognition, and decreased muscle strength. A targeted musculo-skeletal examination should include an examination of the legs (joints and range of motion) and feet. Cardiovascular examination should include postural blood pressure and a more detailed investigation is required where syncope is suspected (see following text). A standard electrocardiogram may demonstrate arrhythmias as a possible explanation for falls and should be a routine part of the examination. The assessment of vision is also important and the examination should focus on visual acuity, depth perception and contrast sensitivity, as well as cataracts. The assessment is completed by a review of medication use with special emphasis on high-risk medications (e.g. benzodiazepines, hypnotics, neuroleptics, antidepressants, anticonvulsants and class 1a antiarrhythmics) and the overall number of medications. The assessment should be completed by a home-visit for home-hazard evaluation.

Inspection of gait and balance is essential. It is recommended that mobility and balance be assessed in a structured way. Persons reporting a single fall should be observed as they stand up from a chair without using their arms, walk a short distance and return (i.e. the "Timed up and go" test). Those demonstrating difficulty or unsteadiness need further assessment.

The often used 6-minute walk measures the walking distance (in meters) in 6 minutes at normal pace. In older people, the distance covered in the 6-minute walk depends on multiple physiological, psychological, and health factors and provides a measure of the overall mobility and physical functioning rather than a specific measure of cardiovascular fitness (Lord and Menz, 2002).

As shown in several studies, decreased lower limb muscle strength is associated with increased risk of falling. One recommended test is the sit to stand functional strength test, which is easy to administer and has been found to be a good predictor of falls. Another modification of this test is the five-chair-rise, where the patient is asked to sit in a chair and then stand up without using his arms for assistance five times.

Reaction time declines with increasing age and it has been shown that slow reaction time is associated with an increased risk of falls. Most tests of reaction time require specialized equipment and thus cannot be used in a broad range of settings.

One test to administer is the rod-catch-test. Patients while seated are asked to catch a wooden rod that is dropped vertically from just above the top of the hand. The point where the patient catches the rod is recorded as a method of simple reaction time.

TO ASSESS BALANCE

Numerous balance tests have been described in the literature. One recommended test is the sharpened Romberg Test, in which the subject stands with one foot in front of the other, referred to as *the tandem position*. However, a lot of older people are unable to perform the test. Thus, we use in our hospital the modified Romberg test with three standing positions and eyes open: both feet parallel for 10 seconds, feet in a tandem position with one foot half of the foot length in front of the other, and the tandem position with one foot in front of the other. The modified Romberg test

is more sensitive and good at predicting falls. Another new measure of standing balance is a test developed by Lord. This test requires patients to stand in a near tandem position for 30 seconds with eyes closed and with the feet separated by 2.5 cm and the heel of the front foot 2.5 cm anterior to the toe of the back foot. An inability to hold the standing position without taking a protective step in the 30-second test-period indicates impaired balance.

Dynamic standing balance can be measured by the functional reach test, where the subject stands and stretches the arm forward against a fixed scale. This has been shown to correlate with other methods of balance and mobility and also has a relationship with the risk of falls and performance in activities of daily living (ADL). Various other methods of balance and gait have been developed for research, but most of them are complex and not appropriate for clinical situations.

TO EVALUATE GAIT

The modified "Get up and go Test" is recommended (refined as the "Timed up and go Test"). The test requires the subject to get up from a chair, walk a short distance, turn around and return to the chair, and sit down again. A more complex assessment test is the "performance-oriented mobility assessment (POMA)" developed by Tinneti for research purposes. The test provides more specific information about balance and gait abnormalities and has been shown to correlate with laboratory gait and balance measures and predict falls, death, and nursing home placement.

However, it is complex to administer and score, and difficult for frailer elderly subjects to perform.

DIZZINESS AND SYNCOPE

Fallers often complain of dizziness, but it is frequently unclear what is meant by dizziness. The term dizziness can include true vertigo, presyncope/syncope, unsteadiness, and some less-specific sensations. There are many problems because the loss of consciousness may not be recalled, and in the absence of a witness, important diagnostic features maybe overlooked. There is often an element of rationalization in the patient's explanation of their fall. Some elderly persons fall because of carotid sinus syncope; in these cases, an in-depth assessment is required. This will usually include tilt table testing with carotid sinus massage and possibly Holter monitoring if the episodes are very frequent, and electrophysiological studies if initial evaluation has shown a myocardial infarct or structural heart disease. Some falls that have a cardiovascular cause may be amenable to intervention strategies such as a medication change or cardiac pacing (*see* **Chapter 45, Arrhythmias in the Elderly**).

The role of these cardiac investigations and treatment is not yet clear. Preliminary studies suggested that patients with recurrent unexplained falls and a bradycardiac response to carotid sinus stimulation experience fewer falls after implantation of a permanent cardiac pacemaker. However, these results have not been confirmed, and pacemaker therapy cannot be recommended for unexplained falls at present.

FALLS CLINICS

Because of the growing evidence base relating to risk factors and intervention strategies, falls clinics are being established in several European countries and in the United States and Canada. Equipment and staff make an in-depth examination and assessment of fallers so that relevant physiological and pathological problems can be identified and appropriate interventions organized.

In such units, the diagnostic accuracy is considerably higher than in nonspecialized clinics. This is also true for the effects of the interventions.

REHABILITATION FOLLOWING FRACTURE

There is still a lack of evidence regarding how best to rehabilitate a faller. A part of the rehabilitation process is the prevention of future falls. The rehabilitation process per se has to address some very important points:

- fear of falling
- ability to get up after a fall
- behavioral changes (coping at home with declining functional abilities)

The rehabilitation program must be targeted on the problems of the individual faller. There may be a need for gait reeducation, particularly if the fall has resulted in a period of immobilization. Improving balance with graded balance exercises may be helpful. Another important issue is training and practice in getting up independently after a fall. If the faller can get up on his or her own after a fall in a relatively safe and supervised situation, this may help him or her to face a return home with more confidence. Exercise programs to increase muscle strength are an important part of the rehabilitation process. Teaching and education should accompany the process in order to initiate behavioral changes if decreasing functional capabilities have contributed to the fall. Education on the risk factors for falling and how to avoid them may increase confidence and reduce the fear of falling.

PREVENTION

The best evidence for the efficacy of interventions to prevent falling emerges from large well-conducted randomized controlled trials. It has been clearly demonstrated that the

most consistently successful approach to prevention is multifactorial assessment followed by interventions targeting the identified risk factors (Tinetti, 2003). In a study of community-dwelling elderly people presenting to an accident and emergency department with a fall, an intervention with a detailed medical and occupational-therapy assessment and referral to relevant services when indicated resulted in a reduction in the rate of falls by 39% (Close *et al.*, 1999).

Pooled data of multidisciplinary, multifactorial intervention programs show a risk reduction of more than 25% for older people with a history of falling. Successful components of these interventions include review and possible reduction of medications, balance and gait training, muscle strengthening exercise, evaluation of postural blood pressure followed by strategies to reduce any falls in postural blood pressure, and targeted medical and cardiovascular assessments and treatments (Tinetti *et al.*, 1994; Fiatarone *et al.*, 1994; Hauer *et al.*, 2001). In these studies there are some shortcomings. Most studies evaluating the multifactorial interventions were conducted in community-settings, neglecting the high-risk population in the settings of long-term care, assisted living, and acute hospitals.

The individual elements of the interventions were described inconsistently and the relative efficacy of the different components is not always clear; taking these flaws into consideration some specific recommendations can be derived for multifactorial interventions. Among community-dwelling older persons, multifactorial interventions should include strength and balance training, home-hazard assessment and intervention, vision assessment and referral, review and modification of medication especially psychotropic medication, and treatment of cardiovascular disorders including cardiac arrhythmias.

In long-term care and assisted living settings, multifactorial interventions should include staff education programs, gait training and advice on the appropriate use of assistive devices, and review and modification of medications especially psychotropic medications. In a prospective, cluster-randomized study with 981 long-stay residents, a staff and resident education program on fall prevention, advice on environmental adaptations, progressive balance and resistance training, and hip protectors resulted in a 45% reduction rate of falls. The number of frequent fallers was reduced by 44% (Becker *et al.*, 2003).

Single intervention programs do not show such consistent results. Although exercise has many proven benefits, the evidence for the effectiveness of group exercise interventions remains limited (Lord *et al.*, 2003). Furthermore, the optimal type, duration, and intensity of exercise for falls prevention remain unclear. There is strong evidence that an individually tailored exercise program of progressive muscle strengthening, balance retraining, and a walking plan is effective in reducing falls. The program should be prescribed and monitored by a trained health-care professional. Tai-Chi has demonstrated effectiveness in reducing falls in one study (Wolf *et al.*, 1996), but before it can be recommended generally it requires further evaluation. In general, there is a dearth of studies involving men. In the long time care settings, there is no evidence of benefit for exercise alone.

Despite its face validity, modification of home hazards shows no clear effect in reducing falls. The results of studies published so far remain controversial. Modification of the home environment without the other components of multifactorial interventions showed no beneficial effect. However, two studies found that for a subgroup of older patients with recurrent falls, a facilitated home modification program after hospital discharge was effective in reducing falls. In one of these studies, (Nikolaus and Bach, 2003) a home intervention based on home visits to assess the home for environmental hazards, providing information about possible changes, facilitating any necessary modifications, and training in the use of technical and mobility aids showed a reduction in the rate of falls and the number of frequent fallers by more than 30% in the subgroup of subjects with a history of recurrent falls. It is hypothesized that the beneficial effect in the cited studies is caused not only by home modifications alone but also by behavioral changes.

The role of footwear in falls prevention remains unclear. There is some preliminary evidence derived from epidemiological studies for an association between footwear and falls. A clear causal relationship between wearing a particular style of shoe and falling cannot be established as there are clearly a multitude of other factors involved.

In a small randomized controlled intervention study with 26 subjects (median age 87 years), habitual shoes and two types of newly designed senior shoes differing in heel height were investigated with respect to static balance and gait. There was no difference found in static balance and gait with the habitual shoes when compared to either of the new footwear offered (Lindemann *et al.*, 2003).

Although behavioral and educational programs are often included in multifactorial interventions, cognitive and/or behavioral interventions alone do not show an effect in reducing the frequency of falls in elderly people.

MEDICATIONS

For all settings, there is a consistent association between the use of psychotropic medication and falls. Thus, it is astonishing that there has been only one placebo-controlled trial of medication withdrawal for fall prevention (Campbell *et al.*, 1999). The reduction of medication is a prominent component of many multifactorial studies in community-based and long-term care settings, and there should be a stronger evidence base to justify any recommendation to review medications or stop them as considered appropriate. The problem is that we do not know whether the risk of falls outweighs the benefits of psychotropic drugs. Shortly after the study by Campbell *et al.* was over, most patients had restarted the medications that had been withdrawn, indicating the dilemma faced by patients and their doctors. The association between taking four or more drugs and falls also needs closer examination in the light of modern

recommendations for the prescriptions for ischemic heart disease, hypertension, and so on.

ASSISTIVE DEVICES

Several studies of multifactorial interventions have shown that assistive devices (e.g. bed alarms, canes, walkers, and hip protectors) are beneficial in reducing fall-related injuries although they do not appear to affect the risk of falling. On the basis of cluster-randomized trials, the use of hip protectors for prevention of hip fractures in high-risk individuals living in extended care settings can be supported. In a cluster-randomized controlled trial of 49 nursing homes with 942 participants, an intervention of a single education session by the nursing staff who educated residents and the provision of three hip protectors per resident resulted in a relative risk reduction of hip fractures by 43% (Meyer *et al.*, 2003). However, trials that have used individual patient randomization have produced no evidence to show that hip protectors are effective for older people living either in extended care settings or in their own home. Until further trials clarify the situation, the use of hip protectors should probably be restricted to carefully evaluated high-risk individuals.

Other potential interventions like bone-strengthening medications have proven effective in reducing fracture-rates. However, these agents do not reduce rates of falls *per se*. Whether vitamin D supplementation has a potential effect on muscle strength and can thus reduce the risk of falling remains to be clarified.

Visual acuity, reduced contrast sensitivity, decreased visual field, posterior subcapsular cataract, and nonmyotic glaucoma medication is clearly associated with an increased risk of falling. Multifocal glasses impair edge-contrast sensitivity and depth perception at critical distances for detecting obstacles in the environment and increase the risk of falling (Lord *et al.*, 2002). Despite this clear evidence of increased risk, there are no randomized control studies demonstrating that referral for correction of vision as a single intervention for community-dwelling older people is effective in reducing falls. However, it is a valuable component of multifactorial falls prevention programs.

Restraints have been traditionally used as a falls prevention approach. However, there is no evidence to support the use of restraints for the prevention of falls taking into account that they have major drawbacks and can contribute to serious injuries. Thus, restraint use should be strictly avoided.

AREAS OF FUTURE RESEARCH

It remains uncertain whether the interventions that are effective in reducing falls are equally effective in reducing fractures or other serious injuries. In Europe, a network of researchers plans to design and perform a study to answer this question. The first step of the Prevention of Falls Network Europe (ProFaNE) is to harmonize assessment tools and to standardize assessment, management, and intervention strategies considering the cultural differences and including the different clinical approaches across the European countries included in the study.

Additional information on the prevention of falls in hospital settings is necessary. So far, no randomized controlled trials exist.

The exercise programs found to be effective have been short term and usually lasting 1 year or less. Most of the improvements last only as long as physical exercises are carried out on a regular basis. Thus, it is important to design programs for enhancing long-term adherence. Furthermore, it is not clear as to what are the effective elements of the exercise programs, such as type, duration, intensity, and frequency.

There is some preliminary data suggesting that patients who have had recurrent unexplained falls and presenting with a carotid-sinus-syndrome may have fewer falls with cardiac pacing (Kenny *et al.*, 2001). These findings need to be confirmed in further clinical trials.

Another open field is how to best intervene in reducing medications. In the only placebo-controlled trial published so far, gradual withdrawal of psychotropic medication significantly reduced the risk of falling, but participants in this study were reluctant to comply permanently.

Other areas of uncertainty are how falls can be prevented in patients with cognitive impairments, whether treatment of visual problems alone will prevent falls, and for whom and when a home-hazard assessment should be carried out.

MAIN POINTS

1. As previous falls are one of the most important risk factors for future falls, all older persons should be asked at least once a year about falls.
2. Persons with previous falls and who are shown on physical examination to have gait and balance problems require a further assessment addressing all the major risk factors for falls.
3. Multifaceted interventions have shown benefits in reducing falls in older community-dwelling people.
4. Home assessment of older people at risk of falls without referral or direct intervention is not recommended. Home assessment has only shown benefit in a selected group of frail-older subjects with a history of recurrent falling.
5. Assessment of high-risk residents in nursing homes with relevant referral has demonstrated positive effects on fall rates.
6. Multifaceted interventions that include an exercise component are effective in preventing falls in institutionalized elderly people.
7. Hip protectors may be of benefit to high-risk individuals in preventing hip fractures, but their effectiveness remains controversial.
8. A pacemaker is not currently recommended for patients with unexplained falls and cardioinhibitory carotid sinus hypersensitivity.

KEY POINTS

- Falls occur in one-third of people over 65 years; rates rise with increasing age and are higher in women.
- Impaired peripheral sensation, reduced muscle strength in the legs, poor vision, and slowed reaction time are the key factors affecting balance.
- Since previous falls are one of the most important risk factors for future falls, all older persons should be asked at least once a year about falls.
- Persons with previous falls who are shown on physical examination to have gait and balance problems require a further assessment addressing all major risk factors for falls.
- Individualized multifaceted interventions that include strength and balance exercises have shown benefits in reducing falls in older community-dwelling people.

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Foot Problems in the Elderly

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INTRODUCTION

The human foot is unique. It has been evolved to serve as an interface between man and whatever territory he or she most commonly traverses. As a consequence, feet will demonstrate a wide range of adaptations to use. Those whose footwear is minimal because of climatic conditions or the nature of territory require little or no covering; have feet that are different than city dwellers. Within these groups, there will be considerable variation, which also relates to the needs of society and custom. In all cases though, the feet share certain common features that are of significance to the clinician (Helfand and Jessett, 1998; Jessett and Helfand, 1991).

Feet are required to withstand stress imposed by activities and occupations, which are extremely variable. The forces of pressure, the adaptations required for ambulation, prior care, and the effects of disease and aging, present different problems in the elderly, which makes comprehensive podogeriatric assessment an essential in patient evaluation (Helfand, 1981, 1987, 1993a).

At one extreme may be the long periods of limited movement experienced by those who work on a production line or operate machinery, which presents a particular occupational risk. At the other end of the scale may be those occupations, activities and/or interests involving great variability of movement, such as ballet dancing, delivery men, sports related activities, and weight/stress related involvements. All these leave their mark upon the foot in the form of a wide range of morbidities, which usually manifest in later life and produce residual disability in the elderly. Some may produce discomfort or temporary disability. Others will produce insidious but cumulative effects that cause pain, ambulatory dysfunction, and limit activities (Helfand, 1993b).

As age increases, problems that may have been tolerated in earlier years will limit the mobility of the individual and decrease the quality of life. One also needs to remember that the focus in the management of the older patient many times, turns from cure to comfort and providing a means to maintain ambulation in order to retain one's independence and dignity (Helfand, 2002).

To all of these functional adaptations to life must be added the consequences of age and disease, such as bone and joint diseases, arthropathies, neuropathies, and also atrophy of soft tissue and integument. These invariably occur to a greater or lesser degree in every individual as age advances. All of these conditions, collectively, serve to diminish activity and increase the need for the regular assessment and examination of the feet and related structures, followed by appropriate care, management, surveillance, health education, and preventive strategies.

The foot is that part of the human body at the greatest extremity of circulatory and neurologic systems. In addition, the ambient temperature of the feet is lower than that of most other parts of the body (Helfand and Motter, 2004).

The feet are covered with hosiery and then thrust into coverings that hide them from view for long periods of time. Footwear, either hosiery or shoes, does not always compliment the size and/or shape or function of the foot. Extremes in width, length, or depth of the foot will complicate shoe fitting, even with a relatively wide range of mass-produced footwear. This potential incompatibility between anatomy and coverings potentiates problems, which become more evident and pronounced in later life. Congenital and/or acquired disease processes may deform feet in a variety of ways which will result in difficulties throughout life and require proper care over long periods of time to manage these chronic diseases and impairments. The primary treatment goals include the relief of pain, restoring the individual to a level of maximum function, and maintaining that function once achieved.

Fashion in footwear cannot be disregarded. When style predominates over fit and function, foot problems are again initiated and/or exacerbated due to this functional incompatibility, that is many times, with a foot to shoe last (model, design, or shape) incompatibility.

It also should to be noted that foot problems and their management are not regarded as a part of many general health

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programs or even being related to general health. It is significant but regrettable, that many believe that feet are part of the body that are designed to hurt. This is true for patients, other elements of the health-care systems, and in the field of occupational health. A majority of patients expect to be able to pursue their normal activities and occupations despite the presence of foot conditions that require rest, but not necessarily hospitalization. With advancing age and the changes in older adult lifestyle, these concerns magnify and may be the difference between living life with some quality and sedentary institutionalization. In addition, because of age-related changes and disease, patients are frequently unable to reach their feet because of arthritis, failing eyesight, obesity, postural hypotension, or some other related disorder. Continuing assessment, evaluation, and appropriate care is most essential for the "at-risk" older patients. Tables 1 and 2 identify some of the primary risks associated with the development of foot problems in the older population (Brodie, 2001).

DISORDERS WITH PEDAL MANIFESTATIONS

The primary risk diseases that present with significant pedal manifestations as identified by Medicare are summarized in, but not limited to, Table 3 as follows:

Table 1 Generalized risks (Collet, 2000; Crausman and Glod, 2004)

The process of aging
History of diabetes
Poor glucose control
History of prior amputation
Impaired vision
Inability to bend
Patients who live alone
Tobacco use (smoking)
Dementia and Alzheimer's disease
History of alcohol use
Risk taking behavior
Obesity
Sensory loss, loss of protective sensation, and neuropathy
Altered biomechanics and pathomechanics
Structural abnormalities including:
Limited joint mobility
Hallux Valgus
Digiti flexi (hammertoes)
Prominent metatarsal heads and prolapse (declination)
Altered Gait, Ambulatory Dysfunction, and Fall Risk
Abnormal or excessive foot pressure
Soft tissue and plantar fat pad atrophy
Subkeratotic and/or subungual hematoma
History of previous foot ulcers
Peripheral arterial and venous disease
Toenail pathology
Xerosis and fissures
Other related chronic diseases and complications
Cardiovascular disease
Renal disease
Retinal disease
Osteoarthritis
Rheumatoid arthritis
Gout

Table 2 Other related risks

The Degree of ambulation
The duration of prior hospitalization
Limitation of activity
Prior institutionalization
Episodes of social segregation
Prior care
Emotional adjustments to disease and life in general
Multiple medications and drug interactions
Complications and residuals associated with risk diseases

Table 3 Primary risk diseases

ALS
Arteriosclerosis obliterans (A.S.O., arteriosclerosis of the extremities, occlusive peripheral arteriosclerosis)
Arteritis of the feet
Buerger's disease (thromboangiitis obliterans)
Chronic indurated cellulitis
*Chronic thrombophlebitis
Chronic venous insufficiency
*Diabetes mellitus
Intractable edema – secondary to a specific disease (e.g. CHF, kidney disease, hypothyroidism)
Lymphedema – secondary to a specific disease (e.g. Milroy's disease, malignancy)
Peripheral neuropathies involving the feet
*Associated with malnutrition and vitamin deficiency
Malnutrition (general, pellagra)
Alcoholism
Malabsorption (celiac disease, tropical sprue)
Pernicious anemia
*Associated with carcinoma
*Associated with diabetes mellitus
*Associated with drugs and toxins
*Associated with multiple sclerosis
*Associated with uremia (chronic renal disease)
Associated with traumatic injury
Associated with leprosy or neurosyphilis
Associated with hereditary disorders
Hereditary sensory radically neuropathy
Angiokeratoma corporis diffusum (Fabry's)
Amyloid neuropathy
Peripheral vascular disease (Arterial and Venous)
Raynaud's disease

Note: ALS, Amyotrophic lateral sclerosis.
Those conditions marked with an asterisk (*), require medical evaluation and care within 6 months of their primary foot care service.

A secondary list of systemic "at-risk" conditions are summarized but not limited to, in Table 4, as follows:

There are also specialized risks identified in, but not limited to, Table 5.

The joint diseases such as, the arthroses, gout, rheumatoid arthritis, and osteoarthritis frequently manifest in the feet. Their primary clinical findings are noted but not limited to those listed in Table 6 (gout), Table 7 (rheumatoid arthritis) Figure 1, Table 8 (osteoarthritis or degenerative joint disease), and Figure 2.

In the older patient, the consequences of these diseases usually result in deformity, swollen joints, impaired foot function, and an altered and potentially podalgic gait. In many cases, the foot may be the primary site of deformity, disability, and limitation of activity. Each tends to

Table 4 Secondary risk conditions

Collagen vascular disease
Malignancy
Lymphedema
Postphlebitic syndrome
Venous (peripheral) insufficiency
Acromegaly
Cerebral palsy
Coagulopathies
Poststroke
Sarcoidosis
Sickle-cell Anemia
Reflex sympathetic dystrophy
Chronic obstructive pulmonary disease
Hypertension
Mental illness
Mental retardation
Hemophilia
Patients on anticoagulant therapy
Paralysis
Ambulatory dysfunction
Parkinson's disease
Immunosuppressed states (HIV, AIDS)

Table 5 Specialized risks

Vascular grafts
Joint implants
Heart valve replacement
Active chemotherapy
Renal failure – dialysis
Anticoagulant therapy
Hemorrhagic disease
Chronic steroid therapy

Table 6 Gout

Acute
Inflammation
Painful
Swelling
Redness
High uric acid levels
Podalgia
Limitation of motion
Ambulatory dysfunction
Chronic tophaceous gout
Deformity
Pain
Stiffness
Soft tissue tophi
Atrophy of soft tissue
Loss of bone substance
Gouty arthritis
Joint deformity
Excessive pain associated with the acute episodes and exacerbations

Table 7 Rheumatoid arthritis

Hallux limitus
Hallux rigidus
Hallux valgus
Hallux abducto valgus
Cystic erosion
Sesamoid erosion
Sesamoid displacement
Metatarsophalangeal subluxation
Metatarsophalangeal dislocation
Interphalangeal subluxation
Interphalangeal dislocation
Digiti flexi (hammertoes)
Ankylosis (fused joints)
Phalangeal reabsorption
Talonavicular arthritis
Extensor tenosynovitis
Rheumatoid nodules
Bowstring extensor tendons
Tendon displacement
Ganglions
Rigid pronation
Subcalcaneal bursitis
Retrocalcaneal bursitis
Retroachillal bursitis
Calcaneal ossifying enthesopathy (spur)
Prolapsed metatarsal heads
Atrophy of the plantar fat pad
Soft tissue displacement
Digiti quinti varus
Tailor's bunion
Early morning stiffness
Pain
Fibrosis
Spurs
Periostitis
Bursitis
Plantar fasciitis
Nodules
Contracture
Deformity
Impairment of function
Loss or reduction of normal ambulation

produce deformities that make weight bearing difficult and cause significant problems in obtaining adequate footwear to compensate for the residuals of these diseases (Robbins, 1994).

Variable and wide-ranging effects accompany endocrinopathies, such as diabetes mellitus, in the cardiovascular and neurologic systems. Many of the symptoms and complications associated with the disease are manifested in the feet and produce potential and serious complications in the older patient. The changes involving the foot are the cause for a significant number of potentially life threatening hospitalizations. In addition, it has been estimated in the United Kingdom and United States, that 50–75% of all amputations relating to the complications associated with diabetes mellitus could be prevented and reduced with an appropriate program of preventive foot care and foot health education.

The most common clinical findings relating to the diabetic foot are listed but not limited to those in Figure 3 and Table 9.

To these problems one must add the effects of repeated microtrauma from footwear, environmental surfaces, lifestyle, neglect, and heat-reflecting surfaces, which produce hyperkeratosis and subcallosal hemorrhage, a predisposing factor for ulceration. Diabetic foot problems in the elderly are characterized by paresthesias, sensory impairment, motor weakness, reflex loss, neurotrophic arthropathy, absence of

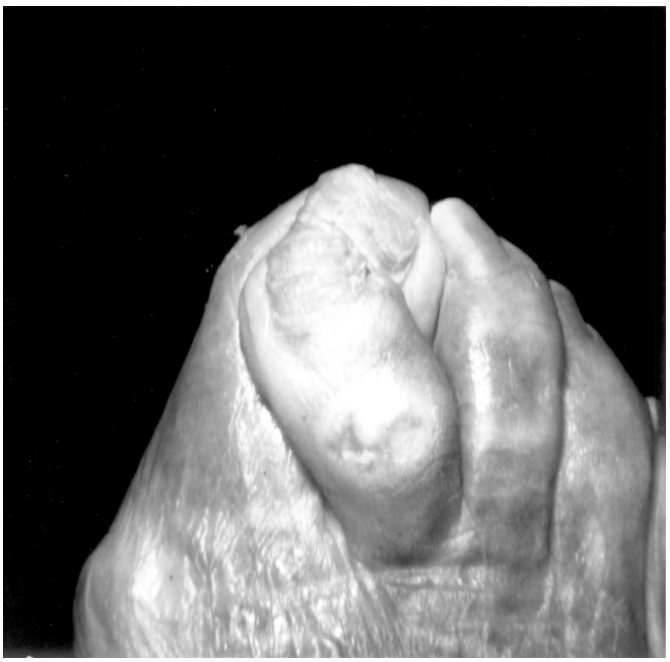

Figure 1 Overriding second toe, hallux valgus, pressure ulcer second toe, interphalangeal joint, onychodystrophy, and arterial insufficiency

Table 8 Degenerative joint diseases – osteoarthritis

Pain related to minimal trauma
Inflammation
Strain
Plantar fasciitis
Spur formation
Periostitis
Myofascitis
Decalcification
Stress fractures
Tendonitis
Tenosynovitis
Residual deformities
Pes planus
Pes cavus
Hallux valgus
Digiti flexus (hammertoes)
Rotational digital deformities
Joint swelling
Increase pain
Limitation of motion
Reduced ambulatory status

pedal pulses, atrophy, infection, dermopathy, angiopathy, neuropathy, ulceration, and necrosis/gangrene.

Clinically, the most marked change perhaps for the elderly diabetic is sensory neuropathy. Where it is combined with poor eyesight, the elderly can be completely unaware of their feet. As Bloom has written, the elderly diabetic may be "divorced from his feet since he can neither see them or feel them properly". Paralysis of muscles due to motor neuropathy will result in deformities of the toes, claw toes. The bony prominences thus formed on the dorsum of the toes

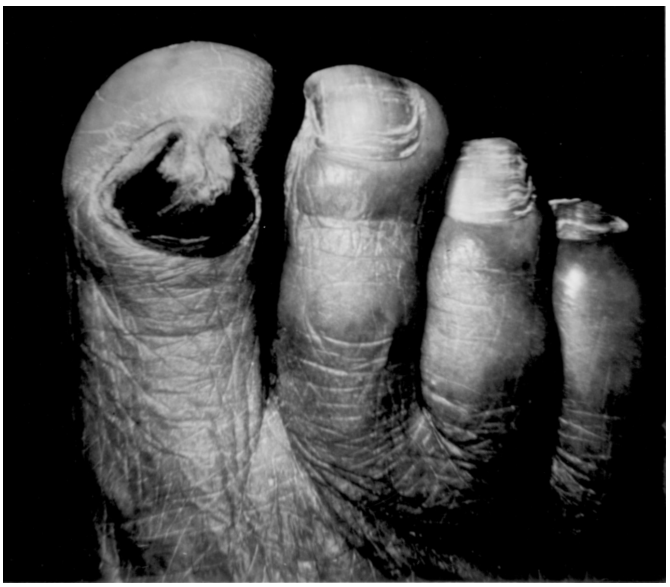

Figure 2 Multiple hammertoes, subungual hematoma, onychodysplasia (marked involution of hallux toe nail) xerosis, and onychauxis with onychomycosis

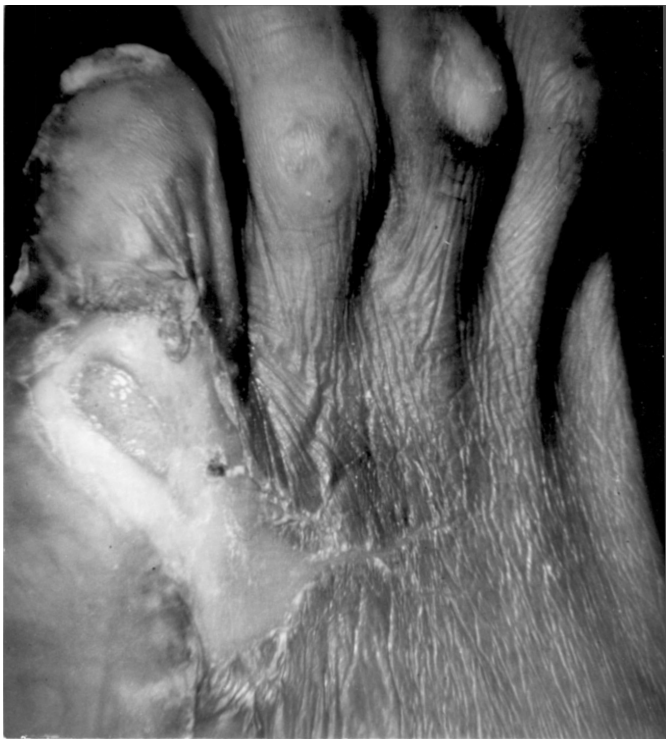

Figure 3 Diabetic ulcer, arteriosclerotic changes, multiple hammertoes, bow string tendons, heloma, and soft tissue atrophy

and the plantar aspect of the metatarsophalangeal joints may be the site of skin lesions, such as hyperkeratosis (tyloma and/or heloma, i.e. corns and calluses) and/or the sites of ulceration, due to pressure, residual subkeratotic hemorrhage, and local tissue ischemia.

Table 9 Diabetic foot changes (ACFAS, 2000; ADA, 2003)

Vascular impairment
Degenerative changes related to aging
Neuropathy
Dermopathy
Atrophy
Deformity
Insensitivity
Pain
Fatigue
Paresthesia
Sensory impairment to pain and temperature
Motor weakness
Diminished or lost Achilles and patellar reflexes
Decreased or vibratory sense (pallesthesia)
Loss of proprioception
Neuropathy
Loss of protective sensation
Blebs
Excoriation
Hair loss
Xerosis
Anhidrosis
Neurotrophic arthropathy
Neurotrophic ulcers
Disparity in foot size and shape
Higher prevalence of infection
Necrosis
Gangrene
Pallor
Absence or decrease in posterior tibial and dorsalis pedis pulses
Dependent rubor
Decreased venous filling time
Coolness of the skin
Trophic changes
Numbness
Tingling
Claudication
Pigmentation
Cramps
Pain
Loss of the plantar metatarsal fat pad
Hyperkeratotic lesions
Tendon contractures
Claw toes (hammertoes)
Ulceration
Foot drop
Diabetic dermopathy (pretibial lesions – shin spots)
Necrobiosis
Arthropathy
Deformity
Radiographic
Thin trabecular patterns
Decalcification
Joint position change
Osteophytic formation
Osteolysis
Deformities
Osteopenia
Osteoporosis
Pruritus
Cutaneous infections
Dehydration
Trophic changes
Fissures
Onychial changes
Onychodystrophy
Diabetic onychopathy (nutritional and vascular changes)
Onychorrhexis (longitudinal striations)
Subungual hemorrhage (bleeding in the nail bed)
Onychophosis (keratosis)
Onychauxis (thickening with hypertrophy)
Onychogryphosis (thickening with gross deformity)
Onychia
Paronychia
Onychomycosis (fungal infection)
Subungual ulceration (ulceration in the nail bed)
Deformity
Hypertrophy
Incurvation or involution (onychodysplasia)
Splinter hemorrhage (nontraumatic)
Onycholysis (freeing from the distal segment)
Onychomadesis (freeing from the proximal segment)
Autoavulsion

The plantar surface of the foot has been the most common site for the development of diabetic ulceration, which is trophic in character. These ulcers develop underneath keratosis with pressure and thus the skilled and proper débridement of the keratosis is a prerequisite to the successful management of the diabetic ulcer and in the prevention of ulcer development. Appropriate weight diffusion and dispersion procedures are also essential elements to management, particularly in the elderly.

Skin texture and sweating patterns are also markedly altered in the elderly diabetic, due to autonomic neuropathy. It is probably also implicated as an additional and local factor in edema. The consequent enlargement of the foot is another cause of epidermal abrasions of the skin from footwear and other forms of trauma and pressure. In addition, with infection, management of infection becomes complicated unless appropriate metabolic management is instituted and maintained early in the disease process. The resulting sepsis can lead to necrosis, gangrene, and amputation of the limb, which additionally complicates the management of the disease in the elderly as well as necessitating changes in the patient's lifestyle (Alexander, 1997).

Varicose veins are a common manifestation in the legs and feet of the elderly. Varices may be observed on the dorsum of the foot sometimes extending as far as the toes, and also along the medial plantar arch area. Hemosiderin deposited in the skin over the lower one-third of the leg and the foot, giving them a freckled appearance and sometimes imparting a coppery hue where the change becomes marked. Edema of the foot and ankle also are a frequent accompaniment of varicose veins. Accidental damage to these vessels can produce hemorrhage. The diminished blood flow resulting from the presence of varicose veins impairs wound healing and causes trophic changes in the skin and nails. Adhesive dressings, even though they may be hypoallergenic, are not well tolerated by such skin for prolonged periods of time. Appropriate treatment may be required to improve both the appearance and function of the extremity.

Complicating factors of venous disease in the elderly include thrombophlebitis, deep venous thrombosis, and postphlebitic syndrome, which produce an "at-risk" status for the patient with foot problems.

The more common arterial diseases that can be observed in the elderly include the residuals of vasospastic disease, such as Raynaud's Disease or Phenomenon, acrocyanosis, livedo reticulosis, pernio, and erythromelalgia. Occlusive diseases such as arteriosclerosis obliterans, the residuals of thromboangiitis obliterans and related diseases, such as arteritis, periarteritis nodosa, polymyalgia rheumatica, systemic lupus erythematous, erythema nodosum, erythema induratum, nodular vasculitis, and hypertensive arteriolar disease. The primary risk factors for the development of peripheral arterial diseases in older patients include smoking, diabetes mellitus, hypertension, Buerger's, and Raynaud's diseases. With inadequate perfusion, nonhealing wounds, infection, tissue loss, and amputation are complications. The primary clinical findings associated with arterial insufficiency are summarized but not limited to those listed in Figures 4 and 5 and Table 10.

In the geriatric patient, arterial insufficiency is heralded by rest pain or nocturnal cramps and/or intermittent claudication. Although it is usually brought on by exercise or use, it may also occur at rest in severe cases of arterial occlusion, especially when bedclothes warm the foot, for example. One also needs to remember that any muscle may claudicate and thus foot pain in the elderly may be related to arterial insufficiency

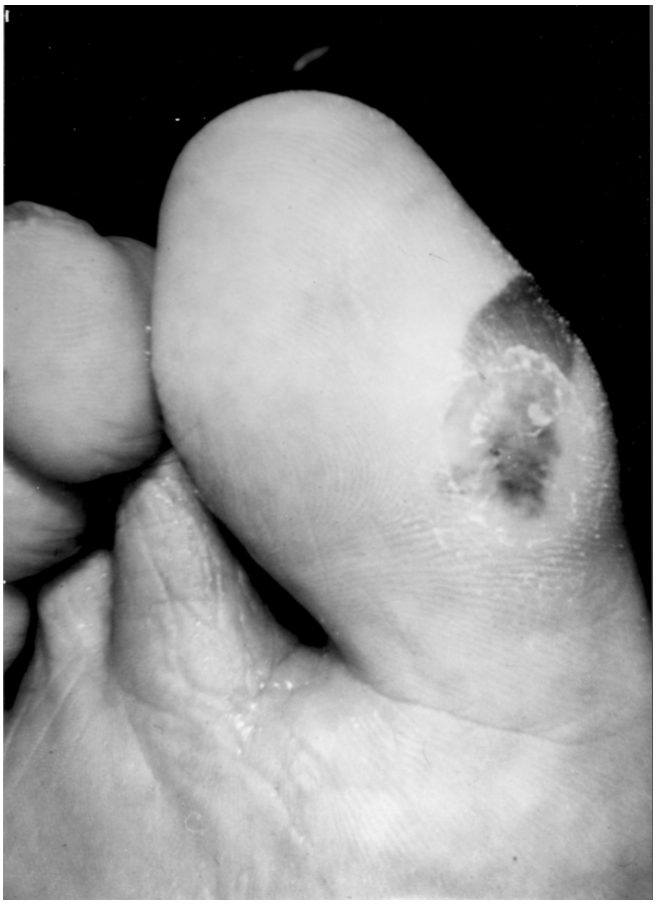

Figure 4 Subkeratotic hematoma, osseous deformity of the hallux with predisposition to ulceration

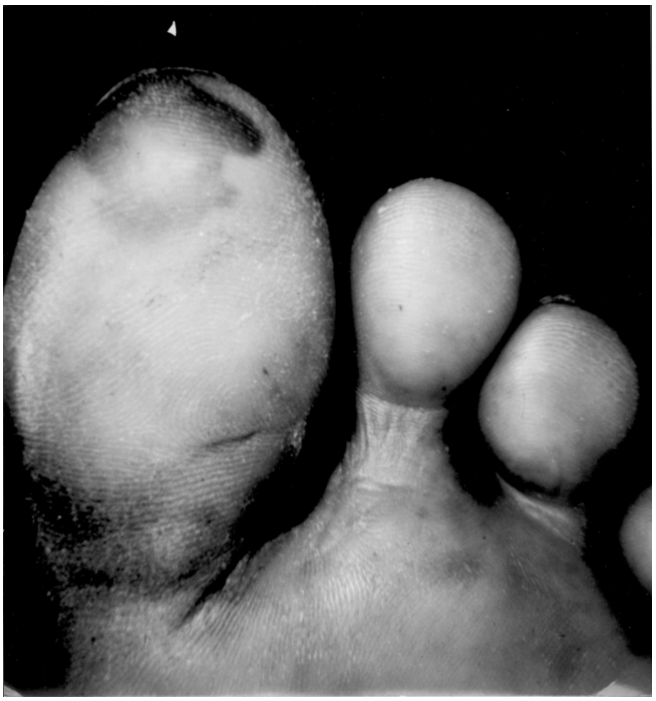

Figure 5 Distal thrombosis associated with arteriosclerotic changes and xerosis

rather than biomechanics or pathomechanics. Painful ulcerations may occur over bony prominences and result from minor trauma and/or pressure. To desist from smoking is a significant contribution to management and the prevention of complications. Appropriate vascular studies, such as; imaging (arteriography, digital subtraction angiography, MRI, CT arteriography, and Doppler imaging), noninvasive studies (Doppler, oscillometric, ankle-brachial index, segmental pressure measurement, plethysmographic waveform analysis, pulse volume recording, skin perfusion pressure, laser Doppler pressure, color Doppler, ultrasonography, transcutaneous oxygen content (TcPO3), cutaneous oximetry, and treadmill exercise testing), and surgical consideration should be provided when pain is uncontrolled and/or when ulceration is significant.

CLINICAL ASSESSMENT (Merriman and Tollafield, 1995; Merriman and Turner, 2002)

Because of the risk involved in the geriatric patient and the relationship to multiple chronic diseases, assessment, examination, and evaluation of the feet of the elderly is essential. Essential as elements of this process include needs, relationships to ambulation and activities of daily living (ADL), and the fact that foot pain can result in functional disability, dysfunction, and increased dependency.

A Comprehensive Podogeriatric Assessment Protocol (Helfand Index), as developed by the Pennsylvania Department of Health is included as Table 11.

Table 10 Primary clinical vascular findings

Fatigue
Rest pain
Coldness
Decreased skin temperature
Burning
Color changes
Absent or diminished digital hair
Tingling
Numbness
Ulceration
History of phlebitis
Cramps
Edema
Claudication
History of repeated foot infections
Diminished or absent pedal pulses
Popliteal and/or femoral pulse change
Color changes – rubor – erythema and/or cyanosis
Temperature changes – cool – gradient
Xerosis, atrophic, and dry skin
Atrophy of soft tissue
Superficial infections
Onychial changes
Onychopathy
Onychodystrophy
Nutritional changes
Subungual hemorrhage
Discoloration
Onycholysis
Onychauxis (thickening)
Onychorrhexis (longitudinal striations)
Subungual keratosis
Deformity
Edema
Blebs
Varicosities
Delayed venous filling time
Prolonged capillary filling time
Femoral bruits
Ischemia
Necrosis and gangrene

In addition, Medicare in the United States has three additional sets of criteria for Class Findings required to qualify for primary foot care (Table 12); Criteria for Therapeutic Shoes for Diabetics (Table 13); Criteria of the Loss of Protective Sensation (LOPS) (Table 14); Criteria for Onychomycosis (Table 15).

A systems review of known chronic and risk diseases is a key element in the assessment process. Conditions such as diabetes mellitus, arteriosclerosis, anemia, chronic renal disease, CHF, arthritis, stroke, neurologic deficits are examples of these risk conditions. The patients' living conditions should also be noted as they are a relationship to care and needs. The chief complaint of the patient should be identified in the patient's own words and related to their daily lives in terms of activity and social needs. The duration, location, severity, prior treatment, and results should also be identified in relation to the presented condition. A social history is also a part of this assessment process.

The dermatologic symptoms and signs and the onychial findings are listed but not limited to Tables 16 and 17 and Figures 6 and 7.

The neurologic symptoms and signs are included but not limited to Table 18. The vascular findings are noted in Table 10.

A drug history and summary of findings, clinical impressions, and special notations for some of the primary basics for assessment, as anticoagulants, steroids, and medications to control diabetes mellitus present additional risk.

The primary musculoskeletal clinical findings are noted but not limited to Table 19 and Figures 8 and 9.

There are biomechanical and pathomechanical factors that combine with structural abnormalities and deformities to increase the risk for pedal ulceration. They are listed but not limited to Table 20 and Figure 10.

The forefoot (metatarsals and phalanges) is the most mobile part of the foot and the majority of problems that develop, occur in this area. Pressure from deformities and shoe to foot incompatibility, will give rise to keratotic lesions (corns and callosities) an initial response to pressure and friction, but footwear is by no means the only cause of painful lesions in the feet nor the prime etiologic factor. Congenital and acquired deformities will result in malfunction and dysfunction and give rise to secondary lesions as the body attempts to compensate for pain and deformity. Alteration in shape and function can arise from accidental trauma, paralysis, changes in function as a result of surgical revision and/or diseases, such as arthritis, which embarrass normal function. The mobility of the foot has a great influence on the type and extent of painful secondary foot lesions.

Rigid feet usually have circumscribed areas of hyperkeratosis. Mobile feet have more extensive areas of keratotic development. Where the foot is deficient in fibrofatty padding or where the stress is chronic, constant, and severe, the so-called neurovascular heloma or tyloma may develop, creating a disruption in the normal dermal – epidermal relationship. Small blood vessels and nerve endings then extend into the epidermis and are enveloped in the keratotic lesion, creating excessive pain and complicating management. Such lesions may be completely disabling and in some patients, result in distressing hyperesthesia, which is difficult to relieve. Many practitioners will not believe that the patient is suffering so severely as they claim.

To the practiced eye, footwear can also reveal a great deal about disease and dynamic foot function. Neglected footwear generally demonstrates neglected foot care and may indicate social poverty. It may also demonstrate poor eyesight. Urine splashes that have dried on the uppers of shoes are sometimes the first indication of occult diabetes mellitus. Thus, the foot is a mirror of health and disease.

KERATOTIC LESIONS

The presence of hyperkeratotic lesions, such as tyloma and/or heloma (callous or corns) on the foot is symptomatic of some degree of malfunction of the foot, especially in the elderly. Elimination and/or management of the underlying cause are the principle objective of the podiatrist's treatment.

Table 11 Podogeriatric assessment protocol (Helfand, 1999, 2003a, 2003b, 2004a, 2004b)

Date of visit		MR#
Patient's name		Age
Date of birth		Social security #
Address		
City	State	Zip code
Phone number		
Sex M F	Race B W A L NA	
Weight LBS	Height IN	
Social status M S W D SEP		
Name of primary physician/health-care facility		
Date of last visit		
History of present illness		
Swelling of feet	Location	
Painful feet	Quality	
Hyperkeratosis	Severity	
Onychial Changes	Duration	
Bunions	Context	
Painful toe nails	Modifying factors	
Infections	Associated signs and symptoms	
Cold feet		
Other		
Past history		
Heart disease	Diabetes mellitus	
High blood pressure	* IDDM	
Arthritis	* NIDDM	
* Circulatory disease	Hypercholesterol	
Thyroid	Gout	
Allergy	History: Smoking: OH	
	Family – Social	
Systems review		
Constitutional		
ENT	Card/Vasc	GU
Eyes	Musculo-	Neurologic
Skin/Hair	Skeletal	Endocrine
Respiratory	GYN	GI
Psychiatric	Allergic	Immunologic
Hematologic	Lymphatic	
Medications		
Dermatologic		
* Hyperkeratosis	Xerosis	
Onychauxis B-2-b	Tinea pedis	
Infection	Verruca	
* Ulceration	Hematoma	
Onychomycosis	Rubor	
Onychodystrophy	* Preulcerative	
* Cyanosis B-2-e	Discolored	
Foot orthopedic		
* Hallux valgus	* Hallux rigidus-limitus	
* Anterior imbalance	* Morton's syndrome	
* Digiti flexus	Bursitis	
* Pes planus	* Prominent met head	
* Pes valgoplanus	* Charcot joints	
* Pes cavus	Other	
Vascular evaluation		
* Coldness C-2	* Claudication C-1	
* Trophic changes B-2-a	Varicosities	
* DP absent B-3	Other	
* PT absent B-1	* Amputation	
* Night cramps	* AKA BKA FF T A-1	
* Edema C-3	Atrophy B-2-d	
Neurologic evaluation		
* Achilles	Superficial plantar	
* Vibratory	* Joint position	
* Sharp/Dull	* Burning C-5	

Table 11 (*continued*)

* Paresthesia C-4	Other

Risk category – neurologic
0 = No Sensory loss
* 1 = Sensory loss
* 2 = Sensory loss and foot deformity
* 3 = Sensory loss, Hx ulceration, and deformity

Risk category – vascular
0 – 0 No change
* I – 1 Mild claudication
* I – 2 Moderate claudication
* I – 3 Severe claudication
* II – 4 Ischemic rest pain
* III – 5 Minor tissue loss
* III – 6 Major tissue loss

Class findings
A1 Nontraumatic amputation
B1 Absent posterior tibial
B2 Advanced trophic changes
B2a Hair growth (decrease or absent)
B2b Nail changes (thickening)
B2c Pigmentary changes (discoloration)
B2d Skin texture (thin, shiny)
B2e Skin color (rubor or redness)
B3 Absent dorsalis pedis
C1 Claudication
C2 Temperature changes (cold)
C3 Edema
C4 Paresthesia
C5 Burning

Onychomycosis: Documentation of mycosis/dystrophy causing secondary infection and/or pain, which results or would result in marked limitation of ambulation.
Discoloration
Hypertrophy
Subungual debris
Onycholysis
Secondary infection
Limitation of ambulation and pain

Classification of mechanical or pressure hyperkeratosis

Grade Description
0 No lesion
1 No specific tyloma plaque, but diffuse or pinch hyperkeratotic tissue present or in narrow bands
2 Circumscribed, punctate oval, or circular, well defined thickening of keratinized tissue
3 Heloma miliare or heloma durum with no associated tyloma
4 Well-defined tyloma plaque with a definite heloma within the lesion extravasation, maceration, and early breakdown of structures under the tyloma or callus layer
5 Complete breakdown of structure of hyperkeratotic tissue, epidermis, extending to superficial dermal involvement

Plantar keratomata pattern
LT 5 4 3 2 1 RT 1 2 3 4 5

Ulcer classification
Grade – 0 – Absent skin lesions
Grade – 1 – Dense callus but not preulcer or ulcer
Grade – 2 – Preulcerative changes
Grade – 3 – Partial thickness (superficial ulcer)
Grade – 4 – Full thickness (deep) ulcer but no involvement of tendon, bone, ligament or joint
Grade – 5 – Full thickness (deep) ulcer with involvement of tendon, bone, ligament or joint
Grade – 6 – Localized infection (abscess or osteomyelitis)
Grade – 7 – Proximal spread of infection (ascending cellulitis or lymphadenopathy)
Grade – 8 – Gangrene of forefoot only
Grade – 9 – Gangrene of majority of foot

Onychial grades at risk
Grade I Normal
Grade II Mild hypertrophy
Grade III Hypertrophic

(*continued overleaf*)

Table 11 (*continued*)

	Dystrophic
	Onychauxis
	Mycotic
	Infected
	Onychodysplasia
Grade IV	Hypertrophic
	Deformed
	Onychogryphosis
	Dystrophic
	Mycotic
	Infected

Footwear satisfactory Yes No

Hygiene satisfactory Yes No

Stockings: Nylon Cotton Wool Other None

Assessment
Plan
Podiatric referral
Patient education
Medical referral
Special footwear
Vascular studies
Clinical lab
Imaging
Rx

Notes: B, Black; W, White, A, Asian; L, Latino/Hispanic; N/A, Native American; S, Single; M, Married; W, Widow/Widower; D, Divorced; S, Separated; DP, Dorsalis pedis pulse; PT, Posterior tibial pulse; AKA, Above the knee amputation; BKA, Below the knee amputation; FF, Forefoot amputation; T, Toe amputation; Hx, History of; Rx, Prescription for treatment as a part of the key to data analysis and risk stratification, the key notes of number and letter (i.e. 2-a) indicate Medicare Class Findings as risk factors and those noted with an asterisk (*) identify risk factors to qualify patients for Therapeutic Shoes under Medicare.

Table 12 Medicare class findings (CMS, 2002a)

Class findings
Class A findings
– Nontraumatic amputation of foot or integral skeletal portion thereof
Class B findings
– Absent posterior tibial pulse
– Absent dorsalis pedis pulse
– Advanced trophic changes as (three required):
Hair growth (decrease or absence)
Nail changes (thickening)
Pigmentary changes (discoloration)
Skin texture (thin, shiny)
Skin color (rubor or redness)
Class C findings
– Claudication
– Temperature changes (e.g. cold feet)
– Edema
– Paresthesias (abnormal spontaneous sensations in the feet)
– Burning

Table 13 Therapeutic shoe criteria (CMS, 2002b)

History of partial or complete amputation of the foot
History of previous foot ulceration
History of preulcerative callus
Peripheral neuropathy with evidence of callus formation
Foot deformity
Poor circulation

Table 14 Onychomycosis Dauber *et al.*, 2001

Onychomycosis: Documentation of mycosis/dystrophy causing secondary infection and/or pain, which results or would result in marked limitation of ambulation
Discoloration
Hypertrophy
Subungual debris
Onycholysis
Secondary infection
Limitation of ambulation and pain
Dystrophic
Onychodysplasia
Onychauxis
Onychogryphosis

This is a goal that is more easily achieved in younger groups due to the wider range of treatment options available. In the elderly, continuing surveillance, monitoring, and primary management is the chief form of therapy, as is the approach for any other chronic condition, such as hypertension, arthritis, and/or diabetes mellitus.

The normal response of the epidermis to intermittent, chronic pressure, and/or stress is to increase in thickness. The resulting excrescence is called *hyperkeratosis* (*tyloma* or *callous*) and may be both hyperplastic as well as hypertrophic. These commonly occur on the plantar aspect of the metatarsophalangeal joints, the hallux, and around the heel. Callous may also occur on the dorsum of the toes, especially with contracture and in the nail grooves. Atrophy of the adjacent dermis and soft tissue, is a common accompaniment in the case of chronic callosities, especially in the patient demonstrating a LOPS. With continuing pressure, vascular and neurologic elements become involved and the development of associated fibrous tissue may also occur. In

Table 15 Loss of protective sensation (Edmonds *et al.*, 2004; Frykberg, 1991)

Services furnished for the evaluation and management of a diabetic patient with diabetic sensory neuropathy, resulting in a LOPS must include the following:
1. a diagnosis of LOPS
2. a patient history
3. a physical examination consisting of findings regarding at least the following elements:
(a) visual inspection of the forefoot, hindfoot, and toe web spaces
(b) evaluation of protective sensation
(c) evaluation of foot structure and biomechanics
(d) evaluation of vascular status
(e) evaluation of skin integrity
(f) evaluation and recommendation of footwear
4. patient education

LOPS, loss of protective sensation.

Table 16 Dermatologic findings

Exquisitely painful or painless wounds
Slow healing or nonhealing wounds
Trophic ulceration
Necrosis
Skin color changes such as cyanosis or redness
Changes in texture and turgor
Pigmentation
Hemosiderin deposition
Chronic itching – pruritus
Neurogenic, and/or emotional dermatoses
Contact dermatitis
Stasis dermatitis
Atopic dermatitis
Nummular eczema
Scaling
Xerosis or dryness
Excoriations
Recurrent infections
Paronychia
Tinea pedis
Onychomycosis
Pyoderma
Cellulitis
Keratin dysfunction
Keratotic lesions without hemorrhage or hematoma
Tyloma (callus)
Heloma durum (hard corn)
Heloma miliare (seed corn)
Heloma molle (soft corn)
Heloma neurofibrosuum (neuritic)
Heloma vasculare (vascular)
Onychophosis (callus in the nail groove)
Intractable plantar keratosis
Keratotic lesions with hemorrhage or hematoma (preulcerative)
Verruca
Psoriasis
Fissures
Hyperhidrosis
Bromidrosis
Maceration
Diminished or absent hair growth
Diabetic dermopathy
Necrobiosis lipoidica diabeticorum
Bullous diabeticorum
Poroma
Absence of hair
Ulceration

Table 17 Onychial findings

Onychoatrophia (atrophy)
Onychia sicca (dryness)
Onycholysis (freeing from the free edge)
Subungual hyperkeratosis
Onychexallis (degeneration)
Diabetic onychopathy
Onychauxis (hypertrophy)
Onychogryphosis (hypertrophy and deformity)
Onychomycosis (fungal infection)
Onychia
Paronychia
Onychitis (inflammation)
Onychalgia (pain)
Subungual abscess
Subungual heloma (keratosis)
Subungual exostosis
Periungual verruca
Onychophyma (painful degeneration with hypertrophy)
Onychomadesis (freeing from the proximal portion)
Onychoschizia (splitting)
Onychyphemia (hemorrhagic)
Onychoclasis (cracking)
Onychomalacia (softening)
Onychoptosis (shedding)
Subungual spur
Onychophosis (hyperkeratosis in the nail groove)
Subungual hematoma
Splinter hemorrhage
Onychocryptosis (ingrown toenail)
Periungual ulcerative granulation tissue
Onychodysplasia (involuted or pincer nails)
Onychodystrophy (trophic changes)
Onychorrhexis (longitudinal ridging)
Beau's lines (transverse growth cessation)
Pterygium (hypertrophy of eponychium)
Onychoclasis (breaking of the nail)
Diabetic onychopathy (trophic diabetic changes)
Hypertrophic onychodystrophy

some instances, the fibrous tissues bind the skin to the underlying joint capsule and/or tissues.

Hemorrhagic spots indicate where blood has been forced from vessels and is indicative of extensive pressure and/or a complication of an associated systemic disease, such as diabetes mellitus. Occasionally, this makes a "lake" in the area and produces a moist, shallow ulceration, which dries and heals when the area is débrided of keratosis and appropriately managed. In some instances, a frank ulceration may develop, as in the case of a diabetic. Management including débridement of the keratosis is essential if healing is to be generated (Baran *et al.*, 1996).

The characteristic of a heloma durum (corn) is the presence of a nucleus. Heloma appear to represent a reaction to more localized stress than is the case with tyloma (callosity), although heloma are frequently found established in a much larger area of callous. The nucleus is 1 – 2 mm in diameter and may be circular or even crescentic in shape. It is harder due to increased density than the surrounding callous. The nucleus may represent parakeratotic changes histologically, similar to that which occurs in psoriasis.

Like tyloma, heloma are essentially epidermal in origin but may become more complex because of alteration in the

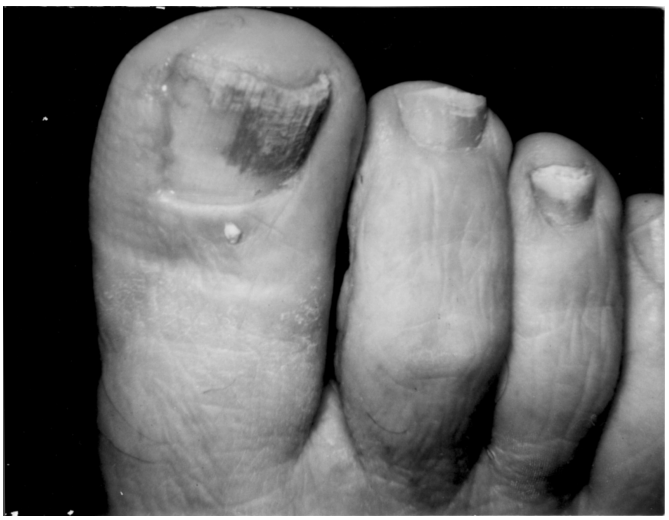

Figure 6 Onychocryptosis (ingrown toenail) with onychia, onychodysplasia (involuted hallux toenail, subungual hematoma, onychomycosis, hammertoes, and hypertrophy of the unguilabia (nail lip)

Figure 7 Onychogryphosis (Ram's Horn Toenails), marked hypertrophic and deformity, onychomycosis, and xerosis

Table 18 Neurologic findings

Sensory changes
Burning
Tingling
Clawing sensations
Pain and hyperactivity
Two-point discrimination
Motor changes
Weakness
Foot drop
Autonomic
Diminished sweating
Hyperhidrosis
Sensory deficits
Vibratory
Proprioceptive
Loss of protective sensation
Changes in pain and temperature perception
Hyperesthesia
Diminished to absent deep tendon reflexes (Achilles and Patellar)
Hypohidrosis with perfusion
Diabetic dermopathy or pretibial lesions (shin spots)
Thickened skin with calluses under high-pressure areas, demonstrating an intrinsic minus foot (marked digital contractures, metatarsal prolapse, prominent metatarsal heads, and plantar fat pad atrophy and displacement)
Bowstring tendons
Charcot Foot

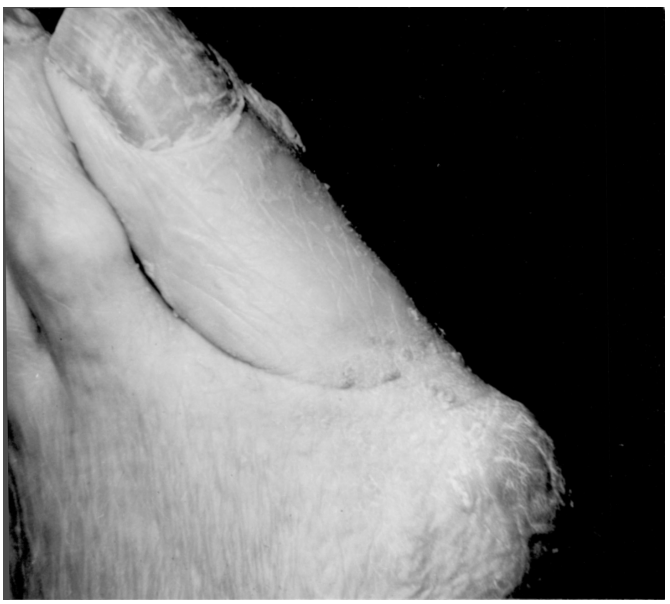

Figure 8 Hallux valgus, rotation of the hallux, onychomycosis, onychauxis, joint deformities, enlargement of the first metatarsal phalangeal joint, degenerative changes, and xerosis

dermis, frequently overlooked, and a source of considerable intractable chronic pain. This is due to the imbalance created in the normal chemo-epidermal function and the development of hyperkeratotic lesions with neural and vascular components, many times encapsulated, giving rise to much pain and discomfort. The resulting neurovascular lesion, heloma neurovarsculare, usually signifies a long-standing lesion. Not infrequently, these result from improper and inappropriate treatment or repeated self-treatment, resulting in hemorrhage and inadequate follow-up care. Sites where broken chilblains have occurred may also become calloused with accompanying neurovascular changes in the dermis, are further complicated by the presence of one or more of such nuclei. Heloma (corn) may arise anywhere on the skin where a bony prominence provides resistance to external pressure. The resulting intermittent stress – a combination of pressure, friction, and shearing – provokes changes in the skin which are not yet well understood, but which are readily recognized

Table 19 Musculoskeletal findings

Gradual change in shape or size of the foot
A sudden and painless change in foot shape with swelling and no history of trauma
Cavus feet with claw toe
Drop foot
"Rocker bottom foot" or Charcot foot
Neuropathic arthropathy
Elevated plantar pressure
Decreased muscle strength
Decreased ranges of motion
Multiple foot deformities
Limited joint mobility
Abnormal foot pressure and subsequent ulceration
Structural abnormalities or foot deformities
Hammertoes
Claw
Prominent metatarsal heads
Atrophy of plantar fat pad
Plantar fat pad displacement
Foot muscle atrophy
Hallux valgus
Hallux limitus
Hallux rigidus
Tailor's bunion
Plantar Fasciitis
Spur formation
Calcaneal spurs
Bursitis
Periostitis
Decalcification
Stress fractures
Tendonitis
Tenosynovitis
Metatarsalgia
Morton's syndrome
Joint swelling
Bursitis
Haglund's deformity
Neuritis
Entrapment syndrome
Neuroma
Sesamoid erosion
Sesamoid displacement
Tendo-Achilles contracture
Digital amputation
Partial foot amputation
Charcot's joints
Phalangeal reabsorption
Functional abnormalities
Pes cavus
Equinus
Pes planus
Residuals of arthritis (degenerative, rheumatoid, and gouty)
Biomechanical and pathomechanical variations
Gait evaluation
Shoe evaluation
Type of shoe
Fit and size
Shoe wear and patters of wear
Shoe lining wear
Foreign bodies
Insoles
Orthoses

even by a laymen. In the elderly, atrophy of soft tissue and a reduction in the fluidity and elasticity of the soft tissues predispose the elderly to the development of these lesions.

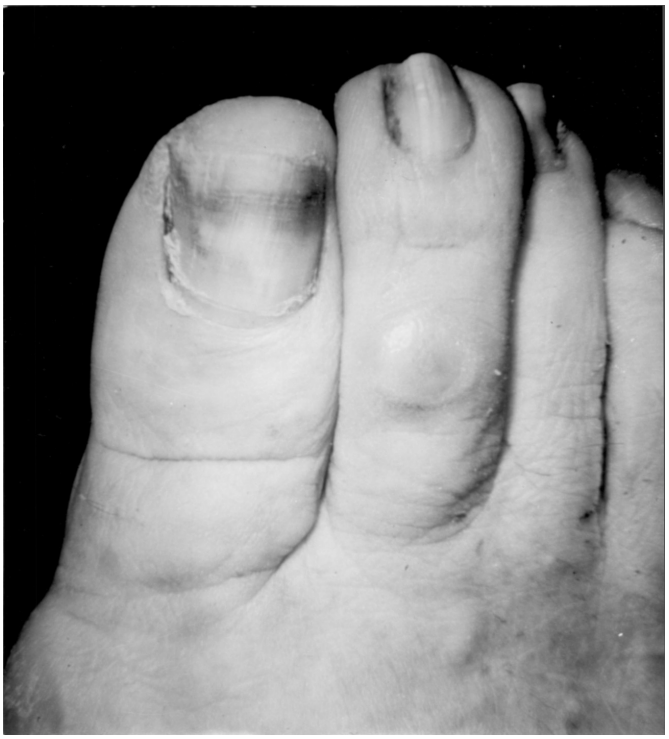

Figure 9 Subungual hematoma, xerosis, pterygium, early keratosis (heloma), and trophic changes

Table 20 Factors leading to ulceration

Body mass
Gait
Ambulatory speed
Tissue trauma
Weight diffusion
Weight dispersion
Pathomechanics, defined as structural change in relation to function
Biomechanics, defined as forces that change and affect the foot in relation to function
Imbalance, defined as the inability to adapt to alterations of stress
Force – alteration in physical condition, either shape or position
Compression stress – one force moves toward another
Tensile stress – a pulling away of one part against another
Shearing stress – a sliding of one part on the other
Friction – the force needed to overcome resistance and usually associated with a sheering stress
Elasticity – weight diffusion and weight dispersion
Fluid pressure – soft tissue adaptation and conformity to stress

Bursae may occur in the tissues adjacent to a heloma. Localized pinpoint lesions, heloma miliare, or seed corns, occur with extreme localization of pressure, such as a protruding irregularity in a shoe. Heloma molle or soft corns are found between the toes and are macerated and soft due to excessive moisture. Their etiology is usually due to digital compression accompanied by bony abnormality and/or digital deformities, such as hammertoes and rotational deformities.

Management in the elderly is essential to prevent infection, particularly from improper débridement. Given the atrophy of soft tissue in the elderly, localized pressure from keratotic

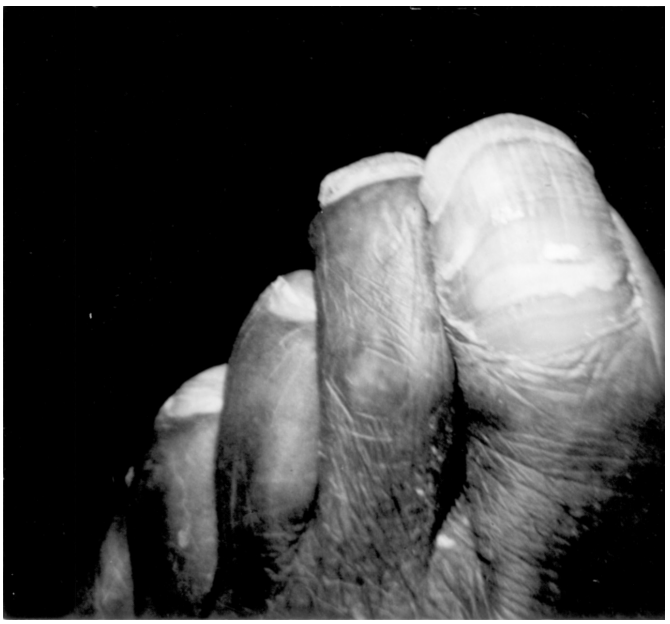

Figure 10 Onychomycosis with Beau's Lines, contracted and rotated toes, onychodystrophy, onychorrhexis, arterial insufficiency, and xerosis

lesions, may produce ulceration and can lead to osteomyelitis, with chronicity and intractable states.

Treatment includes initial débridement, the use of emollients such as 20% urea or 12% ammonium lactate, and materials to reduce pressure are essential elements in the management of the elderly. Silicone molds to compensate for deformity, padding materials to provide weight diffusion, orthotics to provide stability and weight dispersion, and shoe modifications as needed are also considerations in a long-range approach to the management of these lesions in the elderly.

ULCERS

Diabetes mellitus, peripheral arterial insufficiency, and vasculitis are probably the most common predisposing etiologies in the development of ulcerations in feet. Ulcerations resulting from vasculitis are usually superficial and treatment involves the relief of pressure. Healing is usually rapid and a resolution of the ulcer can be maintained with periodic management to prevent excessive localized pressure to stressful areas of the feet. The underlying cause should also be appropriately treated (Bild *et al.*, 1989; Cavanagh *et al.*, 2000).

Diabetic ulceration commonly occurs on weight bearing areas of the foot, although the tissue overlying any bony prominence exposed to pressure may breakdown and ulcerate. Even bed-ridden patients may develop ulcers due to the weight of bed-cloths or that of one limb upon another. Diabetic ulcers (perforating) may penetrate to involve deeper structures. Surgical intervention will then be required for more extensive débridement of tissue, drainage, and some times, skin grafting. The use of contact casts or removable cast walkers can be considered, but the patient's ability to adapt to these ambulatory changes must be part of the consideration for their use (Kozak *et al.*, 1995).

Ulcers that are due to arterial insufficiency are usually very painful and present with pending necrosis and gangrene. The changes are usually dry and at some point, the decision to manage and/or amputate will need to be considered. Decisions are based on the total clinical picture and the needs of the patient.

Ulcer etiology and assessment are initial considerations. Location, wound size, and shape, wound bed, color, drainage, wound edges, pain, periwound area, odor, edema, and the signs of infection are important issues. Management includes removing devitalized tissue by débridement, autolytic enzymes, mechanical, chemical, and cleansing are considerations. Managing the potential for an infection are critical issues. Preventing local injury and supporting the repair process are equally important. Vascular complications require indication, consultation, and possible surgical intervention. Topical recombinant platelet – derived growth factor can assist in wound care. Continuing evaluation, local wound care, management, and prevention are continuing issues, particularly in the older patient.

Management should include relief of pressure, control of infection, and appropriate débridement (Bottomley and Lewis, 2003). Note should be made of the duration of the ulcer, size of the ulcer, depth of the ulcer, and the amount of necrotic tissue present. Treatment parameters also include assessment of the patient's mental status, mobility, infection, tissue oxygenation, chronic pressure, arterial insufficiency (small vessel ischemia), venous stasis, edema, type of dressings, and chronic illnesses such as diabetes mellitus, uremia, COPD (chronic obstructive pulmonary disease), malnutrition, CHF (congestive heart failure), anemia, iron deficiency, and immune deficiency disorders. In addition, signs and symptoms, other medical conditions, the wound status, the patient's response to treatment, and early consultation are also important factors to preserve the patient's limb and life (Bolton *et al.*, 2000; Bowker and Pfeifer, 2001).

TOENAILS

As appendages of the skin, nails very readily reflect its state, becoming hard, dry, and brittle as age advances. Not infrequently, the nail plate is thinner than usual due to atrophy. In other instances, the toenails become so thickened and deformed that the patient cannot cut them and they are ashamed to show their nails to another person. The resulting discomfort may prevent them from wearing any other footwear than a house slipper, making the patient housebound. In addition, the deformity may present a podalgic gait and produce a degree of ambulatory dysfunction, making the patient partially functionally disabled.

Trauma is a precipitating factor in the development of thickening of the nail plate. The trauma may have been

acute and marked or may be chronic and minimal, such as the constant friction or impaction of the toenail against the inferior portion of the toe box of the shoe. The nail plate may grow and twist across the foot. This is onychogryphosis or "Ram's horn nail". It also presents as a residual of inappropriate or no treatment. The danger of this condition is that the nail may penetrate the skin and provide a portal of entry for pathogens, resulting in infection (Evans *et al.*, 2000).

Toenails sometimes assume a claw-like appearance due to a dramatic increase in the transverse curvature (involution or convolution). They may also become thickened (onychauxis). Unskilled and inappropriate attempts to "dig out" the corners of this so-called ingrown toenail, because it is painful, very often lead to inflammation (onychia) and infection (paronychia). Temporary relief may be obtained but skin retraction usually results in increased pain and infection a short time after this attempt. Patients who have poor peripheral arterial supply may face serious consequences from the improper management of this condition. Very thin nail plates may also penetrate the skin of adjacent toes, with similar results.

Hyperkeratosis in the nail grooves (onychophosis) or under the free edge of the nail also creates pain. Periodic débridement of the thickness and length of the toe nail then permits débridement of the keratotic tissue. This is achieved with the use of a nail forceps, curette, and drill, and an appropriate burr. Suitable dressings of chamois, leather, ointments, or silicones, such as Viscogel can be utilized as nail packing under the nail plate to prevent it from digging into the surrounding tissue. The use of emollients such as 20% urea or 12% ammonium lactate also helps as a preventive measure. Depending on the patient's general health and the pain and deformity, avulsion of the whole nail or part of the nail plate, under local or regional anesthesia may be considered.

Another relatively common cause of thickening of the nail plate is mycotic infection. Streaks of yellow or brown discoloration may extend from the free edge, proximally to the lunula. One or more nails are usually involved, become thickened, brittle, and produce a characteristic musty odor. The patient's concern may be the unsightly nail that makes a hole in hosiery and sometimes the uppers of their foot wear. Pain is associated with deformity. However, this chronic infection may produce a mycotic onychia and may serve as a focus of infection (Baran *et al.*, 1999).

The most common organism producing these changes is *Trichophyton rubrum*. Although it is generally confined to the nails, the surrounding skin, and interdigital spaces may become scaly and itch intensely. Sometimes the infection spreads more extensively over the so-called moccasin area. Miconazole nitrate is an example of an antifungal agent that is effective in the treatment of mycotic infections of the skin. Oral terbinafine hydrochloride, itraconazole, and topical ciclopirox are available for the management of onychomycosis. Forty percent urea gel is also utilized as a topical application to assist in local onychial débridement. The appearance of the nail plate can be improved and the patient's comfort increased by reducing the thickness of the nail plate and providing a smooth surface to the plate.

BURSITIS

Bursae are found in a number of situations in the foot. The adventitious bursa over the medial aspect of the first metatarsophalangeal joint frequently becomes inflamed when the joint it overlies is deformed and enlarged, as in hallux valgus. Bursae are also found superficial and deep to the Achilles tendon, the plantar aspect of the heel and the lateral aspect of the fifth metatarsal-phalangeal joint (tailor's bunion). If for any reason, a superficial bursa is ruptured, secondary infection can ensue. A sinus may be formed and chronic subacute bursitis is then a persistent problems.

Enforced rest for long periods due to debilitating illness or accidental injury may lead to laxity and atrophy of the plantar calcaneal fibro-fatty padding, associated with dehydration. The plantar calcaneal bursa is then vulnerable due to overuse and bursitis results. Plantar calcaneal spurs and plantar myofascitis may also become troublesome in these circumstances (Birrer *et al.*, 1998).

The immediate treatment for bursitis is to reduce the inflammation and to manage any secondary infection that may be present. Pressure on the areas can be reduced with padding and shoe modifications. Physical modalities, such as heat and ultrasound can be of assistance if properly utilized. Local steroid injections as the use of nonsteroidal anti-inflammatory drugs are indicated, when appropriate, in the elderly.

In the long term, stress on the bursae has to be reduced to minimize an exacerbation of the condition, once the acute symptoms are resolved. This may involve modification to footwear an/or the wearing of an appropriate shield (orthotic), such as a silicone mold. Plantar bursitis can be improved with the use of heel cups, silicone heel pads, and/or orthosis that provide weight diffusion and modify the weight/pressure relationships in a superior, lateral, and posterior direction. Insoles from Plastazote, PPT, and other similar materials can aid in weight diffusion and dispersion. The normal warmth of the foot, even in the geriatric patient, will help mold the Plastazote. The resulting wear marks can be a good guide when constructing a more durable orthotic from materials such as Vitrathane. Plastazote as an insole or lining material in combination with Vitrathane will relieve the patient of the feeling that they are walking on pebbles, which is the result of soft tissue atrophy and atrophy of the plantar fat pad.

SCARRING

Scarring of the plantar surface of the foot may result from accidental injury, for example, penetration of a foreign body, when walking barefoot. It is not infrequently iatrogenic in

origin, that is, following surgery. The plantar metatarsal is the commoner site for painful scars on the foot, which in the geriatric, is already deficient in fibro-fatty padding. This can be completely disabling. Patients will require primary podiatric care to débride the keratotic lesions (callous and corns) that usually develop within the scar tissue. Appropriate orthotics and insoles as noted above, should be employed to reduce friction and pressure by weight diffusion and dispersion.

FISSURES

Moist or dry skin may develop fissures. In either case, the fissuring may extend into the dermis and create hemorrhage in the soft tissues. In the geriatric, stress marks along the outer portion of the heel also serve as an etiologic factor and form the initial stages of pressure ulcerations. Fissures around the heel are usually dry and vertically oriented. Secondary infection is always an added risk. Interdigitally, fissures are usually moist and follow the flexures of the skin. Infection of the interdigital fissures may penetrate the fascial planes and require surgical drainage. The edges of the fissures usually become hyperkeratotic and indurated in the elderly patient, which prevents healing and can be extremely painful.

Moist fissures respond well to simple antiseptic dressings and when healed, the skin should be carefully washed daily. The hard edges of the dry fissures should be débrided. This may be aided by the use of 12.5% salicylic acid in collodion. Its action is to soften the hyperkeratosis and make débridement easier and less painful for the patient. Tissue stimulants can also be employed, once débridement is completed. Bland emollients that help soften keratosis and maintain skin integrity can also be suggested, such as 20% urea creams and 12% ammonium lactate lotion, in addition to daily hygiene (Lorimer *et al.*, 2002).

MANAGEMENT CONSIDERATIONS

Since healthy feet are essential for mobility and independence, as well as a catalyst to maintain patient dignity, none who are concerned with health and well-being of older persons should disregard foot care. The particular knowledge and skills of the podiatrist are vital for the multidisciplinary team caring for the geriatric patient. Regular assessment and inspection of the feet are an effective means of monitoring the preventive aspects of the complications of diabetes mellitus and arthritis for example. Other symptoms and overt abnormalities are many times detected during a foot evaluation, with appropriate referral for care to justify the secondary preventive aspects of chronic disease. The period evaluation also provides an appropriate time for health education. For the diabetic, this may be the difference between dignity and ulceration, gangrene and amputation. Projected changes in Medicare Regulations in the United States will mandate appropriate foot care as a Condition of Participation and quality assurance as a condition for approval (Helfand, 2000; Strauss and Spielfogel, 2003; Tollafield and Merriman, 1997).

FOOTCARE

Advice regarding foot care will benefit all elderly people whatever their state of general health. Daily washing of the feet should be encouraged. The skin should be dried carefully, dabbing rather than rubbing – especially between the toes. Extreme care should be taken to check that the temperature of wash water does not exceed 40 °C. An appropriate thermometer is best for this purpose. Immediately after bathing, emollients may be applied to the skin to increase hydration and lubrication. This helps in minimizing the drying out of the skin.

Toenails must not be picked or torn, but carefully trimmed, without cutting back the corners. Patients, who have any degree of abnormality, disease, or who cannot bend, see or maintain manual dexterity, should seek professional care. This is especially true for the "at-risk" patient. Ingrown toe nails (onychocryptosis) can readily result from badly trimmed or torn nail plates penetrating otherwise healthy skin.

The application of patent "corn cures", plasters, or paints must be avoided. These preparations contain salicylic acid and can create a second-degree chemical burn, initially; infection, ulceration, necrosis, and gangrene may result for their use in the "at-risk" patient, such as diabetics.

Any minor cut or abrasion should be covered with a sterile dressing. If healing of any breach in the skin is delayed, this should be brought to the attention of the attending practitioner or nurse. Sudden changes in skin color or pain should also be reported. Sitting too close to open fires or radiant heaters of any kind should be strongly discouraged. During winter months, adequate and appropriate warm clothing should be worn, such as long johns, thick tights, or socks.

Hot water bottles or electric blankets may be used to heat the bed but not the individual. Bottles should be removed from the bed and electric blankets switched off before retiring. Loose-fitting bed socks help maintain warmth. Garters should not be used where the circulation of the limb is compromised.

Patients should avoid footwear with pointed toe boxes. This is a frequent cause of impaired circulation in the toes. Hosiery should be free of darns and ridges. Shoes should be inspected before wearing for any roughness, nails, or even foreign bodies that have dropped into the shoe. Neuropathic feet will be insensitive to such problems and may cause significant and serious damage.

Foot health information and preventive strategies for the older patient, particularly with an "at-risk" concern can be found in the *FEET FIRST* and *IF THE SHOE FITS* booklets and videos, available from the Pennsylvania Department of Health, Diabetes Control Program, Harrisburg, PA (USA).

A professional education program entitled *Assessing the Older Diabetic Foot* is also available from the same source (Helfand, 2001).

FOOTWEAR

The treatment and long-term management of foot morbidities cannot be successful without the foot being adequately accommodated in footwear. The shoe or boot must have adequate width, depth, and length, especially in the region of the toes. A lace-up shoe ensures that the foot and shoe are held in the correct relationship as well as having the added virtue that the lace is infinitely adjustable – important where the foot may enlarge because of edema. The Thermold shoe is an example of such a shoe. The Darco Shoe, Hotter, or Walker style is ideal when specific dressing changes are required. High arched feet do sometimes have difficulty with a high lacing shoe. Here a slip-on shoe with an elasticized gusset may be more acceptable. An alternative may be an elastic lace. This is also useful when the patient is unable to tie his/her shoes. A broad heel with a maximum height of 1/5 in. (38 mm) will provide stability. The cobbler, floating it out or flaring the heel on one side or the other to further enhance stability, can modify such a heel (Burns, 2002; Cailliet, 1997).

The upper of boots or shoes should be plain – devoid of fancy stitching or designs, which involve the overlapping of several pieces of the upper material. These all limit the "give" of the material and the footwear fails to mold and accommodate minor foot deformities, such as hammer toes and bunion deformities.

Traditionally, leather has been the best material for the uppers of footwear, but very satisfactory man-made materials can provide lighter and economical made-to-measure footwear for patients with feet deformed by disease or altered in shape as a result of surgical intervention.

Synthetic materials used for the sole and heels of modern footwear have good wearing qualities. Their thickness provides a surface, which is shock absorbing and insulating. Modern manufacturing processes easily produce shoes that are relatively waterproof. Flexion of the first metatarsal-phalangeal joint can be limited by the addition of a steel splint or rocker sole. This can also be helpful in the management of osteoarthrosis of the first metatarsal-phalangeal joint or in incipient rigidity of this joint. Patients should be encouraged to keep all footwear in good repair. Serious injuries to the ligaments of the ankle and subtalar joints are frequently the result of badly worn heels (Helfand, 1995, 1996, 1998).

ORTHOTICS

The prolonged application to the foot of adhesive pads and dressings is undesirable, even with modern hypoallergic adhesives. It is also aesthetically unacceptable. The warmth and moisture resulting from occlusion of the skin may provoke contact dermatitis or infection, particularly in the elderly. Because of the fact that for many elderly patients, correction or cure is not possible, comfort becomes a primary goal. Deformities may need to remain but care should be directed to relieving pain, restoring a maximum level of function, and maintaining that restored degree of pain free activity. Many forms of orthotics are available. Some include the chairside fabrication of silicone molds. Others include devices that can be made to prescription and fabricated from man-made materials of varying thickness and density. Thermoplastic materials may be combined in one orthotic to give cushioning or support or redistribute the pressure load. These are all fabricated to meet the individual needs of individual patients and the presenting condition. The resulting appliance is more desirable and aesthetically more pleasing since it can be removed, cleaned, and utilized in many pairs of footwear (Helfand and Bruno, 1984).

Where patients are unable to fit and remove these devices themselves, relatives or neighbors can help. A molded shoe, made from light microcellular material and able to accommodate the most bizarre deformities is the only other alternative, if need be. Sandals may be a satisfactory alternative also, where the condition and climate are suitable.

KEY POINTS

- Podogeriatrics is that special area of podiatric medical practice that focuses on health promotion, prevention, and the treatment and management of foot and related problems, disability, deformity, and the pedal complications of chronic diseases in later life.
- Foot problems are common in the older population as a result of disease, deformity, complications, and neglect, resulting from a lack of preventive service, at the primary, secondary, and tertiary levels. They contribute to disability and can reduce an older persons independence and quality of life.
- It has been estimated in the United States, that 50%–75% of all amputations relating to the complications associated with diabetes mellitus could be prevented and reduced with an appropriate program of preventive foot care and foot health education.
- Because of the risk involved in the geriatric patient and the relationship to multiple chronic diseases, assessment, examination, and evaluation of the feet of the elderly is essential. Essential as elements of this process include needs, relationships to ambulation and activities of daily living, and the fact that foot pain can result in functional disability, dysfunction, and increase dependency.
- For the older patient, the ability to prevent complications, maintain mobility, and continue to ambulate will be reflected in the quality of life and permit older individuals to live life, to the end of life.

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Hip Fracture and Orthogeriatrics

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BACKGROUND

Fractures affecting elderly people are a major and increasing health problem in the Western world. Over 40% of women and 13% of men will sustain an osteoporotic fracture during their lifetime (Melton *et al.*, 1992). The incidence and cost of osteoporotic fractures will rise by 1% per year – simply as a result of aging of the population (Burge *et al.*, 2001).

Fracture risk is multifactorial and reflects general frailty and falls-risk as much as it does bone fragility. Each year, 8% of women over 85 years of age will suffer a fracture. Hip fracture is the predominant injury in these older women with an annual fracture risk of 4% at the hip compared to 1.5% at the wrist and forearm, 0.6% at the upper arm, and 0.4% each at spine, hand, foot, and ankle (Johansen *et al.*, 1997). People living in residential and nursing homes are at nine times greater risk than the general population (Brennan *et al.*, 2003).

Patient frailty is reflected in the outcome of the injury, with around 10% of people dying in hospital within a month of their fracture. Over one-third of people will die during the year after fracture. The hip fracture can be shown to be responsible for less than half of these deaths (Parker and Anand, 1991), but the patient and their family will often identify the hip fracture as playing a central part in their final illness. A quarter of hip fractures affect residents in institutional care, and the distress of this illness can be compounded by recrimination in respect of failure to prevent the fall and fracture in the first place.

Only half of those who survive hip fracture will return to their previous level of independence. Most who survive the injury can expect to be left with at least some hip discomfort, and around half will suffer deterioration in their walking ability such that they will need an additional walking aid or physical help with mobility. 10–20% of people will need to move to a more supportive residence such as residential or nursing care. Such a move is greatly feared by patients, and in a study of quality of life 80% of elderly women indicated that they would prefer to die, rather than lose their independence as a result of a "bad hip fracture" that required their placement in a nursing home (Salkeld *et al.*, 2000).

Figures vary considerably between units, but length of stay in the orthopedic ward averages between 2 and 3 weeks, and overall hospital stay may average as much as 5 weeks. This leads to a cost of operation and hospital stay of around £7000 per case. The cost of complex home and institutional care for those individuals who make a poor recovery can be very high, leading to a mean cost of medical and social aftercare in the first 2 years of £13 000 and a cost of hip fracture of £20 000 overall (Torgerson and Dolan, 2000).

This profile of mortality, morbidity, loss of independence, and the resulting clinical and financial burden on health and social services underpins the need for effective management of this injury. The complexity of multiprofessional cooperation that is necessary for effective hip fracture care makes this condition an ideal tracer condition for the hospital care of frail and elderly people in general.

DIAGNOSIS

The typical presentation of a patient with a hip fracture is an elderly woman, who has tripped and fallen while walking within her own home (Parker *et al.*, 1997). Her symptoms are pain in the hip and inability to walk. Clinical examination reveals a shortened and externally rotated limb with any attempt at moving the hip-causing pain. The diagnosis is readily confirmed by x-ray.

Unfortunately in about 10–15% of patients the diagnosis is missed or delayed (Pathak *et al.*, 1997). The reasons for this may be:

- patient or carers do not seek medical help
- patients seen by doctor but no xray requested
- x-rays undertaken, but misinterpreted as not showing a fracture

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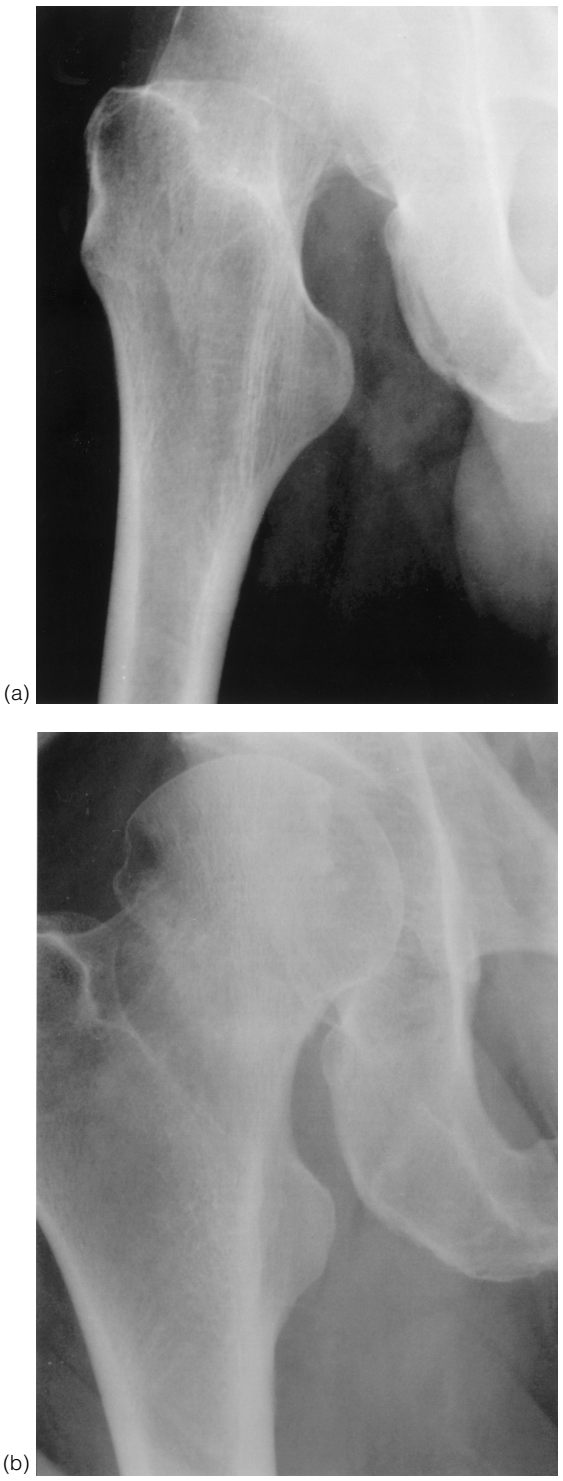


Figure 1 (a,b) An undisplaced intracapsular fracture, which only becomes apparent on an x-ray take in 10° internal rotation

- x-rays of such poor quality such that the fracture was missed
- fracture not visible on x-rays even with hindsight.

Factors contributing to missing the diagnosis include absence of a history of a fall in 5% of patients (Pathak *et al.*, 1997). The fracture may very rarely occur spontaneously or be related to a pathological weakness of the bone. Confusion and dementia may make the history and interpretation of physical finding more difficult. Approximately 15% of fractures are undisplaced which will mean there is no shortening or external rotation of the limb, hip movements, although painful, may be possible, and the patient may even be able to walk, albeit with difficulty. The x-ray changes of an undisplaced fracture may be minimal or even completely absent in about 1% of hip fractures.

Some experience is necessary in interpreting hip x-rays for suspected fractures. Firstly, two views must always be taken; an anterioposterior (AP) and a lateral view. The basic AP view is of the pelvis with hips at the bottom corners of the film. The x-ray beam is not centered on the hip. In addition, for a person with a painful hip, the leg is generally in external rotation. This external rotation means the greater trochanter lies posterior to the femoral neck obscuring details for this area (Figure 1). For an ideal hip AP view, the limb should be in 10 degrees of internal rotation so that the femoral neck is at right angles to the x-ray beam. Such a film will enable a "hidden" fracture to become visible (Figure 1).

No patient can have a hip fracture excluded without a lateral x-ray. The correct exposure of such films may be difficult in order to get good clarity of detail in the femoral neck. For those patients in whom the pelvis and lateral x-rays appear normal but a hip fracture is suspected, a third view is indicated. This is an AP with the film centered on the hip in question with 10 degrees internal rotation.

If doubt about the diagnosis of a fracture persists, additional investigations are indicated. An MRI scan is currently the investigation of choice. Alternative investigations are an isotope bone scan or CT scan of the hip. Another management option is to repeat the x rays after a delay of 1 to 2 weeks. Any invisible fracture or those with minimal radiographic changes will become apparent. The physician must be aware that the presence of apparent normal initial x-rays does not exclude a hip fracture.

In addition to the unnecessary pain caused by missing a fracture, an undisplaced fracture generally displaces if left untreated. The outcome for an undisplaced fracture is better than that for a displaced fracture, particularly if the fracture is intracapsular. Prolonged delays in diagnosis may have devastating consequences for the patient. Treatment for a late diagnosed fracture is more complex, and recovery of function is less likely.

CLASSIFICATION

Once the diagnosis has been established, the fracture may be classified depending on the site of the femur in which the fracture line is predominately located (Figure 2). The blood supply to the femoral head enters along the line of the hip capsule's attachment and this explains the importance of drawing a distinction between intracapsular and extracapsular fractures in terms of diagnosis and management.

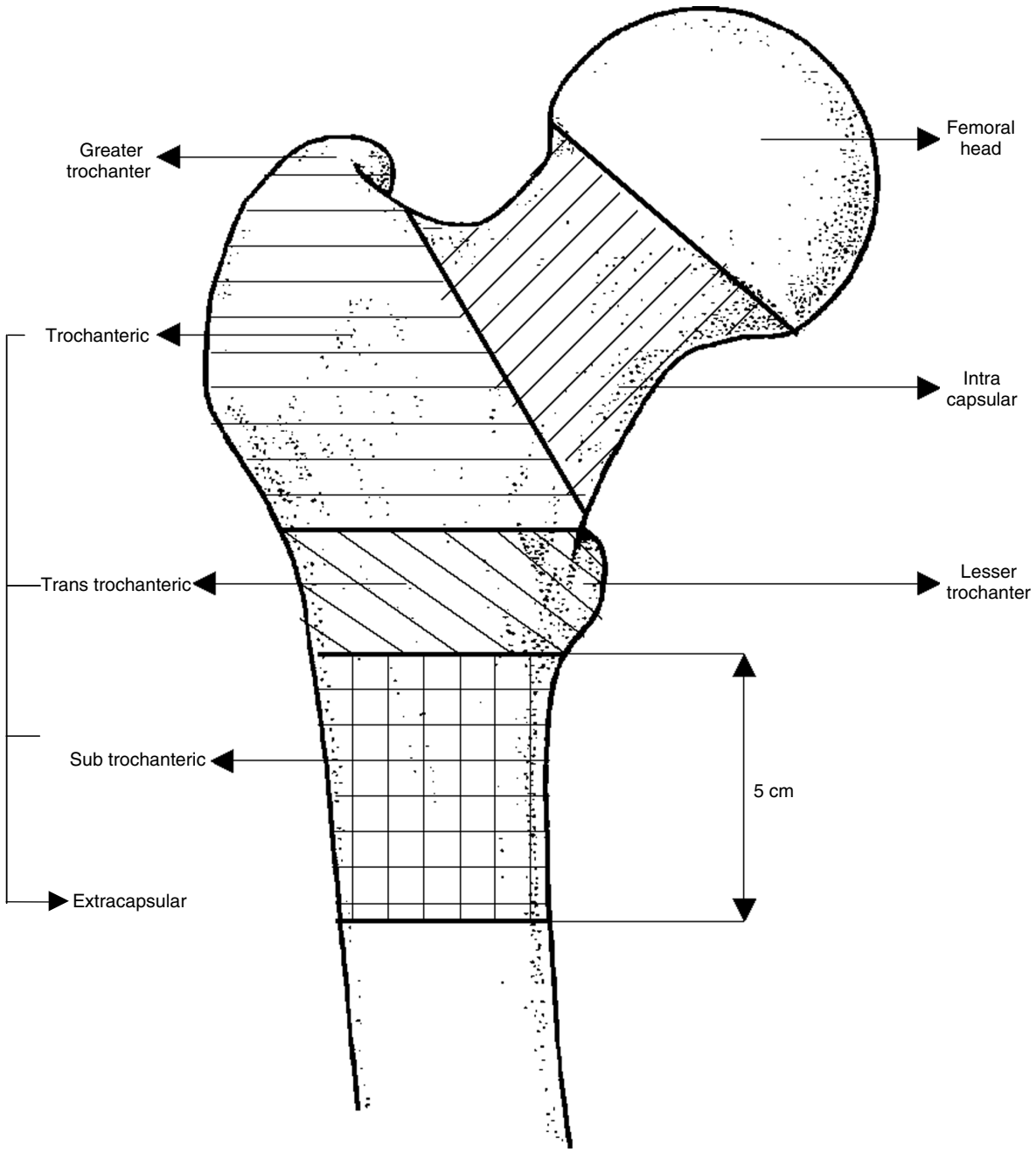


Figure 2 Radiographic classification of hip fractures

Intracapsular fracture may be subdivided into those which are essentially undisplaced (Figure 1) and those which are displaced. Extracapsular fractures are divided into trochanteric and subtrochanteric. Basal fractures are two-part fractures in which the fracture line runs along the intertrochanteric line. These fractures are uncommon and best thought of as two part trochanteric fractures. Trochanteric fractures may be subdivided into two part fractures, which are also termed *stable fractures*, and comminuted or multifragmentary, which may be termed *unstable fractures*. Subtrochanteric fractures are those in which the fracture is predominately in the 5 cm of bone immediately distal to the lesser trochanter.

INITIAL MANAGEMENT

The Cochrane collaboration has considered the published evidence in respect of hip fracture care, and has identified a number of key interventions that can be shown to improve outcome. These include perioperative prophylaxis against infection and thromboembolism, attention to

nutritional supplementation, and secondary fracture prevention. Comprehensive guidelines for the management of hip fracture patients have been published in Scotland (SIGN, 2002), and these are an invaluable summary of the priorities of surgical, anesthetic, and multidisciplinary care.

Fast-tracking Policy and Guidelines

Many casualty departments have fast-tracking policies to speed the patient's progress through the department. A checklist of the following items can be completed:

- diagnosis established
- pressure relieving mattress used
- patient assessed for other injuries and medical conditions
- pain relief as appropriate
- intravenous fluids commenced
- routine bloods taken (FBC, U&E, group and save)
- ECG recorded
- chest x-ray presurgery, if clinically indicated
- transfer to the orthopedic ward without further delay.

Analgesia

The amount of pain experienced after a hip fracture can vary from moderate to severe. Therefore analgesia needs to be tailored to the individual patient. Initially and in the immediate postoperative period opiates still form the mainstay of treatment. These are preferably given orally or intramuscularly. Intravenous opiates may be used, but only with small incremental doses because of the unpredictable response in the elderly. Other analgesia should be paracetamol and codeine phosphate. Nonsteroidal analgesics are an alternative, but older people are at greatly increased risk of gastrointestinal bleeding and renal toxicity. These side effects may be more common in the perioperative period in conjunction with the stress of the fracture and surgery.

A femoral nerve block may be used and repeated as required. Such blocks are effective in reducing pain, but it remains unproven as to what extent they reduce the complications related to analgesia (SIGN, 2002). Traction for a hip fracture prior to surgery is no longer used, having been shown to have no benefit in reducing pain (SIGN, 2002).

Fluid Balance and Resuscitation

At the time of admission to hospital the patient may be dehydrated from lack of fluid intake, particularly if they have been unable to seek help for some time. In addition, there will be a variable amount of blood loss from the fracture site. This loss will vary from a few milliliters for an undisplaced intracapsular fracture to over a liter for a multifragmentary or subtrochanteric fracture. Intravenous saline should be started from the time of admission in casualty; the rate of infusion adjusted according to the estimated blood loss and degree of dehydration.

Pressure Areas

In 1985, it was reported that one-third of hip fracture patients developed pressure sores (Versluysen, 1985). A pressure sore risk assessment is recommended for hip fracture patients (SIGN, 2002). Factors contributing to pressure sores are:

- patient lying on floor at home for a prolonged time;
- delays in the casualty department (a maximum of two hours in casualty has been recommended)
- hard surfaces on the casualty department trolleys
- hard mattresses on the ward
- poor nutrition
- anemia
- delays from admission to surgery
- prolonged surgery
- failure to mobilize the patient immediately after surgery.

Thromboembolic Prophylaxis

The incidence of thromboembolic complication will be determined by how intensively one seeks to identify the condition (*see* **Chapter 55, Venous Thromboembolism**). It seems probable that most patients have some degree of venous thrombosis after a hip fracture, but in only a small proportion does this cause clinical symptoms. If all patients are subjected to venography, the reported incidence varies from 19 to 91% for deep vein thrombosis. Similarly, when routine isotope lung scans are used, between 10 and 14% of patients can be shown to have pulmonary embolism. However, in clinical practice the incidence is much lower with rates of about 3% for venous thrombosis and of about 1% for pulmonary embolism.

The most important methods to reduce the occurrence of thromboembolic complications are:

- early surgery
- avoid prolonged surgery
- immediate mobilization after surgery
- avoidance of overtransfusion.

Cyclic leg compression devices or foot pumps may reduce the incidence of venous thrombosis from 19 to 6% (Handoll *et al.*, 2004). They are, however, quite time-consuming to use and can be expensive. Controversy continues over whether any pharmacological prophylaxis should be given, what is the best pharmacological agent, and the duration of prophylaxis. The incidence of clinically significant thrombosis has declined as a result of earlier surgery and mobilisation. These changes may now mean that the adverse effects of therapy outweigh any benefits from the reduced thromboembolic complications.

Heparins reduced the incidence of venographic thrombosis from 39 to 24%, but in a systematic review of randomized trials (Handoll *et al.*, 2004), overall mortality showed a trend to be increased with heparin (8 vs. 11%). Warfarin, while popular in the United States has not been adequately assessed within randomized trials. Low dose aspirin has been studied in one large randomized trial (PEP Trial, 2000). 28 days

of 150 mg aspirin reduced clinical endpoints of deep vein thrombosis from 1.5 to 1.0%, nonfatal pulmonary embolism from 0.6 to 0.4% and fatal pulmonary embolism from 0.6 to 0.3%. The incidence of wound healing complications was increased in the aspirin group (2.4 to 3.0%), as was gastrointestinal hemorrhage (2.1 to 3.1%). There was no difference in mortality between groups.

Nutrition

Poor nutritional state is a powerful risk factor for hip fracture, and practical problems with feeding and nutrition commonly pose a major threat to recovery following the injury. Many people do not eat and drink adequate amounts while in hospital, putting their health and recovery from illness at risk (*see* **Chapter 24, Epidemiology of Nutrition and Aging**). Dietary insufficiency is a significant problem, with many frail elderly inpatients achieving only half their recommended daily energy, protein, and other nutritional requirements (Duncan *et al.*, 2001). Nutrition is an interdisciplinary concern that requires effective liaison and communication between all members of the clinical and operational services teams. A number of approaches to nutritional support have been studied (Avenell and Handoll, 2004).

The strongest evidence for the effectiveness of nutritional supplementation exists for oral protein and energy feeds, but the evidence is still very weak as the quality of trials to date is poor. Oral multinutrient feeds (providing energy, protein, vitamins, and minerals), evaluated by seven trials, may reduce the risk of death or complications (Avenell and Handoll, 2004). Four randomized trials examining nasogastric feeding showed no evidence for an effect on mortality. The effect of protein in an oral feed, tested in three trials, showed no evidence for any effect on mortality, but may have reduced the number of long-term complications and days spent in rehabilitation wards.

In practical terms it is unrealistic to impose nasogastric feeding as a routine approach to nutritional supplementation, and patients' acceptance of supplement drinks is often poor. It is therefore crucial that all staff dealing with patients recovering from hip fracture understand the importance of adequate dietary intake and that specific attention is given to helping people to eat at meal times. Simple practical measures can be very effective in this respect (Duncan *et al.*, 2002).

FRACTURE REPAIR

Conservative or Operative Treatment

Historically, hip fractures were managed conservatively by traction, bed rest, or "skillful neglect". Clinical studies including some randomized trials have indicated improved outcomes for those treated operatively. This is particularly true for displaced intracapsular fractures, where conservative treatment leads to nonunion of the fracture and a painful hip of limited function. With the appropriate medical facilities and surgical and anesthetic expertise, the vast majority of hip fractures will be managed surgically.

Undisplaced intracapsular fracture may be treated conservatively with a regime of bed rest followed by gentle mobilization. The risk of nonunion of the fracture treated conservatively is about 30 to 50%. This falls to about 5–10% after internal fixation. Nonunion generally requires treatment with a replacement arthroplasty; therefore most surgeons elect to treat this type of fracture surgically by internal fixation.

For displaced intracapsular fractures, nonunion is inevitable after conservative treatment. This means that the hip cannot be used for weight bearing and is generally painful on all movements. Conservative treatment may be employed for those with very limited life expectancy or the immobile, but even for those of limited mobility, surgery is useful to relieve pain and provide a limb that can be used for limited walking or transfers (Hay and Parker, 2003).

Extracapsular fractures may be managed conservatively using traction. Traction will reduce the fracture, enabling it to heal in a reasonable position. Conservative treatment will inevitably result in a markedly increased hospital stay and an increase in the number of patients who are unable to return back to their original residence, in comparison with operative treatment (Hornby *et al.*, 1989). Conservative treatment for extracapsular fractures is therefore recommended for only those patients of a very limited life expectancy, those who refuse surgery, and in the absence of appropriate surgical facilities.

The presence of specialized medical staff in the acute orthopedic ward is of benefit in improving preoperative medical assessment so that surgery is not unnecessarily delayed. Many frail older people presenting with hip fractures will need to undergo surgery while their medical state remains suboptimal. The decision as to whether hip fracture surgery can go ahead is not the same as that appropriate for elective orthopedic surgery, where postponement carries little risk to the patient's long-term functional outcome and survival. In the setting of hip fracture the question is whether there is anything that can be done that will immediately improve the patient's operative risk so that surgery can go ahead. Judgment of whether surgery is appropriate despite the presence of acute and chronic medical problems can be difficult, and is eased by the involvement of clinical staff familiar with the assessment and treatment of older people.

Operative Care

Undisplaced Intracapsular Fractures

Undisplaced intracapsular fractures, as illustrated in Figure 1, may be managed conservatively as discussed earlier, but to reduce the risk of the fracture displacing, internal fixation is recommended. This is a relatively minor surgical procedure, which can even be undertaken using local nerve blocks

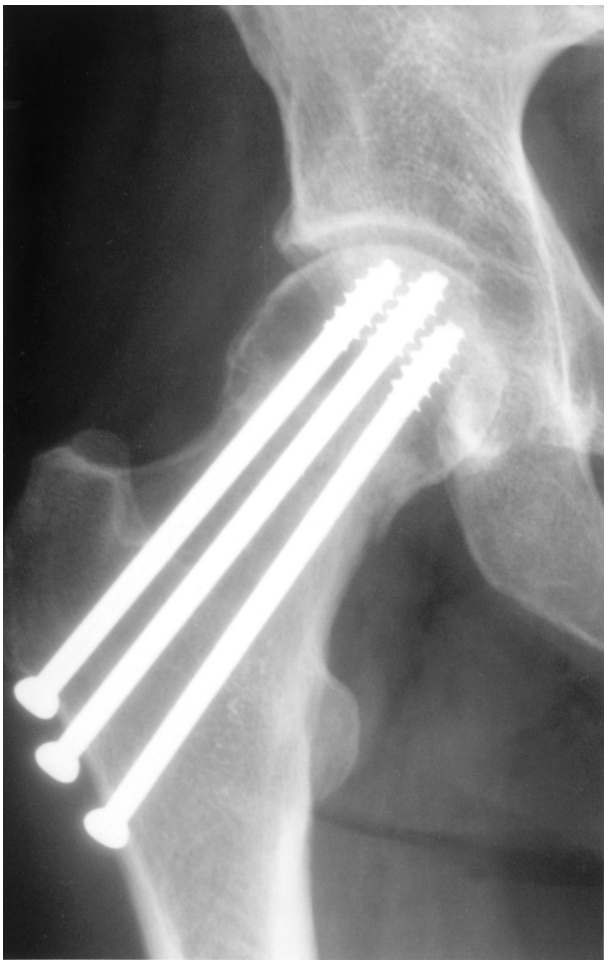


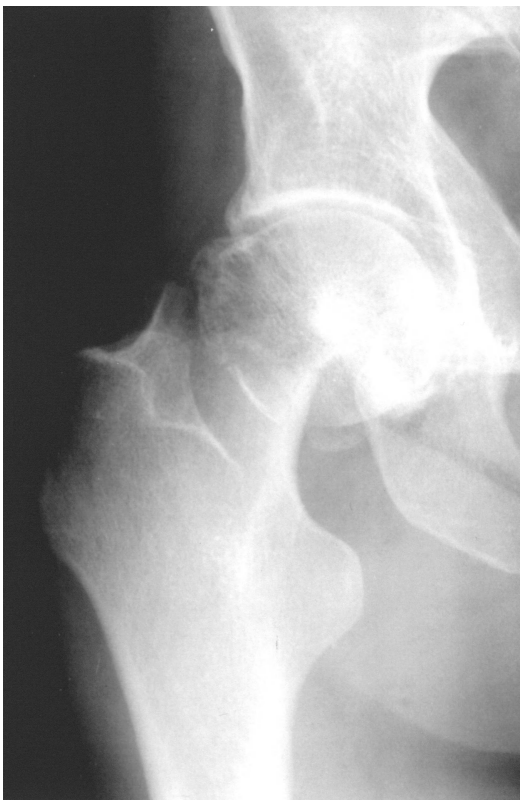
Figure 3 An intracapsular fracture fixed with three screws

and a percutaneous procedure. There are many different implants used, the most frequently used being two or three parallel screws (Figure 3) or a sliding hip screw (SHS). Postoperatively, most patients recover quickly with hospital stays of 7–10 days. Arthroplasty is not an appropriate method of treatment for this fracture type because of the increased surgical trauma and risk of postoperative complications.

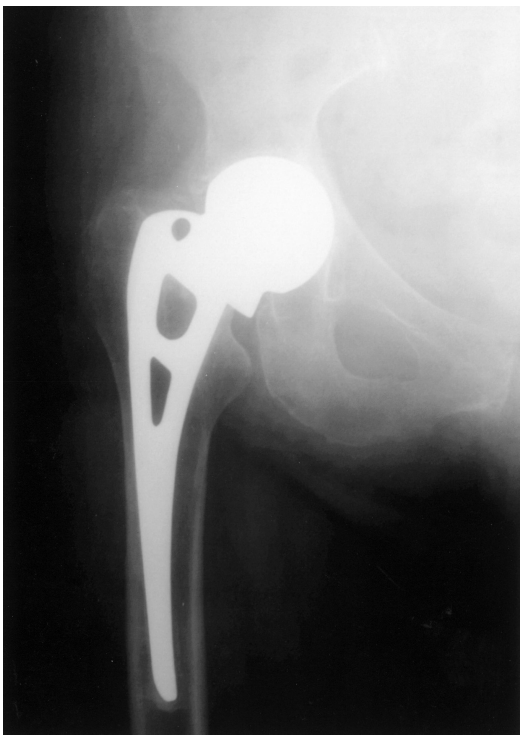
Displaced Intracapsular Fractures

Surgical management of this fracture is either by internal fixation as illustrated in Figure 3 or using an arthroplasty (Figure 4). The main advantages and disadvantages of internal fixation and their approximated incidences of complications are:

- patients are able to retain their own femoral head
- less surgical trauma giving marginally lower mortality and morbidity
- low risk of wound sepsis (up to 1%)
- low risk of wound hematoma (1–2%)
- risk of nonunion incurred (20–33%)



(a)



(b)

Figure 4 (a,b) A displaced intracapsular fracture treated with an uncemented Austin Moore hemiarthroplasty

- risk of avascular necrosis incurred (10–20%)
- risk of fracture around the implant (1–2%)
- markedly increased reoperation rate (20–36%).

For arthroplasty the advantages and disadvantages are:

- lower reoperation rate (6–18%)
- larger surgical procedure than internal fixation
- increased risk of deep infection around the implant (3%)
- increased risk of superficial wound infection (5–15%)
- increased risk of wound hematoma (2–5%)
- risk of dislocation incurred (2–5%)
- risk of fracture around implant (1–3%)
- later risk of prosthesis loosening (2–10%)
- later risk of acetabular wear (4–20%).

The main factor influencing choice of treatment is the risk of nonunion. Factors that will increase this risk are delays from fracture occurrence to fixation, pathological lesions of the bone such as tumor or Paget's disease, metabolic bone disease, and rheumatoid arthritis. Table 1 details the recommended treatment methods for the different situations.

Considerable controversy still exists about the optimum choice of treatment for an elderly patient with a displaced intracapsular fracture. By "elderly" one is referring to someone of around the age of 70 years, although others may choose a more functional assessment such as, an elderly patient is one who has some restriction in mobility or activities of daily living. The Cochrane review on this topic (Masson *et al.*, 2003) concludes that both treatment methods produce similar final function results of pain and regain of function. Internal fixation has a tendency to a lower mortality but an increased reoperation rate.

If arthroplasty is chosen as the method of treatment, a "partial" hip replacement may be used with only the femoral head being replaced (hemiarthroplasty) (Figure 4). Alternatively, a total hip replacement can be used, in which the acetabular articular surface is also replaced. The hemiarthroplasties entail a less complicated surgical procedure than a total hip arthroplasty and have a lower risk of dislocation. Therefore, they tend to be preferred to a total hip arthroplasty for the frail elderly patient, but controversy still exists about the final functional results and later requirement for revision surgery. The limited randomized trials to date on this topic have been summarized in a Cochrane review on this topic (Parker and Gurusamy, 2004).

An arthroplasty may be either cemented in place or uncemented as a press fit. No clear consensus exists which is better. Cementing does add the possibility of additional operative problems and should a later revision arthroplasty be necessary, it is more difficult for a cemented implant. However using cement may make the hip less painful with better function (Parker and Gurusamy, 2004).

Table 1 Possible treatment methods for displaced intracapsular fractures

	Internal fixation	Arthroplasty
Rheumatoid arthritis	Occasionally	Generally
Delay in treatment	Rarely	Generally
Pathological fractures	Rarely	Generally
Chronic renal failure	Rarely	Generally
Metabolic bone disease	Rarely	Generally
Arthritis of joint	Rarely	Generally
Paget's disease	Never	Always
Age less than about 70 years	Generally	Rarely
Age more than about 70 years	Occasionally	Generally

Trochanteric Fractures

A variety of implant are available for the treatment of this fracture. The SHS remains the foremost implant and should be regarded as the gold standard (Figure 5). It is also termed the *dynamic hip screw, compression hip screw* or *Abmi hip screw*. Numerous case series reports and randomized trials have all demonstrated the superiority of this implant over other designs. The more recently developed implants are the short intramedullary nails, which have shown considerable developments over the last 10 years. These include the Gamma nail, intramedullary hip screw (IMHS), proximal femoral nail (PFN), Holland nail, and Targon nail. Comparisons of these implants against the SHS have been made in numerous randomized trials, the summary of which showed an increased risk of fracture-healing complications (7.5 vs. 3.6%) and an increased reoperation rate (5.6 vs. 3.5%) for the nails (Parker and Handoll, 2004). The main problem with the nails was the occurrence of fractures at the tip of the intramedullary nails, and it may be that future modification to the design of these nails will reduce this complication.

Subtrochanteric Fractures

These fracture are less common accounting for about 5–10% of all hip fractures. They present a considerable challenge to the surgeon as the high mechanical forces in this area of bone leads to an increased risk of fixation failure. The SHS remains an acceptable method of treatment for this fracture, but is a technically difficult surgical procedure and requires an extensive surgical exposure. An alternative method of treatment is using an intramedullary nail (Figure 6). This method of treatment is currently becoming more extensively used as the design of these nails and instrumentation to accompany them continues to improve.

POSTOPERATIVE CARE

After surgery, it should be normal practice to sit the patient out of bed and begin to stand the patient on the day after surgery. After this, progress will vary considerably and will depend on each individual patient and the type of their fracture. Patients with an extracapsular fracture will tend to take longer to mobilize than those with intracapsular fractures.

Weight Bearing

With current surgical techniques and implants, there should be very few occasions in which weight bearing is restricted.

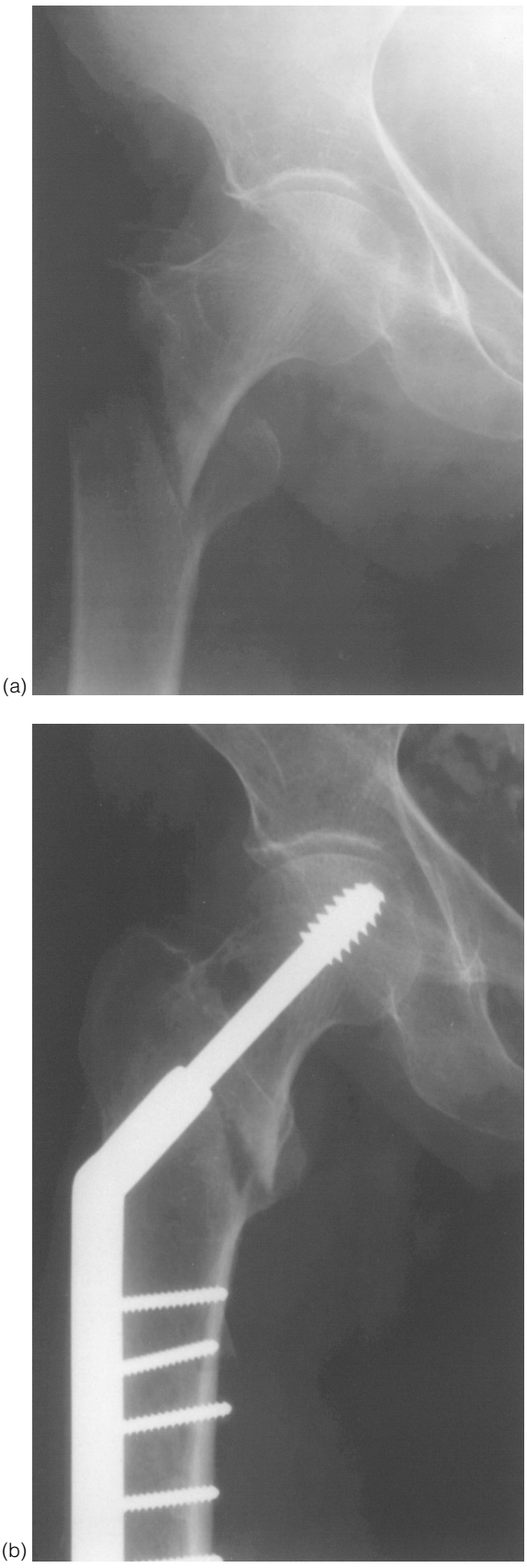


Figure 5 (a,b) A trochanteric fracture fixed with a sliding hip screw

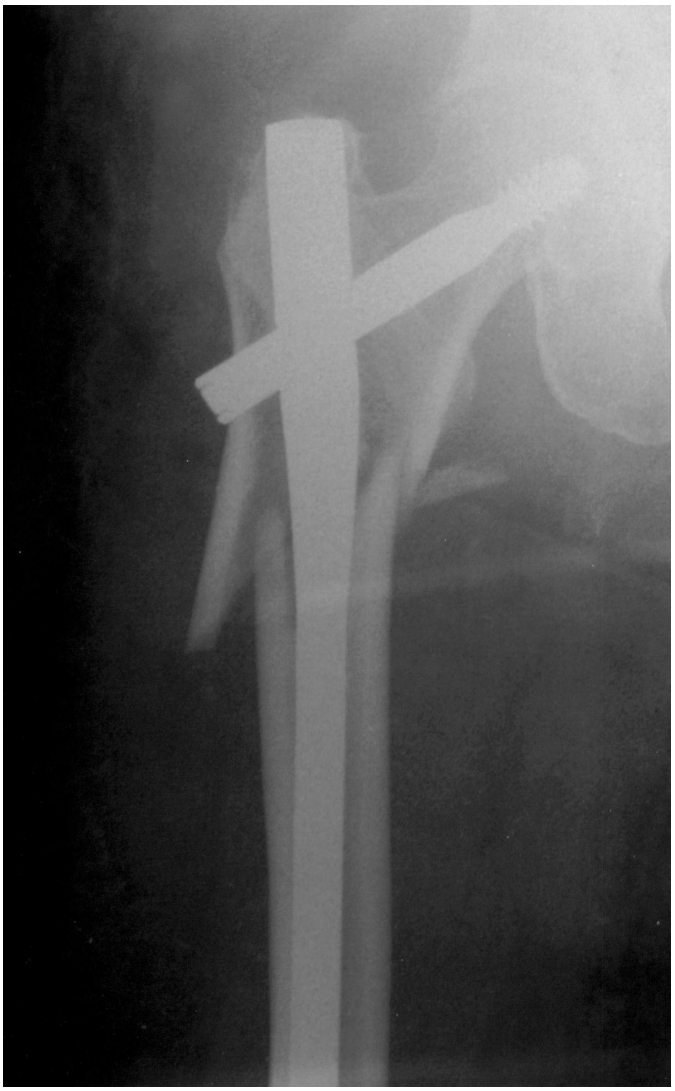


Figure 6 A subtrochanteric fracture fixed with an intramedullary nail

Most elderly patients who sustain a hip fracture will be unable to comply with any weight bearing restriction and certainly not the difficulties of walking "non-weight bearing". In practice, most patients will bear weight as pain tolerates, then become fully weight-bearing as the fracture heals.

Hip Movements

Traditional practice was to restrict hip flexion after an arthroplasty. This was to reduce the risk of prosthetic dislocation. This meant the patient required a raised bed and chairs, and was restricted from getting in and out of a car or bath. Such measures are still used for a total hip replacement, but for a hemiarthroplasty, should no longer be necessary. Refinements in surgical techniques with a more careful repair of the hip joint capsule reduce the risk of dislocation, and should make any restrictions on hip movements unnecessary.

Surgical Complications

Wound Healing Complications

Wound hematoma are the most common form of wound healing complication with an incidence of about 2–10%. Varying definitions of what constitutes a hematoma lead to differences in incidence, with some degree of bruising to be expected for all wounds. Small hematomas can be allowed to resolve spontaneously but larger collections will require surgical drainage.

Deep wound infection is the most devastating of complications that may occur after surgical treatment of a hip fracture, with a mortality approaching 50%. It is defined as infection of the wound below the level of the deep fascia and invariably involving the implant used. The incidence varies from about 1–5%, being somewhat higher after arthroplasty than after internal fixation of fracture. Treatment generally involves surgical debridement and often removal of the implant. This may mean that the patient is left with a "Girdlestone" hip – without a femoral head. A younger patient may be able to regain some degree of mobility with walking aids, but this is unlikely of older, frailer patients.

Superficial wound sepsis refers to infection of the wound that does not extend below the deep fascia layer. It is more common than deep sepsis but can be more effectively treated with antibiotics and, if indicated, with surgical debridement.

Internal Fixation of Intracapsular Fractures

The most common complication after this operation is failure of the fracture to heal (Figure 7). This may be seen as displacement of the fracture, which can occur within days or weeks of the fracture being treated. This is also termed *redisplacement of the fracture*. The terms *nonunion, pseudoarthrosis* or *delayed union* are generally used for those fractures that fail to heal after a period of a few months. Avascular necrosis or late segmental collapse refers to collapse of the femoral head due to insufficient blood supply (Figure 8). It normally occurs after 1 to 2 years of the fracture. Treatment of these complications is generally a replacement arthroplasty, although for a younger patient in whom there is a desire to retain the femoral head, various bone osteotomies or revascularization procedures may be used.

Other complications of internal fixation are irritations of the local tissues by the implant backing out into the local tissues. The patient may complain of pain around the implant and inability to lie on that side or of clicking around the hip. There will be local tenderness over the implant. Treatment is the removal of the implant.

Arthroplasty

Progressively increasing pain or reducing mobility after an arthroplasty may be due to one of a number of complications. Loosening of an arthroplasty is reported in about 2–30% of cases and is much more common after an uncemented implant (Figure 9). The incidence is lower for cemented prosthesis and in those patients with limited functional demands or life expectancy. Treatment is by revision arthroplasty if symptoms are sufficiently severe. Acetabular wear can only occur after a hemiarthroplasty (Figure 10), as the acetabulum is resurfaced with a total hip replacement. Reported incidence varies from 5 to 50%, depending largely on the length of follow-up and is strongly related to the activities of the patient. Treatment is again by revision arthroplasty.

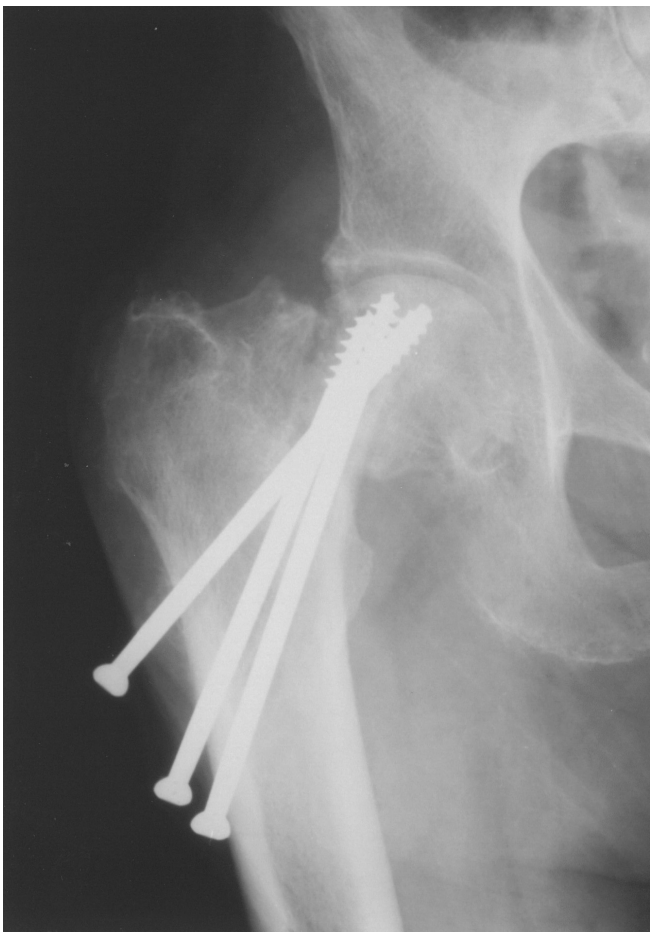


Figure 7 Redisplacement of a displaced intracapsular fracture that had been reduced and fixed with three screws

Other complications of arthroplasty are refracture around the implant which occurs in 1–5% of patients, generally after another fall. Treatment may be conservative with bed rest, bracing, traction, or alternatively operatively with either fixation of the fracture or replacement of the arthroplasty.

Sliding Hip Screw Fixation and Intramedullary Nail Fixation of Extracapsular Fractures

The most common surgical complication after this operation is cutout of the implant from the femoral head (Figure 11). The implant may protrude into the surrounding tissue or penetrate into the acetabulum. Symptoms will be increasing pain and impaired mobility. Treatment depends on the degree

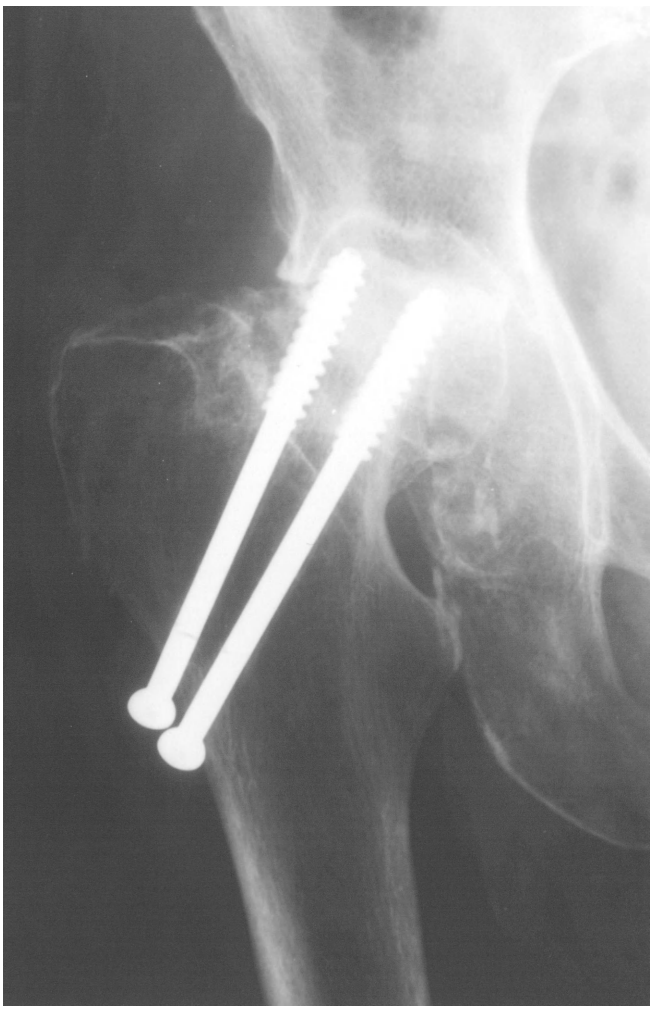


Figure 8 Avascular necrosis of the femoral head occurring after an intracapsular fracture

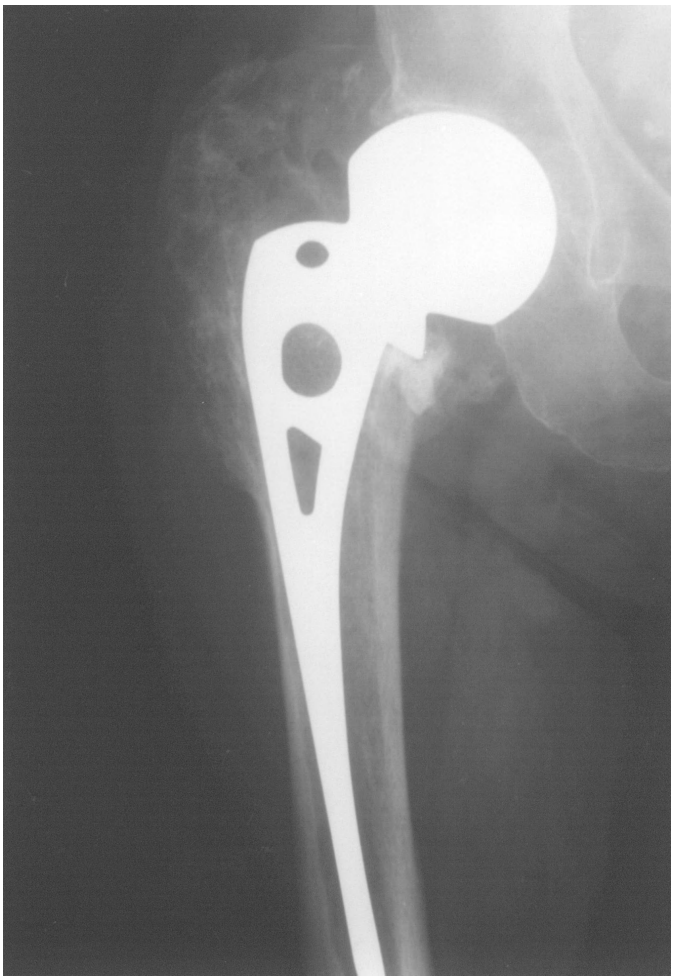


Figure 9 Loosening of an uncemented Austin Moore prosthesis. There is an area of radiolucency around the tip of the prosthesis. In addition, the prosthesis has sunk within the femur and there is ectopic calcification in the tissues around the hip joint

of the symptoms and fitness of the patient to undergo what may be a major revision surgery. Surgical treatment may be refixation of the fracture, replacement arthroplasty, or simple removal of the implant.

Other complications of SHS fixation are breakage of the implant, detachment of the plate from the femur, refracture around the implant, fracture below the implant, or nonunion of the fracture. All these complications may be treated by surgical methods. For subtrochanteric fractures, cutout of the implant is less common but for nonunion of the fracture, it is more common. The complications of intramedullary nail fixation are essentially the same as that of a SHS except that fracture around the tip of the nail is a specific complication related to nails, with an incidence of about 1–2%.

MEDICAL CARE

The management of older people with a fracture is increasingly recognized as an area requiring collaboration between the orthopedic surgeon, the geriatrician, and the multidisciplinary team on the trauma unit. The frailty of the elderly people who suffer a hip fracture means that their inpatient medical care is quite comparable to that of patients in a geriatric medical ward. There is a strong case for all patients admitted with this injury being assessed in respect of the four "giants of geriatrics" – falls, immobility, confusion, and incontinence. These commonly pose practical challenges to staff dealing with a patient with a hip fracture, and all four are recognized risk factors for poor outcome following this injury, as well as being risk factors for the development of the hip fracture, and for subsequent further fractures.

Apart from the ongoing surgical element of care described previously, the predominant way in which care differs from that on a geriatric medical ward is in patients' need for attention to secondary fracture prevention.

Secondary Fracture Prevention

The vast majority of older people admitted to a trauma ward, and nearly all of those admitted with hip fracture will have

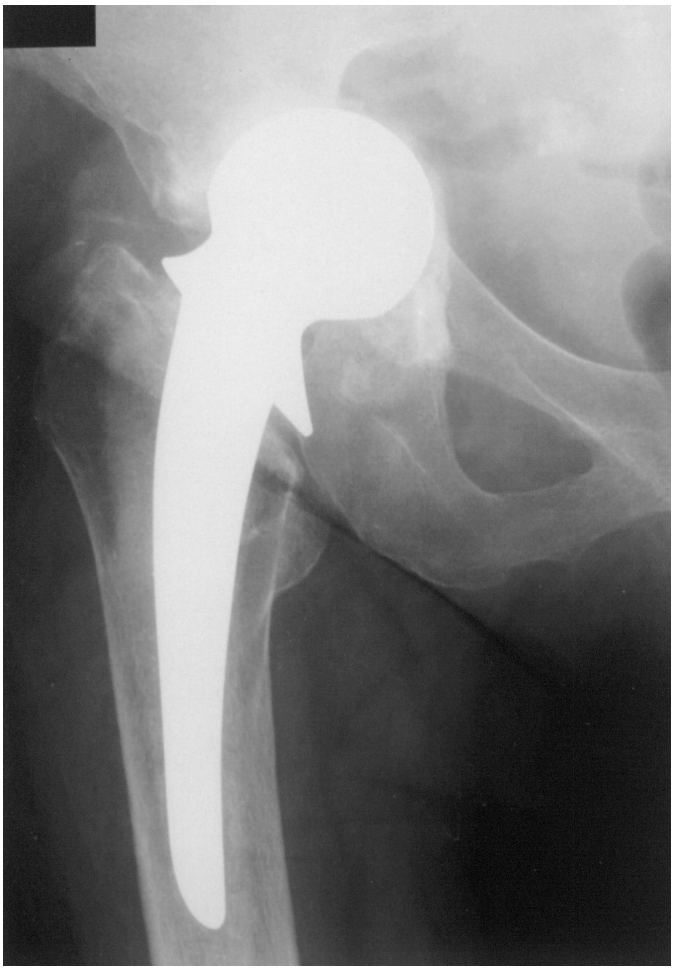


Figure 10 Acetabular wear of a cemented Thompson hemiarthroplasty. The prosthesis is eroding into the pelvis

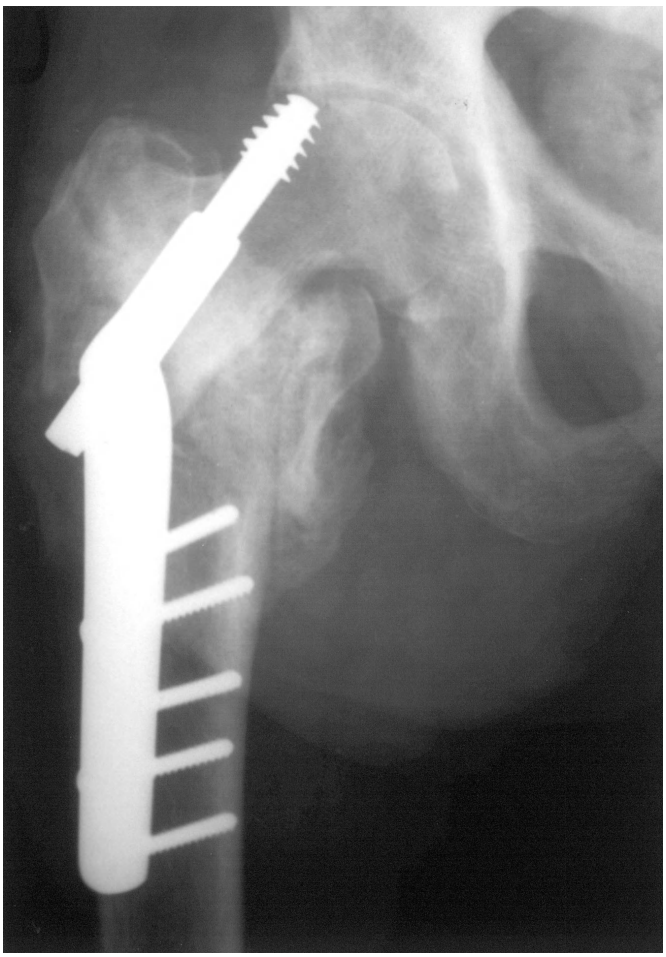


Figure 11 Cut-out of a sliding hip screw fixation of an unstable trochanteric fracture

sustained a "fragility" fracture (Johansen *et al.*, 1999) – a fracture resulting from only moderate trauma, usually a fall from standing height or less.

This implies that bone fragility and osteoporosis is contributing to the etiology of most hip fractures, and all people presenting with hip fracture in such circumstances need assessment of their risk of future fracture.

Hip fracture can be considered as the consequence of three factors:

- a fall leading to a fracture
- an impact that exerts stress on the hip
- a fragile bone.

The evidence for effective approaches to hip fracture prevention reflects this threefold causation with falls assessment, hip protection, and osteoporosis management each potentially playing a part.

Falls Assessment

It is beyond the scope of this article to try and look at falls assessment in depth. The complexity of the subject reflects its multifactorial nature, and the multidisciplinary approach necessary to its management (*see* **Chapter 112, Gait, Balance, and Falls**). However, optimal approaches to falls assessment are increasingly well defined, with international consensus as to the crucial elements of effective fall prevention (American Geriatrics Society, 2001). These guidelines argue for the assessment of all patients who have presented with a fall, or who exhibit gait and balance problems with a past history of falling (Figure 12). Nearly all patients with hip fracture will meet one or both of these indications, and so falls assessment should be made a routine part of their inpatient care.

A familiarity with this document is vital to any clinician involved in care of patients with hip fracture.

Many of the recommended elements of effective falls assessment will automatically form part of the rehabilitation process, with different members of the multidisciplinary team focusing attention on:

- gait and balance disorders
- optimization of mobility
- appropriate walking aids and footwear

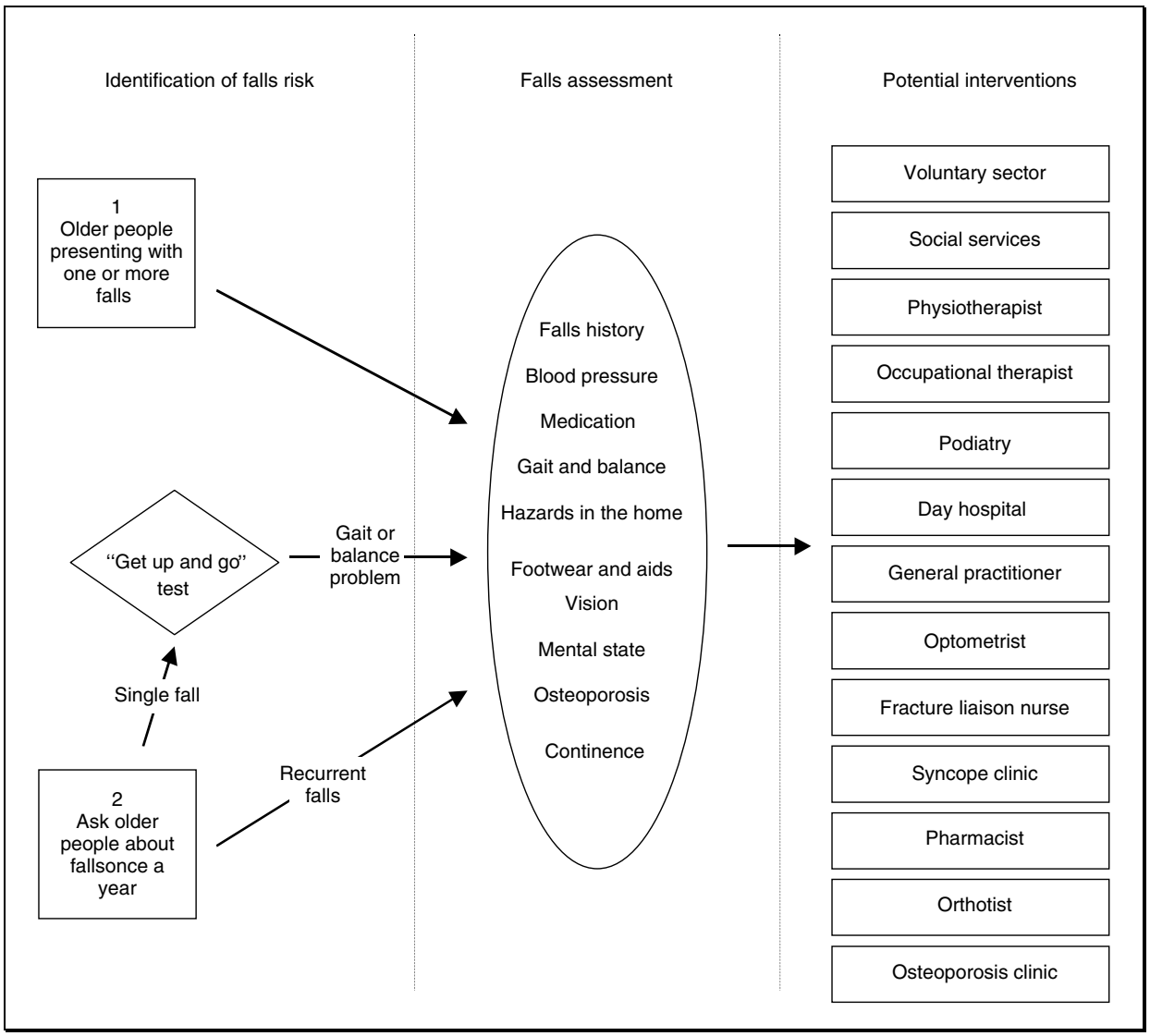


Figure 12 Falls assessment algorithm

- home environmental hazard modification
- assessment of vision, cognition, and continence.

A small proportion of patients will require specialist assessment, and the geriatrician is well placed to try and ensure that appropriate patients are triaged to specialist attention – for instance, in syncope and osteoporosis clinics.

A majority of patients will not need such specialist attention, but to complement the multidisciplinary issues listed, specific medical attention should be given to:

- assessment of the fall or falls that precipitated the fracture
- hip protection
- osteoporosis management
- medication review.

Most falls are simple accidents, with slips and trips resulting from gait and balance as the second commonest cause of hip fractures. Cardiovascular causes of falls are less frequent with hypotension, orthostatic hypotension, carotid sinus hypersensitivity, and vasovagal syncope predominating over cardiac arrhythmias (*see* **Chapter 83, Abnormalities of the Autonomic Nervous System**).

A detailed history of the circumstances leading to the fall including enquiry into previous falls is vital, as the description of the fall will allow examination and investigation to be most effective.

Where a medical cause of falls is suspected, the history is often suggestive of a specific diagnosis. Attention to medication history, examination including lying and standing blood pressure measurements (once the patient has recovered from postoperative hypovolemia), and a 12-lead ECG are most profitable. Such an approach will establish the cause for falls in a large proportion of patients presenting with hip fracture, so that more complex investigations such as 24-hour

ECG monitoring and echocardiography are relatively rarely needed.

Hip Protectors

It is recognized that a fall is less likely to lead to a fracture if it occurs on a carpeted surface, and it is possible that absorption of the force of impact may be effective in preventing a fracture.

Hip protectors are devices that are either based on a rigid exterior shell, or employing some form of foam laminate – integrated into underclothing so that they lie over the hip to protect the bone from the impact of a fall. There is no evidence of effectiveness of hip protectors from studies in which randomization was by individual patient within an institution, or for those living in their own homes.

Data from cluster randomized studies indicate that, for those living in institutional care with a high background incidence of hip fracture, a program of providing hip protectors appears to reduce the incidence of hip fractures. Acceptability by users of the protectors remains a problem due to discomfort and practicality. Cost-effectiveness remains unclear (Parker *et al.*, 2003).

These devices are of particular relevance to patients whose rehabilitation is impaired by anxiety over their risk of suffering a further fall and fracture and to patients who are at risk of repeated falls because of confusion and restlessness.

Osteoporosis Assessment

If a hip fracture results from "low trauma" (trauma no greater than a fall from a standing height), then this is suggestive of underlying bone fragility. Osteoporosis is by far the commonest underlying cause. Only 2–3% of hip fractures are "pathological", the majority of these reflecting metastatic disease, with only a very small proportion resulting from primary bone tumors, bone cysts, or Paget's disease.

Attention to the assessment and management of osteoporosis should be routine, following any low-trauma hip fracture. Strategies should be as inclusive as possible so that the frail and confused patients who are at highest risk of further falls and fractures are not excluded from receiving secondary prevention.

Results of trials specifically addressing the secondary treatment of osteoporosis after hip fracture are still awaited, but evidence from other clinical settings would support attention to the use of calcium and vitamin D status. Deficiency of sunlight exposure and dietary calcium is common among older people and can lead to secondary hyperparathyroidism, osteoporosis, and perhaps an increased risk of falls (Bischoff *et al.*, 2003). In a placebo-controlled study, the use of a daily supplement offering 1.2 g calcium and 800 IU vitamin D_3 led to a 28% reduction in hip fractures among elderly, mobile women living in residential care (Chapuy *et al.*, 1994).

Part of any approach to the secondary prevention of hip fracture should be to extrapolate these findings – and to offer calcium and vitamin D supplementation to frail older people who present with a low-trauma hip fracture, if they are expected to be house bound or institutionalized in the future.

These supplements are well tolerated, but should be avoided in patients known to have primary hyperparathyroidism, sarcoidosis, urinary calculi, and metastatic malignancy or myeloma. It is prudent to check that patients' serum calcium is not elevated before starting such supplementation to avoid precipitating hypercalcemia in patients with unrecognized hypercalcemia.

Calcium and vitamin D supplementation is unlikely to be effective in more younger and fitter patients who are not expected to be house bound and who already have an adequate calcium intake (broadly equating with consumption of a pint of milk a day). However, routine consideration of the need for supplementation is still important in these individuals, as correction of calcium and vitamin D deficiency is necessary before antiresorptive osteoporosis treatments are considered.

In the secondary prevention of low-trauma hip fracture, the first-line antiresorptive agent should be an oral bisphosphonate such as alendronate or risedronate (NICE, 2005). These agents are highly effective and have been shown to halve the risk of future fracture in patients with osteoporosis.

These drugs are usually taken as a single tablet once a week. Gastrointestinal intolerance is not uncommon, and the drugs should be taken first thing after getting up in the morning, washed down with a glass of tap water to minimize the risk of nausea, dyspepsia, and oesophageal pain or dysphagia. Effective absorption of the drug requires that no food, drink, or other medication is taken for at least half an hour after the tablet. Many patients with hip fracture will be unable to remember or cope with this prescription regime, unless appropriate supervision is available.

Consideration of bisphosphonate therapy usually requires assessment of bone mineral density to be undertaken (Royal College of Physicians, 1999; Eastell *et al.*, 2001). However, three-quarters of hip fracture patients are women, and their mean age is 83 years. An 83-year-old Caucasian woman with average bone density for her age would be expected to have a T-score of around -2.5, the WHO threshold for the diagnosis of osteoporosis. Thus, nearly half of this patient population would be predicted to have osteoporosis simply on the basis of their age, even before taking into account the additional risk demonstrated by the hip fracture itself.

The National Institute for Clinical Excellence has demonstrated that confirmation of osteoporosis is unnecessary in the over-75-year-old women who make up the majority of presentations with low-trauma hip fracture (NICE, 2005). These women should be offered a bisphosphonate without measuring their bone density. Bone densitometry should be performed in younger postmenopausal women and in men, as in these people bisphosphonate therapy is less cost-effective, unless a T-score of less than -2.5 has been confirmed.

Consideration should be given to the exclusion of other disease that will cause osteoporosis, especially if clinical

assessment, operative findings, or a low Z-score on bone densitometry indicate greater bone fragility than would be expected for the patient's age. This is especially important in men where an underlying cause can be identified in half of the individuals. Clinical assessment might include questioning alcohol intake, breast examination, and screening investigations such as blood count, urea, electrolytes, liver and thyroid function tests, parathyroid hormone, serum and urine electrophoresis, with prostatic specific antigen and testosterone levels in men (*see* **Chapter 15, Alcohol Use and Abuse**).

Patients with moderate or severe renal impairment will not necessarily benefit from vitamin D supplementation and should not be given bisphosphonates. Activated vitamin D in the form of calcitriol (Tilyard *et al.*, 1992) or α-calcidol could be considered in these circumstances. Such drugs can be also used as second-line antiresorptive agents in patients who are unable to take a bisphosphonate for other reasons. Selective oestrogen receptor modulators (SERMs) are another form of second-line antiresorptive agent (NICE, 2005), but their use increases the risk of thromboembolism, making them unsuitable for use in the acute trauma setting.

One strategy for the secondary prevention of low-trauma fracture is the appointment of a specialist "fracture liaison" nurse. Though much of their work will be focused on the fracture clinic, they can also visit trauma wards to identify and assess low-trauma fracture patients, give advice, and arrange bone densitometry when appropriate. They will then follow up patients with the results of densitometry to advise on secondary prevention including the use of antiresorptive therapy where indicated. A clinician should report the scan, and availability of specialist clinic follow-up for more complex cases is clearly necessary to support such a nurse-led approach. Such an approach is superfluous if the geriatrician is routinely involved in hip fracture aftercare, as the management of osteoporosis will then be a routine part of comprehensive patient assessment.

Medication Review

Over a third of patients exhibit features of acute or chronic cognitive impairment and their medical history is often difficult to elicit. In such circumstances it is important to seek a collateral medical and medication history, and a phone call to the GP surgery will quickly elicit a drug list that can indicate relevant and unrecognized medical comorbidity. Many falls and fractures are a reflection of complex, often inappropriate polypharmacy, and a review of medication must be performed at an early stage of patient assessment.

The necessity for antipsychotic, sedative, hypnotic, and antidepressant therapy needs to be addressed alongside assessment of the patient's mental state. Such drugs may have been started during an acute upset in the past, and may have been continued unnecessarily. A period of observation in hospital offers the opportunity to assess the consequences of their withdrawal. Such drugs are associated with an increased risk of falls, and the inappropriate use of sedating medication will slow patients' rehabilitation and recovery.

Medical assessment should similarly include a review of the indication for vasodilator and diuretic therapy. Hypotension is common around the time of surgery, but persistent hypotension or postural hypotension in the postoperative period may necessitate a reduction in antihypertensive, antianginal or antifailure therapy.

Nonsteroidal therapy should be avoided in the perioperative period because of the increased risk of renal impairment and gastrointestinal bleeding during a period of stress and hypotension. Steroid therapy, anticonvulsant, and thyroid treatments can all be indicators of increased osteoporosis risk, and should be noted while previous and future osteoporosis treatment is being considered.

MODELS OF ORTHOGERIATRIC COLLABORATION

In addition to the medical aspects of hip fracture, many patients fear that the diagnosis of a hip fracture will lead to either death or loss of independence. Adequate information supported by a patient information booklet on the proposed treatment and outcome is useful to the patient. Planning for discharge of the patient back home should start from the time of admission.

Since the original descriptions of the benefits of collaboration between orthopedic surgeons and geriatricians in the 1960s (Irvine and Devas, 1963; Clarke and Wainwright, 1966), most trauma services in the United Kingdom have moved to develop at least some form of formal geriatrician input into the care of older inpatients recovering from fractures. A number of models of orthogeriatric care can be defined, but in general these are variations on the following four approaches.

Traditional Orthopedic Care

The elderly fracture patient is admitted to a trauma ward and the orthopedic surgical team manage their care and subsequent rehabilitation. Geriatrician input to such wards can take a variety of forms. In some units medical queries are dealt with by a consultative service, but in others there is regular input including weekly geriatrician visits.

Geriatric Orthopedic Rehabilitation Unit

Perioperative management by the orthopedic team is followed by early postoperative transfer to a geriatric rehabilitation unit, often between 5 and 10 days. The identification of appropriate patients may be left to orthopedic staff, or it may be led by specialist liaison nurses (Blacklock and Woodhouse, 1988), or be part of routine geriatrician rounds of the acute trauma wards.

The extent of orthopedic input to the rehabilitation ward also varies, depending on how early patients are moved from

the acute trauma wards. Easy access to orthopedic surgical advice is necessary if momentum in rehabilitation is to be maintained. A weekly surgeon visit at a predictable time will allow all members of the multidisciplinary team to present concerns, problems, and x-rays.

Combined Orthogeriatric Care

The fracture patient is admitted to a specialized orthogeriatric ward under the care of both geriatricians and orthopedic surgeons. Surgical and geriatrician ward-rounds may happen independently, or be combined in weekly or twice-weekly multidisciplinary ward rounds. This degree of collaboration is central to the concept of a Geriatric Hip Fracture Service, with preoperative patient assessment by the geriatric medical team who will take the lead in postoperative multidisciplinary care. Rehabilitation may occur in this setting or in a separate rehabilitation unit.

Early Supported Discharge and Community Rehabilitation

Increasingly, community rehabilitation schemes are being implemented which help more able hip-fracture patients to be discharged directly home from the orthopedic ward. Earlier discharge may be facilitated by referral to a geriatric day hospital or a community rehabilitation team. Multidisciplinary assessment including contribution from the geriatrician is essential to ensure optimal patient selection for different forms of early supported discharge. Postdischarge rehabilitation will allow patients to maximize their independence, and graduate from a zimmer to a stick or no walking aid as appropriate. Practice walking out-of-door and advice about when to return to driving may also be given if appropriate.

Evidence for Effective Orthogeriatric Collaboration

The National Service Framework for Older People in England (Department of Health, 2001) states that "at least one general ward in an acute hospital should be developed as a center of excellence for orthogeriatric practice". However, evidence as to the effectiveness and cost-effectiveness of the different models is complex, and the National Service Framework does not recommend a particular type of orthogeriatric collaboration, but advocates that this should be agreed at local level.

A number of research trials have been published describing different models of care but only a few of these were of sufficient quality to allow their inclusion in the Cochrane review of Coordinated Multidisciplinary Hip Fracture Care (Cameron *et al.*, 2003). These studies consider different models of care, each adapted to local needs, and as a result it is difficult to draw clear conclusions from their findings. The Cochrane review concludes that there is "no conclusive evidence of the effectiveness of coordinated postsurgical care... but a trend towards effectiveness in all main outcomes".

The NHS Health Technology Assessment Programme has performed a systematic review of the evidence in respect of Geriatric Rehabilitation Following Fractures in Older People (Cameron *et al.*, 2000). This very comprehensive document considers four broad categories of approach that have been proposed as alternatives to traditional orthopedic care. The review is guarded in its conclusions about Geriatric Orthopedic Rehabilitation Units, and raises concern that the additional cost of such units does not appear to be justified by improvements in patient outcome. Pressures on acute hospital sites may encourage Trusts to consider such developments, but this may not be the most effective way for geriatricians to improve the outcome for older trauma inpatients.

Such concerns are supported by the results of the East Anglia Hip Fracture Audit (Parker *et al.*, 1998), which indicated increased length of stay in units that routinely transferred large proportions of trauma patients to rehabilitation in other wards. This is perhaps because the expectation of a move to a different unit for rehabilitation may encourage staff on the trauma ward to neglect discharge planning, as "rehabilitation is someone else's problem". Furthermore, momentum in rehabilitation can be lost at the time of the move while the patient settles in, and is reassessed by a new multidisciplinary team. Work in other countries has also shown that a focus on reduction of acute orthopedic length of stay and earlier transfer to other settings will tend to prejudice patients' rehabilitation, leading to increases in dependency and care costs in the long term (Fitzgerald *et al.*, 1988).

In contrast, the Cameron review concludes that there is good evidence to suggest that collaborative approaches in the acute setting such as the Geriatric Hip Fracture Service do appear effective in improving outcome. It also suggests a benefit from the use of intermediate care initiatives such as Early Supported Discharge schemes to expedite rehabilitation and discharge.

Thus, involvement of the geriatrician in the acute trauma wards is crucial. This will allow many aspects of high quality care to be built into the routine management of older trauma inpatients, perhaps through the development of evidence-based assessment and treatment protocols for patients with hip fracture (Johansen, 2004). It has been suggested that such protocols should be developed into formal Integrated Care Pathways for hip fracture (Cameron *et al.*, 2000), but our experience is that such pathways are often inconsistent with the needs of the heterogeneous population who present with this injury.

KEY POINTS

- Hip fracture is the most common cause of acute orthopedic admission in the elderly.

- Treatment is generally surgical – to fix the fracture or replace the femoral head.
- Perioperative mortality is about 5–10% with most patients having some loss of functional capacity.
- Multidisciplinary rehabilitation is necessary to optimize the chance of patients returning home.
- Interventions to reduce the risk of further fracture should routinely be considered.

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Diseases of the Joints

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INTRODUCTION

The clinical presentation of arthritis is one of joint pain, swelling, morning stiffness, and limitation of motion (Nesher and Moore, 1994). These are symptoms common to all types of arthritis. Different diseases of the joint can present with signs and symptoms that appear quite similar. There are over a 100 types of arthritis that can affect the elderly (Table 1).

Nevertheless, a thorough medical history and physical examination, together with radiographic and laboratory testing, will identify the correct diagnosis in most cases of diseases of the joints (Table 2).

Arthritis has to be differentiated from periarticular or other musculoskeletal pain syndromes that commonly occur in the aged including fibromyalgia, rotator cuff tendinitis, trochanteric bursitis, polymyalgia rheumatica, and temporal arteritis.

OSTEOARTHRITIS

Osteoarthritis (OA) or degenerative joint disease is a chronic disorder characterized by softening and disintegration of articular cartilage with secondary changes in underlying bone, new growth of cartilage and bone (osteophytes) at the joint margins, and capsular fibrosis (Solomon, 2001). It is by far the most common form of chronic arthritis among the elderly. Its prevalence increases with age, occurring in greater than 50% of individuals older than 60 (Felson, 1990). Interphalangeal OA is particularly common in elderly people, affecting more than 70% of those older than 70 years (Solomon, 2001). Susceptibility to OA involves systemic factors affecting joint vulnerability including age, gender, genetic susceptibility, and nutritional factors; intrinsic joint vulnerabilities including previous damage, muscle weakness, malalignment, and so on; and extrinsic factors including obesity and physical activity (Felson, 2004) (Mankin and Brandt, 2001). The most common joints involved are those of weight bearing including the knees, hips, cervical and lumbosacral spine, proximal intraphalangeal (PIP) and distal intraphalangeal (DIP) joints of the hands, first carpometacarpal joints, and metatarsophalangeal (MTP) joints (Nesher and Moore, 1994; Solomon, 2001). Involvement is typically symmetric, although it can be unilateral at first depending on previous trauma or unusual stress. The pain may be insidious and relieved by rest initially, but as the disease progresses it becomes persistent and more severe with activity. Stiffness following periods of inactivity may also become common. The patient may complain of problems such as knee locking, unsteadiness, or giving away. Some patients, especially women, experience inflammatory OA or erosive OA, which particularly involves the PIPs and DIPs of the hands. These may exhibit inflammatory manifestations such as redness, tenderness, and local heat. Knees are often swollen with synovial fluid produced. Cervical and lumbosacral pain is a result of arthritis of hypophyseal joints, bony spur formation, pressure on ligaments or other surrounding tissues, or reactive muscle spasm. Impingement on nerve roots by osteophytes can cause radicular symptoms. Cord compression may result in spinal stenosis. In the cervical area, it causes localized pain and gait unsteadiness. At lumbar areas, it may result in spinal claudication, consisting of pain in the buttocks or legs while walking, which is relieved after 10 to 15 minutes of rest. Lumbar flexion and sitting usually relieve these symptoms, as opposed to aggravation of radicular disc symptoms by these positions.

Examination of the joints may detect crepitus, deformities, subluxation, swelling, bony overgrowths such as Heberden's nodes of the DIPs or Bouchard's nodes of the PIPs, and limitation of motion. Neurological evaluations may detect a radicular pattern of motor or sensory abnormalities, lower motor neuron or upper motor neuron signs in spinal stenosis, and sphincter abnormalities (Nesher and Moore, 1994).

No diagnostic laboratory tests are currently available. The synovial fluid, when present, is noninflammatory with a white count less than 1000 cells mm^{-3}. Radiological abnormalities may lag behind symptoms. Typical findings

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Table 1 Common arthritides in the elderly

Osteoarthritis
Rheumatoid arthritis
Gout
Calcium pyrophosphate Deposition disease
Connective tissue diseases
Infectious arthritis

Table 2 Studies to screen for arthritis

Complete blood count (CBC)
Urinalysis
Erythrocyte sedimentation rate (ESR)
C-reactive protein (CRP)
Chemistry panel including studies for kidney, liver, muscle, and uric acid
Rheumatoid factor (RF)
Antinuclear antibody (ANA) and profile if indicated
Synovial fluid analysis if indicated (White count, crystal analysis, cultures)
X rays of appropriate joints or spinal areas

are joint space narrowing, subchondral sclerosis, osteophytes, and periarticular bone cysts. Oblique films of the spine must be obtained to evaluate the neuroforamina. Computerized tomography (CT) or magnetic resonance imaging (MRI) give better evaluation of the spine pathology and can differentiate OA changes from discopathy, another common problem in older persons (Solomon, 2001).

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory symmetrical disease of joints of unknown etiology, affecting about 1% of the general population worldwide and about 2% of persons 60 years and older in the United States (Firestein, 2001; Rasch *et al.*, 2003). Extraarticular manifestations may also contribute to disease symptomatology (Nesher *et al.*, 1991). Most elderly patients with RA have the disease onset before age 60 and commonly present with additional therapeutic problems when older because of the long duration of the disease and other illnesses. Older persons are more likely to develop joint deformities. Involvement of the cervical spine may result in pain, decreased range of motion, and neurological deficits. Extraarticular manifestations, such as rheumatoid nodules, secondary Sjögren's syndrome (SS), and vasculitis are more frequent in this group of patients (Nesher *et al.*, 1991).

Patients with elderly-onset rheumatoid arthritis (EORA) are those in whom RA develops after the age of 60. Most patients present with a gradual onset of pain, swelling, and stiffness in symmetrical joints, while in others, the onset may be more acute. Fatigue, malaise, and weight loss may be present. Joint symptoms are characteristically symmetric, although asymmetric presentation may occur. In the aged, asymmetric involvement may be seen in hemiplegic patients with sparing of the paralyzed side. All peripheral joints may be involved, but the most common are the PIPs and metacarpophalangeals (MCPs) of the hands involved in 90% as are the wrists, MTPs, and ankles. More centrally located joints, knees, hips, elbows, and shoulders are involved to a lesser extent. DIPs of the hands are usually spared. Large joints are commonly involved in EORA, the shoulders more often than in younger patients (Nesher *et al.*, 1991; Deal *et al.*, 1985).

The majority of patients experience intermittent periods of active disease alternating with periods of relative or complete remission. A minority will suffer no more than a few months of symptoms followed by complete remission, whereas a small group will have severe, progressive disease. EORA is considered by many to be milder than RA developing at a younger age, which may be related to the lower incidence of rheumatoid factor (RF) positivity in the elderly. RF-positive EORA patients are likely to have more severe disease (van der Heidje *et al.*, 1991). Most laboratory abnormalities are not specific for RA, with the possible exception of high-titer 19 seconds IgM RF. It should be noted that RF in low titers may occur in a small percentage of healthy older individuals, so a positive RF test by itself may not be diagnostic. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually increased in RA, often correlating with disease activity. Radiological evaluation of involved joints in early stages is likely to show only soft tissue swelling. Later, the typical findings of symmetric joint space narrowing and erosions can support the clinical diagnosis (Nesher and Moore, 1994; Firestein, 2001; Nesher *et al.*, 1991).

GOUT

Gout is an inflammatory arthropathy caused by deposition of sodium monourate crystals in the joint (Wortman and Kelley, 2001). Its prevalence increases with age (Pascual and Pedraz, 2004). The typical presentation is that of an acute monoarthritis, most commonly occurring in the first MTP joint. The joint is usually extremely tender because it is associated with swelling and overlying erythema that sometimes mimics cellulitis or septic arthritis. Patients may be febrile and attacks can be precipitated by alcohol intake, use of diuretics, and stress, such as that occurring with surgical procedures or acute medical illness. Gout occurs more readily in joints damaged by other conditions such as OA. Polyarticular involvement of gout is not uncommon in older persons. It sometimes resembles RA. Such attacks tend to have a smoldering onset and longer course with a duration that is as long as 3 weeks. Chronic tophaceous gout is characterized by episodes of acute arthritis, chronic polyarthritis, joint deformities, and tophi. Radiographic findings are nonspecific in early stages. Punched out lesions or periarticular bone with overhanging borders are typically seen in chronic gout (Nesher and Moore, 1994; Wortman and Kelley, 2001; Pascual and Pedraz, 2004).

Laboratory findings include hyperuricemia in most cases (Wortman and Kelley, 2001). Most individuals with hyperuricemia never experience acute or chronic gout. About 10%

have normal serum levels during the attack. Therefore, the diagnosis should be established by the identification of typical sodium monourate crystals in synovial fluid, preferably with the use of a polarized microscope. This is accompanied by evaluating serum uric acid level and also performing a 24-hour urine for total serum urate spillage to define if the patient is an overproducer or undersecreter of uric acid.

CALCIUM PYROPHOSPHATE DEPOSITION DISEASE

Calcium pyrophosphate deposition disease (CPDD) is also a crystalline deposition arthropathy (Gohr, 2004). Its prevalence increases with age, being 10% in age 60 to 75 years and 30% in those 80 years or older (Reginato and Schumacher, 1988). Most cases are primary, but in some people it is associated with certain conditions such as hypothyroidism, hyperparathyroidism, and hemochromatosis. Many patients merely have asymptomatic chondrocalcinosis, commonly noted by X rays in the knees and wrists where linear punctate radiodensities are found within the cartilage (Gohr, 2004).

Typical presentation is usually of two types, that of chronic arthropathy that is sometimes polyarticular and presents with or without acute attacks with the knees most predominantly affected. Clinically, it may resemble OA or RA. Radiography may show features of both OA and CPDD, so it is not clear whether CPDD is primary or secondary. The second presentation is pseudogout, which is an acute monoarthritis, affecting mainly the knees and other large joints primarily and these resolve spontaneously within 3 weeks. It may infrequently affect a few articulations. Attack of pseudogout can be precipitated by stress or local trauma, and fever is common (Reginato and Reginato, 2001).

CONNECTIVE TISSUE DISEASE

Connective tissue disease, primary SS, and systemic lupus erythematosus (SLE), may present in the older population. Five percent of cases of SLE may begin after age 65 (Maddison, 1987). It may present with arthralgias or symmetric polyarthritis involving primarily finger joints, best resembling RA at this stage. Older onset SLE tends to be milder than the disease in younger patients with a lower incidence of nephropathy, neuropsychiatric manifestations, fever, and Raynaud's symptoms. There is an increased frequency of serositis, interstitial lung disease, and increase in sicca symptoms (Hahn, 2001). Primary SS, also, often presents in the aged (Thomas *et al.*, 1998). Patients complain of dryness of their eyes and also dryness in their mouth with swallowing difficulty. Nasal dryness, hoarseness, bronchitis, and skin and vaginal dryness may occur. The parotid glands may be swollen. Sicca symptoms (dry eyes and dry mouth) may be subtle and not obvious to the patients. Individual patients commonly have polyarthritis or arthralgias. Other features of the disease are myalgias, low-grade fever, and fatigue. Most have hypergammaglobulinemia and the frequency of developing lymphoproliferative disease is increased (Theander *et al.*, 2004).

Antinuclear antibodies are present in most SS and SLE patients, with antibodies to SS-A (Ro) and SS-B (La) occurring in the SS patients, and SLE patients having antibodies to double-stranded deoxyribonucleic acid (DNA), Sm, ribonucleoprotien (RNP), and SS-A/SS-B (von Műhlen and Tan, 1995). Other laboratory studies for evaluation include complement levels, antiphospholipid antibody studies, and other specific tests that may be helpful in diagnosing a particular connective tissue disease that is involved in the elderly patient (Illei *et al.*, 2004a,b).

Drug-induced lupus (DIL) is also a disease of older patients because inciting drugs are prescribed more frequently in the elderly. Symptoms are mild in most patients and resemble those of older onset SLE. The diagnosis is suggested by a history of administration of drugs like procainamide, hydralazine, α-methyldopa, propylthiouracil, or minocycline (Rubin, 1999). Most of these patients have positive ANA tests and antibodies to histones in 70 to 95% of the cases and occasional antibodies to myeloperoxidase. Other antibodies occur infrequently (Brogan and Olsen, 2003).

INFECTIOUS ARTHRITIS

Infectious arthritis typically presents as an acute monoarthritis of a large joint. It is associated with systemic signs of infection such as high fever, chills, and leukocytosis. Several factors predispose to an infected joint, including preexisting joint disease, a prosthetic joint, an infectious process elsewhere, or an immunocompromised state such as diabetes mellitus or treatment with corticosteroids (Vincent and Amirault, 1990). Infectious arthritis has to be entertained in all elderly patients with arthritis complaints. The presentation may be atypical in the aged because normal leukocyte counts and a normal temperature are not uncommon (Vincent and Amirault, 1990). In all cases of monoarthritis, synovial fluid should be aspirated, a Gram stain and culture performed, and a leukocyte count and differential determined. The leukocytes counts are usually $>50\,000$ cells mm^{-3}, primarily neutrophils; however, the initial count may be less than $10\,000$ cells mm^{-3} (Coutlakis *et al.*, 2002). The most common pathogen is *Staphylococcus aureus*, followed by streptococci and gram-negative bacilli (Ho, 2001). *Staphylococcus epidermidis* is common in a prosthetic joint infection. Early diagnosis is mandatory to prevent the high rate of complications; a 19% mortality rate has been reported, and 38% of patients may develop osteomyelitis (Vincent and Amirault, 1990). Treatment of infectious arthritis is determined by the type of organism that is isolated and then appropriate therapy is provided.

Table 3 Treatment modalities for arthritis in the aged

Physical therapy
Medications
(Noninflammatory arthritis)
Analgesics
Nonsteroidal antiinflammatories
(Inflammatory arthritis)
Nonsteroidal antiinflammatories
Disease-modifying agents
Biologics
Corticosteroids
Surgery

TREATMENT

Effective treatment of elderly arthritic patients combines physical therapy, medications, and in some cases, surgical intervention (Table 3).

PHYSICAL THERAPY

The value of physical therapy in improving the quality of life of the elderly patients with arthritis cannot be overemphasized. The main goals are pain relief, prevention of deformities, and maintaining mobility and independence (Nesher and Moore, 1994). Pain is relieved by periodic rest, splinting of affected joints, and locally applied heat. Although rest decreases joint pain and swelling, it may contribute to the development of contractures, disuse atrophy of muscles, and osteoporosis. In the aged, even brief periods of rest can result in loss of muscle strength and difficulty in resuming activities. An individual must maintain a certain level of activity even in the presence of active disease. Initial periods of relative rest should be followed by a program of passive and then active exercises designed to maintain range of motion and muscle strength. The patients should be encouraged to participate in body toning exercise programs such as regular swimming, walking, or water aerobics-type programs. Foot, hand, and cervical spine involvement can be helped with proper individualized footwear, paraffin baths, and cervical collars, respectively. Fabricated orthoses can help maintain alignment and support mechanically deranged joints. Assistive devices for walking, dressing, eating, and bathing can greatly improve the quality of life of these patients (Nesher and Moore, 1994; Calkins, 1991; Brandt *et al.*, 2003).

MEDICATIONS

Treatment decisions should consider several age-related changes that may affect drug absorption, distribution, metabolism, and elimination. The possibility exists that various treatments will have altered efficacy and be potentially more hazardous. Also, many elderly patients with arthritis have other diseases requiring other medications that could cause drug–drug interactions with the arthritis preparations.

Analgesic medications are given for mild arthralgias, especially for OA. Acetaminophen is commonly prescribed at a daily dose of 1 gm 3 to 4 times a day as needed. It has been shown to have equal efficacy to other anti-inflammatory agents for pain relief. It is a safe drug when used in therapeutic doses. It appears to be safe for patients with renal dysfunction or peptic ulcers; however, liver function studies must be followed to be sure there are no problems with hepatic toxicity (Brandt *et al.*, 2003). Other analgesics and opioid receptor agonists are effective in pain management, but their use should be limited to a short term, because abuse can lead to adverse effects, such as respiratory depression, drowsiness, constipation, and addiction. Propoxyphene is much safer than codeine for prolonged use and administration is much less addicting (Brandt *et al.*, 2003). The recent use of glucosamine and chondroitin sulfate for OA have been investigated and may be efficacious, especially glucosamine in some patients with OA of the hips and knees (Reginsten *et al.*, 2003). Diabetics and patients allergic to shellfish should not use these compounds. Also, the use of intra-articular injections of hyaluronic acid have been helpful to preserve knee cartilage and hip cartilage in some cases (Day *et al.*, 2004; Berg and Olsson, 2004).

Nonsteroid anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medications for arthritis (Nesher and Moore, 1994). In many cases, they alone are sufficient to induce the desired effect. The use of NSAIDs as primary therapy for older patients with OA and RA is not without problems (Brandt *et al.*, 2003; Johnson and Day, 1991). Advanced age has been identified as a primary risk factor for adverse gastrointestinal (GI) events in users of NSAIDs (Willkens, 2004). Hospitalization for bleeding of the stomach or esophagus occurs far more frequently in older patients who use NSAIDs than those who do not. However, patients are often asymptomatic. The risk factors for such events are advanced age, a history of GI problems, and the simultaneous use of corticosteroids, anticoagulants, alcohol, or tobacco. These factors should be documented in individual patients and treated accordingly (Willkens, 2004). Adverse events such as epigastric pain, mental changes, fluid retention, changes in blood pressure, and occult or gross blood loss should be monitored closely. A complete blood count (CBC), urinalysis, and liver and kidney function tests should be attended initially and every 1 to 3 months thereafter to monitor toxicity in the elderly population. NSAIDs such as naproxen, fenoprofen, sulindac, and diclofenac have proved very effective in the treatment of OA or RA in patients. A concern about peptic ulcer disease has been relieved considerably by the availability of cyclooxygenase-2 (COX-2) inhibitors (Baigent and Patrono, 2003). However, caution is still needed in older patients who have a history of ulcer disease. Some physicians still add proton pump inhibitors to this therapy when it is used in high-risk patients. Also, the use of H2 blockers such as famotidine, and so on, can also be helpful. Both the older NSAIDs and COX-2 selective NSAIDs have the potential for decreasing renal

blood flow causing fluid retention, creating abnormal salt and water metabolism, and interfering with drug excretion, so they are not without their toxicity in the elderly population (Perazella and Tray, 2001). The COX-2 antagonists celecoxib, rofecoxib, valdecoxib, and etoricoxib have been used extensively and have other advantages beyond decreased gastric acidity (Brune and Hinz, 2004). Clinical trials of these drugs have shown no effect on platelet aggregation or bleeding time at therapeutic doses and do not alter this anticoagulant effect of warfarin. However, the possibility of increased blood pressure, peripheral edema, or predisposal to myocardial infarctions or strokes because of their effect on thromboxane A_2 levels may be a contraindication to using some COX-2 inhibitors in the elderly population (Baigent and Patrono, 2003).

The nephrotoxic effect of NSAIDs is well documented. The most common mechanism leading to renal dysfunction is inhibition of renal prostaglandin synthesis, which may adversely affect renal blood flow in certain situations, leading to acute insufficiency (Perazella and Tray, 2001). At special risk are patients with preexisting changes in renal function, such as those changes related to aging, diabetes mellitus, hypertension, congestive heart failure, or use of concomitant diuretics. Preferably, NSAIDs should not be prescribed to patients with these conditions or anybody with a creatinine of 1.5 or higher. NSAID-related psychotic reactions and depression occur more commonly in the aged. Also, NSAIDs can interact with several medications commonly used in older persons, mainly anticoagulants, oral hypoglycemics, digoxin, seizure medications, and lithium (Johnson and Day, 1991). Combining NSAIDs with potassium-sparing diuretics increase the risk of hyperkalemia.

In RA, the baseline therapy is the use of NSAIDs and then the use of remittive agents very quickly to reduce erosions and joint space narrowing, which generally occur in the first 2 years (Johnson and Day, 1991). Disease-modifying agents (disease-modifying antirheumatic drugs or DMARDs) are second line agents in RA, but are used much more quickly today. The first that is usually prescribed is hydroxychloroquine in doses of 200 mg once to twice daily. It is considered effective in mild to moderate cases of RA. It is also effective in treating the arthritis and skin manifestations of SLE and SS (Nesher and Moore, 1996). The mainline therapy in RA now is usually triple therapy including an NSAID, hydroxychloroquine, and in the United States, methotrexate in doses of 10 to 25 mg weekly or in Europe sulfasalazine at doses of 2 to 3 g daily. These regimens appear to be effective for elderly patients with RA, as it is for younger ones. Methotrexate may have some toxicity in the elderly, but is limited mainly to hepatotoxicity and in those with abnormal renal function. The lowest reasonable dose should be used (Willkens, 2004; Nesher and Moore, 1996). CBC, urinalysis, and comprehensive metabolic panel every 6 to 8 weeks to monitor toxicity are recommended. Also, to reduce toxicity, the use of folic acid at 1 to 2 mg day^{-1} is very helpful. Sulfasalazine in 2 to 3 g daily dose should also be monitored every two months by CBC, urinalysis, and comprehensive metabolic panel to reduce toxicity. Other remittive agents such as azathioprine or leflunomide, may be used in RA with efficacy (Smolen, 2004). The recent advent of biologics including etanercept, infliximab, and adalimumab have been very helpful in bringing into remission elderly patients with RA (Calabrese, 2003). These biologics inhibit tumor necrosis factor (TNF). Etanercept, a TNF receptor antagonist, is given as 25 mg subcutaneous twice a week to 50 mg once a week. It has been shown to be very effective in decreasing sedimentation rate, joint activity, arthralgias, and reducing erosions and joint space narrowing. The same can also be said for the other new biologics, which are monoclonal antibodies directed toward TNF. The fully humanized antibody, adalimumab, is given as a 40 mg subcutaneous every 2 weeks, or the chimeric molecule, infliximab, an intravenous preparation, is given at dosages from 3 to 10 mg kg^{-1} at baseline, 2 to 6 weeks, and then every 4 to 8 weeks thereafter (Calabrese, 2003). All have been shown to have long-term efficacy and little toxicity (Cush, 2003). Injection site reactions may occur and are usually managed with antihistamines. The only other toxicity noted is the possible development of exacerbating an indolent tuberculosis infection. Therefore, a tuberculosis skin test and chest X-ray should be performed at baseline and yearly. Also, the possibility of aggravating any new infection has to be entertained. Therefore, a dose should be held if a viral or bacterial infection occurs. Also, the long-term effect of blocking TNF is not well understood (Ellerin *et al.*, 2003). They should not be used for any patient with a demyelinating disorder (Robinson *et al.*, 2001) and monitoring for any type of lymphoproliferative processes should occur (Brown *et al.*, 2002). However, early studies in the United States have shown no increase in lymphomas, tumors, or other side effects with these medications greater than is seen as a late outcome in RA.

Corticosteroids can be used in low doses of 5 to 10 mg of prednisone daily in some elderly seronegative RA patients or in patients with remittive seronegative symmetrical synovitis with pitting edema (RS3PE) (Nesher and Moore, 1996). However, higher doses predispose the patient to the multiple side effects of steroids in the elderly, including sodium and fluid retention, hypertension, hyperglycemia, osteoporosis, infections, and skin changes (Willkens, 2004; Nesher and Moore, 1996). With the advent of the new remittive agents and biologics, the use of steroids should be limited to only those who are unresponsive or cannot afford the other agents. If steroids are used, the use of calcium and vitamin D should be included with that therapy to prevent osteoporosis as much as possible. Intra-articular injections of steroid preparations are commonly employed in RA and OA in conjunction with other treatment modalities, especially when symptoms are limited to one or fewer joints (Nesher and Moore, 1996).

The treatment of acute gout in the elderly is still the use of colchicine, but at lower doses than in the past (Willkens, 2004). Generally, the dosage for long-term use of colchicine is one or two 0.6 mg tablets/day depending on the patient's renal function; however, only 0.3 mg in patients aged 70 years or older. When parental colchicine

is used, the maximum dose used for an acute episode in or out of the hospital should be 1 mg day^{-1} intravenously. In renal compromised patients, the use of colchicine has resulted in neuromyopathy (Kuncl *et al.*, 1987). Allopurinol, a xanthine oxidase inhibitor, is another gout medication that can lower serum urate levels. It is best started slowly at 100 mg day^{-1}. If the hyperuricemia is not responding, the dosage should be advanced to 100 mg twice a day and then finally up to 300 mg day^{-1} (Nesher and Moore, 1994). Platelet counts and hypersensitivity reactions should be monitored. Anti-inflammatory agents such as naproxen or the COX-2 inhibitor, etoricoxib can also be used in acute gout (Rubin *et al.*, 2004). In general, uric acid lowering therapy should be administered when there are tophi, frequent attacks of gouty arthritis of over three per year, or evidence of uric acid overproduction is documented. Baseline 24-hour urine of uric acid spillage over 750 mg/24 hours or uric acid levels over 8 may indicate the need for therapy (Wortman and Kelley, 2001; Maddison, 1987).

In the treatment for pseudogout in adult patients, it has been shown that colchicine is less effective and is usually being managed by NSAIDs. The dosage of naproxen 500 mg twice a day, etoricoxib 60 mg once to twice a day, or diclofenac 50 mg 3 times a day can be very effective in the long-term management of patients with pseudogout (Reginato and Reginato, 2001).

SURGERY

The major goals of various orthopedic procedures are to relieve pain and to improve function (Nesher and Moore, 1994). Joint replacement, tendon repair, carpal tunnel release, and synovectomy are some of the frequently employed measures in RA (Sledge, 2001). In OA, treatments include bunion resection, decompression of spinal roots, and total knee and hip replacements. Arthroscopic lavage of knees has been reported to improve symptoms, but has not been widely employed as a therapeutic measure. Age itself is neither a contraindication to surgery nor a predictor of poor results. Rather, the presence of concurrent medical problems such as heart failure and pulmonary disease contribute more to perioperative morbidity and outcome. The goals, indications, and timing of surgery should be individualized depending on the patient's general health status, function impairment, degree of pain, and rehabilitation potential (Rosandrich *et al.*, 2004).

In summary, arthritis is a common condition among the aged. The most common type is OA and the most common inflammatory process is RA. Optimal management includes physical therapy and medication, possibly combined with surgery, if necessary. Treatment modalities should be offered sometimes to accommodate age-related changes and body mechanics and function. The long-term medical management of arthritis in the elderly requires close monitoring for potential adverse effects of medications.

KEY POINTS

- Arthritis is a common chronic condition among the aged.
- Osteoarthritis is the most common type.
- Rheumatoid arthritis is the most common inflammatory arthritis and can produce long-term morbidity if not treated aggressively.
- There are more than one hundred types of arthritis affecting the elderly.
- Gout, pseudogout, or infectious arthritis can present as red, hot, swollen joints, and only synovial fluid aspiration can differentiate.

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Back Pain

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INTRODUCTION

Back pain is a very common complaint in both developed and developing countries, with a lifetime prevalence ranging from 11 to 84% (Walker, 2000). It has been traditionally perceived to be a problem affecting relatively younger adults where its major impact on the workplace, associated economic burdens and public health implications, have been well described. Both physicians and older patients have been guilty of regarding back pain as an inevitable part of aging, this despite the fact that prevalence of low back pain appears to decline with age, the majority of patients having their first presentation before the age of 65 years (Lavsky-Shulan *et al.*, 1985). The reasons for this decline are unclear but may partly be explained by a change in working life patterns and associated psychosocial adjustments that come with retirement.

While prevalence studies performed in older people are limited, a cohort of older American adults demonstrated that over one-fifth of patients age 68–100 years had back pain on most days, particularly in the lower back. Older people confined mostly to their homes were especially affected, while prevalence was demonstrably higher in women compared to men. This was notably more evident for mid or upper back pain (Edmond and Felson, 2000).

Back pain remains a very challenging assessment and diagnostic problem in elderly people. Its causes are often multiple, while the incidence of serious pathology is considerably higher than in younger people. Older patients commonly have pains that are of a different nature from those found in younger or middle-aged adults and often they show a marked discrepancy between imaging findings and demonstrable pain (Baumgartner, 1996). There is a large spectrum of presentations that range from acute and life-threatening, such as occurs with a leaking abdominal aortic aneurysm, to chronic persistent nonspecific back pain syndromes. While the majority of back pain presentations are self-limiting and will resolve within 6 weeks, identifying more serious causes requires a logical stepwise approach to establish the cause so that optimal treatment can be instigated. The physicians' dilemma is to differentiate between those back pains which may herald more sinister pathology from those of more benign disease. This is of particular importance in older people given the relatively higher proportion of identifiable secondary causes such as cancer, infection, and fracture in this group.

The health-care costs for the patient population suffering from back pain are very substantial. The total expenditure in the United States alone came to over $90 billion in 1998, which represented approximately 1% of its gross domestic product. It was also demonstrated that the elderly population, particularly females in this group, incurred higher costs on average when compared with younger individuals (Luo *et al.*, 2003). The human cost in terms of pain, depression, and disability as a result of back pain cannot be fully quantified but almost two-thirds of older people, again women more so than men, will experience functional limitations as a result of it (Edmond and Felson, 2003). Once back pain becomes chronic in older patients recovery is less effective compared to younger individuals, particularly in the context of an associated specific etiological diagnosis or psychosocial disorder (Van Doorn, 1995; Rossignol *et al.*, 1988).

DEFINITIONS

Back pain has many different phases that need to be defined in order to provide a clearer picture to the physician. This is particularly important for older people when multiple professional disciplines are usually involved in assessing and managing patients. Useful definitions that follow the natural history of back pain have been proposed using the following terms (VonKorff, 1994):

Transient back pain is an episode in which back pain is present on no more than 90 consecutive days and does not recur over a 12-month observation period.

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Recurrent back pain is back pain present on less than half the days in a 12-month period, occurring in multiple episodes over the year.

Chronic back pain is back pain present on at least half the days in a 12-month period in a single or multiple episodes.

Acute back pain refers to pain that is not recurrent or chronic and whose onset is recent and sudden.

First onset refers to an episode of back pain that is its first occurrence in a person's lifetime.

A *flare-up* is a phase of back pain superimposed on a recurrent or chronic course when back pain is markedly more severe for the person.

An *episode of low back pain* is a period of pain in the lower back lasting for more than 24 hours, preceded and followed by at least 1 month without back pain (De Vet *et al.*, 2002).

NORMAL SPINE AGING

Back and neck pain may arise from several anatomical structures in the spine including intervertebral disks, facet joints, paravertebral musculature, spinal nerve roots as well as joint ligaments connecting vertebrae and spinal nerve roots. All of these structures are subjected to age-related degenerative changes and as such they play an important role in the etiology of back pain in older people. A wide range of genetic and environmental insults influence such changes. All parts of the spine undergo degenerative changes with aging (Andersson, 1998). Autopsy studies have shown that significant disk degeneration is evident in most spines by at least the fourth decade (Schmorl and Junghanns, 1971) and is ubiquitous by the sixth decade (Vernon-Roberts, 1988). This appears to occur earlier in men compared to women. The intervertebral disk is a cartilaginous structure but morphologically it is different to articular cartilage. It shows degenerative and aging changes earlier than does any other connective tissue in the body. These changes have frequently been cited as causing spine stiffness, neck and lower back pain which may be chronic or intermittent (Urban and Roberts, 2003).

Disk degeneration involves disruption of the normal annular fibers. Such degeneration occurs as a result of complex biochemical and biomechanical factors that the disk is subjected to throughout a lifetime. These include declining nutrition, loss of viable cells, cell senescence, reduced water content of the nucleus pulposus, accumulation of cell waste products such as proteoglycan fragments, and reduced ability to instigate repair of damaged tissues at a molecular level. Scoliosis for example is associated with decreased endplate permeability, which may reduce diffusion of nutrients leading to accelerated degenerative disease (Bibby *et al.*, 2001). Osteophyte growth from the margins of the vertebral bodies and facet joint osteoarthrosis are other characteristic features of the degenerative process but it remains unclear as to what triggers their progression. It is postulated that the latter occurs as a result of changing stresses on the facet joints with age. Environmental stresses to the spine, especially in those engaged in manual work, also appear to accelerate the development of degenerative changes, the disks being mostly affected. The relative risk ratio for disk degeneration with space narrowing was 1.8 in a comparison between concrete reinforcement workers compared to a matched group of house painters. Such disk narrowing and spondylotic changes occurred significantly earlier in the former group (Riihimaki *et al.*, 1989).

These degenerative changes especially when associated with disease processes in the back such as osteoarthritis, osteoporosis, and vertebral collapse are important contributory factors in causing impairment and resultant disability in older people.

CLINICAL EVALUATION

It has been suggested that instead of laboriously seeking an exact cause for a back pain presentation, the priority should be to answer three pertinent questions (Deyo, 1986). Is there a serious systemic disease causing the pain; is there neurological compromise requiring urgent intervention; and are psychosocial factors contributing to the pain syndrome?

The initial diagnostic evaluation of any back or neck pain presentation demands meticulous care in gathering a comprehensive history and performing a carefully structured examination. Appropriate investigations may then be pursued as guided by the clinical findings. If after the initial assessment no risk factors for a serious cause are evident, then no diagnostic tests are required but patients should be reassured, educated, and offered appropriate pain relief and early return to usual activity encouraged. Patients should be followed up at 2 weeks and if normal activity has not been reestablished a careful review of risk factors and response to initial treatment is recommended. If warning features suggesting serious pathology become apparent, then further investigation is mandatory (Rose-Innes and Engstrom, 1998).

Back pain may arise from several anatomical structures in the spine such as occurs in intervertebral disk herniation or spinal stenosis (*see* **Chapter 85, Cervical and Lumbar Spinal Canal Stenosis**). It may also be the presenting complaint in visceral diseases unrelated to the spine such as occurs in abdominal aortic aneurysm. Given the many demands on physician time, the need to be alert to worrying symptoms and signs, the so-called *red flags*, is of paramount importance in identifying serious disease. In a primary care setting of all patients presenting with back pain, 4% will have compression fractures, 3% will have spondylolisthesis, while a not insignificant 0.7% will have either primary or secondary cancers. One patient in 10 000 will have had spinal infections such as diskitis or osteomyelitis (Deyo *et al.*, 1992). A systematic assessment helps to separate the benign from serious pathology, and distinguishing spinal from nonspinal pain. Patients with a nonmechanical cause of pain such as cancer or those suitable for surgery may thus be identified and referred to the relevant specialist. The remainder may

then be managed with appropriate analgesia and mobilization regimes.

History

A careful and thorough history of pain is essential in establishing the anatomical site of pain. All conventional aspects of pain should be assessed. The time of onset of pain is of particular importance, as well as the following questions: is it acute or insidious; what is the duration of pain, is it intermittent, persistent, or chronic in nature; what were the circumstances of how the pain developed; was there any associated trauma, however trivial; are there associated symptoms such as weight loss or rigors; does the pain radiate; are there any lower limb motor or sensory symptoms; what are the precipitating, aggravating, and relieving factors; what is the severity and intensity of the pain. Pain that is not relieved on lying down, while not specific, should increase suspicion of underlying infection or malignancy.

The past medical history should focus on clues such as a previous history of tuberculosis or trauma. Risk factors for osteoporosis should be sought after (*see* **Chapter 110, Epidemiology of Osteoporosis**). Careful attention to the drug history including over-the-counter and herbal medicines is required, particularly changes in medication that may correlate to the onset of pain. Patients who have received long-term corticosteroid medication should have a vertebral compression fracture assumed unless later excluded.

The family history should explore the possibility of conditions such as rheumatoid arthritis, which have a strong familial inheritance pattern. Points to be established in the social history include past and present smoking and alcohol intake, relevant occupations particularly where manual work or a more sedentary lifestyle was a strong feature. The review of systems should especially focus on symptoms that might point to more sinister pathology such as weight loss or a change in bowel habit. Symptoms of prostate disease in men and breast disease in women, even if deemed trivial by patients, should always be given serious attention.

Depression or anxiety states should also be sought, as these play an important role in the evolution of back pain syndromes.

Difficulties in history-taking may arise in some older patients who are reluctant to report pain or in cognitively impaired individuals. In these situations observation should be made for increased vocalizations such as moaning or crying or behavior changes such as grimacing or irritability, which may herald underlying pain. Caregivers may also be in a position to report any recent changes particularly in function that are not readily apparent. "Red flags" in the history in older patients include pain which is worse at rest or at night, a previous history of cancer or chronic infection, a trauma history, pain which has persisted for more than one month, prior corticosteroid or intravenous drug use, or a change in bladder habits (Rose-Innes and Engstrom, 1998).

Examination

A comprehensive physical examination should be performed when assessing older individuals with back or neck pain. This is important because the source of pain may not originate in the spine structures, or the pain may arise from more than one site. Patients should be examined in both the supine and standing positions with the spinal posture and range and symmetry of movements noted in the latter, while neurological assessment can be performed in the former. Leg length discrepancies, standing posture, as well as gait and postural sway disorders may also contribute to back pain; examination for these conditions should be made (Gurney, 2002).

Patients should also be sufficiently undressed so that the breasts in women and prostate gland in men can both be given careful attention. The genitalia should not be overlooked particularly in male patients as otherwise tumors or large hydroceles may be missed. Additional signs to be looked for in older women include the severity of flexed posture. This has been shown to correlate to the severity of vertebral pain, emotional status, muscular impairment, and motor function. It also has a measurable effect on resulting disability (Balzini *et al.*, 2003).

Alarming signs to be looked for include unexplained pyrexia or evidence of weight loss, a positive Lasegue (straight leg raising) test, percussion tenderness over the spine or costovertebral angles, the presence of an abdominal, rectal, or pelvic mass, or any focal neurological signs especially if these are progressive (Rose-Innes and Engstrom, 1998).

Trigger points may also provide useful diagnostic clues. These are discrete hyperirritable spots located in taut bands of skeletal muscle. In the back, these can manifest as low back pain or gait changes, while in the neck they may be important in the etiology of headache or temperomandibular joint pain. Palpation of the trigger point can elicit pain directly over the affected area or to a referred site (Alvarez and Rockwell, 2002).

Non-radiological Investigations

These will be guided by the clinical presentation. An elevated erythrocyte sedimentation rate (ESR), white blood cell count (WBC), alkaline phosphatase, prostate specific antigen or a monoclonal band on serum, or urine electrophoresis are all indications of serious disease. A septic screen to include urine, stool, and serial blood cultures should be performed wherever underlying sepsis is suspected. Cerebrospinal fluid should be examined and cultured where meningitis is a possibility and there are no contraindications to a lumbar puncture being performed.

It should be remembered that typical markers of infection are not always apparent in older people even in the face of overwhelming sepsis. Readers are referred to the appropriate chapters on metabolic bone disease (*see* **Chapter 109, Paget's Disease of Bone**; **Chapter 111, Osteoporosis and**

its Consequences: a Major Threat to the Quality of Life in the Elderly) and cancer (*see* **Chapter 128, Cancer and Aging**; **Chapter 129, Oncological Emergencies and Urgencies**; **Chapter 125, Prostate Diseases**; **Chapter 130, Breast Cancer in the Elderly**) for appropriate investigations where these are suspected.

Radiological Investigations

A high index of suspicion for most of the sinister causes of lower back pain can be arrived at through careful exploration of the history and examination. Routine imaging in older patients with acute low back pain should not be performed unless they present with suspected serious pathology such as trauma, acute vertebral collapse, a neurological deficit, or suspicion of infection or neoplasm is present.

There is a large spectrum of imaging studies that can be performed, but their use should be tailored to individual presentations. The potential benefits and limitations of such studies should always be borne in mind so as to avoid unnecessary and expensive investigations. Advanced imaging should be reserved for those in whom sinister disease is strongly suspected or those who would consider surgical intervention where appropriate. The simple question of how a patients' management to include diagnosis, treatment, and outcome will change on the basis of a positive or negative test result is a useful guide in determining the appropriateness of particular investigations. Readers are referred to **Chapter 144, Diagnostic Imaging and Interventional Radiology**, which further addresses these issues.

Plain Radiograph

In older adults with self-reported back pain, osteophytes are the most frequent radiographic feature. Together with endplate sclerosis they are found more frequently in men than in women. Disk space narrowing is usually the first indicator of degenerative disease on plain radiograph and appears to be more strongly associated with back pain than any other radiographic feature (Pye *et al.*, 2004). Even though the prevalence of degenerative change is high in older people, the therapeutic consequences of diagnosing this abnormality are minimal.

The diagnostic contribution of the frontal lumbar spine radiograph in community dwelling adults has been prospectively examined. In over 90% of cases the antero-posterior view was noncontributory, while a single lateral lumbar view can pick up important conditions such as infection, malignancy, or benign tumors (Khoo *et al.*, 2003). Plain film sensitivity is poor, however, as infections such as osteomyelitis tend to show up late, sometimes up to 8 weeks after symptoms begin (Smith and Blaser, 1991).

Ultrasound

There are several medical applications for diagnostic ultrasound. It is especially attractive in older people because of its ease of use, relative low cost, and noninvasive nature. It may identify intraabdominal causes of back pain such as abdominal aortic aneurysm, but it can also be used in assessing spine disorders. Such applications include measuring the spinal canal, detecting cord abnormalities, quantifying scoliotic curves, and examining soft tissue abnormalities. Ultrasound may also be used potentially as a preliminary diagnostic procedure for lumbar disk herniation, but it is distinctly inferior to magnetic resonance imaging (MRI) mainly due to lower diagnostic accuracy (Berth *et al.*, 2003).

Radioisotope Bone Scan

This is more sensitive at picking up metastatic disease than plain films and should be used where malignant disease is suspected clinically. It can also be used to identify infection in bone particularly where disease is occult. Degenerative disk disease, especially in its later stages, can also be identified in this way.

Computed Tomography

This is not as useful as MRI in viewing the spine. It is more helpful in diagnosing nonspinal sources of back pain such as abdominal aortic aneurysm.

Magnetic Resonance Imaging

This can be used where either neoplastic or infectious pathology are suspected. It may also be utilized in patients with radicular pain particularly those with a clear level of nerve root impingement or those with sciatica-type symptoms but where nerve root dysfunction is unclear. MRI scanning is often overutilized especially when compared to simple lumbar radiographs where no long-term benefit in terms of disability, pain, or general health status was identified (Jarvik *et al.*, 2003).

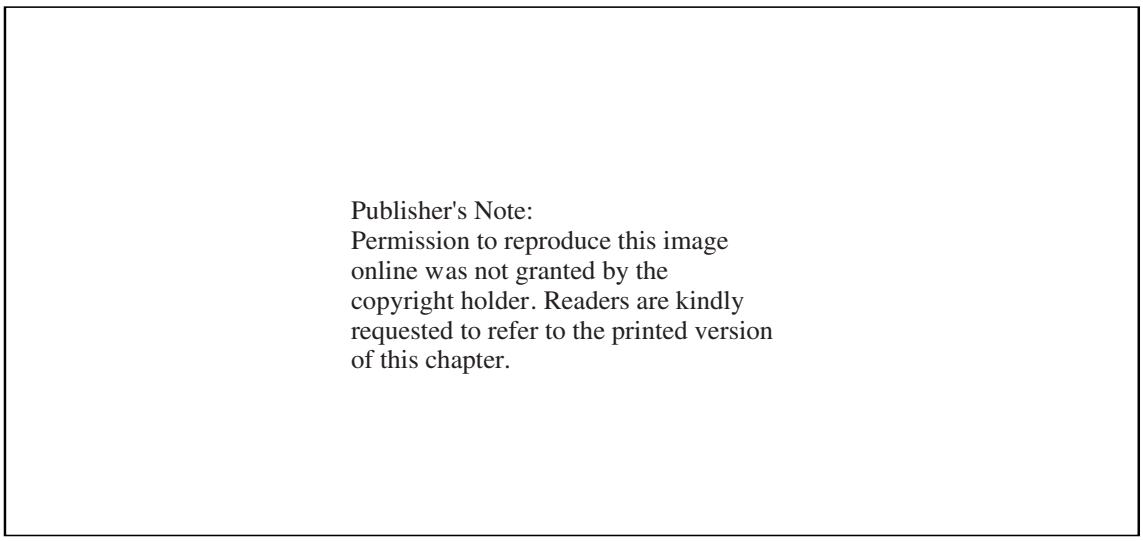
Bone Scintigraphy

This can be used to detect stress fractures and bone metastases. It may also be combined with nuclear medicine studies such as radio-labelled white blood cell scans in identifying and localizing occult infections particularly those deep seated in vertebral bone.

Specific Causes

The differential diagnosis of the many causes of back pain is presented in Table 1. It must be emphasized that the diagnostic probabilities in older patients are considerably different to younger people with a much higher prevalence of compression fractures, cancer, spinal stenosis, and abdominal aortic aneurysm. Readers are referred to the various chapters that address many of these individual causes in more detail.

Table 1 Differential diagnosis of low back pain



Adapted from NEJM by permission of Massachusetts Medical Society.
[a]The term "mechanical" is used here to designate an anatomical or functional abnormality without an underlying malignant, neoplastic, or inflammatory disease. [b]"Strain" and "sprain" are nonspecific terms with no pathoanatomical confirmation. "Idiopathic low back pain" may be a preferable term. [c]Spondylolysis is as common among asymptomatic persons as among those with low back pain, so its role in causing low back pain remains ambiguous. [d]Internal disk disruption is diagnosed by provocative diskography (injection of contrast material into a degenerated disk, with assessment of pain at the time of injection). However, it often causes pain in asymptomatic adults, and the condition of many patients with positive diskograms improves spontaneously. Thus, the clinical importance and appropriate management of this condition remain unclear. "Diskogenic low back pain" is used more or less synonymously with "internal disk disruption". [e]Presumed instability is loosely defined as greater than 10° of angulation or 4 mm of vertebral displacement on lateral flexion and extension radiograms. However, the diagnostic criteria, natural history, and surgical indications remain controversial.

Vertebral Fracture

On a plain x-ray if a fracture is confirmed, referral for specialist opinion should be done to address the underlying cause and to explore treatment options. If a fracture is not clearly evident but suspicions remain, then specialist referral and consideration for performing an isotope bone scan may be considered.

Neoplastic Disease

High suspicion for individual cancers warrants referral to the appropriate specialist. Multiple myeloma and metastatic disease, particularly prostate in men and breast in women, are much more common than primary spine tumors.

Infection

Infections can manifest in several spine structures including the bony vertebrae, the interstitial disks, paraspinal muscles, zygapophysial joints, and meninges. An elevated ESR or WBC supports the diagnosis, but once again it should be remembered that these are not always evident in older people.

The goals of management are early identification of causative organisms, preservation of neurological function, infection eradication with pain resolution, and spine stability. If serious infective pathology such as osteomyelitis, tuberculosis, or diskitis is suspected then appropriate specialist referral is warranted.

Osteomyelitis: The history is commonly of insidious onset over a period of weeks or months, and is usually localized in the thoracolumbar spine having been seeded via the haematogenous route (Lew and Waldvogel, 2004). Vertebral tenderness has sensitivity for underlying infection but lacks specificity. Pyrexia and raised white cell count may be absent in up to 50% of cases while blood cultures are commonly negative. Needle biopsy may be required to allow microbial and pathological examination so as to facilitate targeted and long lasting antimicrobial treatment. The ESR is commonly elevated and may be used as a marker to monitor response to treatment. A multidisciplinary approach involving expertise in orthopedics, radiology, and infectious disease is often required for optimal outcomes. The physiological and anatomical characteristics of bone often pose difficulty in eradicating infection. This is often compounded by the emergence of resistant organisms such as methicillin resistant *Staphloccocus aureus*.

Diskitis: This occurs when there is inflammation of the intervertebral disk space. This is frequently caused by an associated vertebral bone infection while endplate infection can also lead to vertebral osteomyelitis. Its incidence in Europe is approximately 1 in 50 000 inhabitants but is believed to be even higher in older people. Its onset is often insidious making diagnosis difficult. It commonly occurs secondary to a primary infective focus such as in the urinary tract. MRI is the preferred method of investigation, but biopsy may be required to confirm the diagnosis. Clinical symptoms, infective and inflammatory markers,

temperature and interval radiological changes will guide antimicrobial treatment, the duration of which may be up to 12 weeks. Whilst epidural infection with neurological sequelae can occur, the prognosis is generally good (Lam and Webb, 2004).

Tuberculosis: Pott's disease is a common and serious form of tuberculous infection of the spine with potentially catastrophic sequelae including paraplegia. It commonly localizes to the thoracic spine involving the vertebral body. It too may have an insidious onset. Common presenting symptoms include leg weakness (69%), gibbus (46%), local pain (21%), and a palpable mass in 10% (Turget, 2001). Identification and sensitivity patterns of causative organisms, appropriate antituberculous chemotherapy with decompressive surgery when required are the mainstays of treatment.

Prolapsed Intervertebral Disc

Symptoms of prolapsed disk include backache that is commonly of abrupt onset, sciatica, or those suggestive of cauda equina syndrome (CES) as described later. Clinical signs will depend on the level of root involvement and are helpful in improving accuracy of the site of compression. A positive, straight leg-raising test is up to 80% accurate in diagnosing the condition. Pain on crossed straight leg-raising increases diagnostic accuracy even further. MRI should be considered as the gold standard for confirming clinical suspicion. Conservative treatments will incorporate many of the measures used for treating nonspecific low back pain including limited bed rest during the acute period with simple analgesia and controlled weight loss in obese patients. Both nonsteroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants may have a role to play, but they should be used cautiously in older people given their significant adverse effect profile.

Epidural injections and traction under specialist supervision may be useful for pain that is difficult to control. Epidemiological studies suggest that pain will resolve in the majority of patients using conservative measures. Surgical decompression should be reserved for carefully selected individuals not responding to at least 1 month of conservative treatment and where the diagnosis is not disputed. The balance of potential risks and benefits, as always, needs to be carefully considered. There is considerable evidence that surgical diskectomy provides effective clinical relief for such patients. Chemonucleosis (injection of chymopapain into the disk space) is a less invasive, intermediate procedure between conservative and open surgery, which can be considered in less robust individuals, but it is less effective than open diskectomy.

Lumbar Spine Stenosis

This commonly affects older people and is often demonstrated incidentally on CT or MRI imaging (Hudgins, 1983). Disk degenerative disease, facet joint osteoarthritis, and ligamentum flavum hypertrophy are the commonest causes. It is often associated with incapacitating pain in the lower back and extremities, reduced mobility, lower limb paraesthesia, and weakness. In severe cases, bowel and bladder disturbance may become evident. Readers are referred to **Chapter 85, Cervical and Lumbar Spinal Canal Stenosis** for further details.

Cauda Equina Syndrome (CES)

Characteristics of CES include low back pain, sciatica, saddle anaesthesia, decreased rectal tone and perineal reflexes together with lower limb extremity and bowel or bladder dysfunction. There are many causes of this syndrome including infection, neoplasm, trauma (including iatrogenic procedures), and intervertebral disk herniation.

Decompression surgery is the treatment of choice but the optimal timing of this is unclear.

Emergency decompressive surgery compared to the "next available list" did not lead to significantly improved outcomes (Hussain *et al.*, 2003).

Abdominal Aortic Aneurysm

This is an important nonspinal cause of low back pain, which warrants special mention, as its incidence increases steeply with age. It is three times more common in men than women where it may affect up to 5% of individuals age 65–74 years. The only well established risk factor is cigarette smoking. Its natural history is highly variable, varying from an asymptomatic incidental clinical finding to abrupt rupture with presentations including acute severe back pain, an expanding pulsatile mass, as well as sudden death. Ultrasound or CT scanning help to confirm the diagnosis. Ruptured aneurysm is a surgical emergency, which carries a high perioperative mortality of up to 50%, while in untreated patients death is usually inevitable (Ernst, 1993). The UK Small Aneurysm trial suggests observing small aneurysms with transverse diameter between 4 and 5.5 cm with ultrasound surveillance every 6 months with elective surgical repair in suitable candidates if it grows at a rate of more than 1 cm per year. Once again the benefits and risks of major elective surgery must be carefully assessed for individual patients (UKSAT, 1998).

Nonspecific Low Back Pain

This is defined as pain between the costal margins and the inferior gluteal folds that is generally accompanied by painful limitation of movement. It remains the commonest cause of back pain in older people. It is affected by physical posture and activities and may be associated with referred pain. The diagnosis is made when no underlying disorder such as fracture or infection is evident. In the majority of patients no organic cause is identified although degenerative processes are often sited (Deyo and Weinstein, 2001). Many of the treatments used in its management have also been used for mechanical neck pains with varying degrees of success.

Nonpharmacological Interventions

Most patients including older people with acute back pain of a non-serious etiology will get better without any treatment or with simple analgesia alone. Nonspecific chronic low back pain, however, requires both a physical and psychosocial evaluation that may incorporate various nonpharmacological treatment measures. This is especially important in the context of multidisciplinary team management. Many older patients with lower back pain as well as their physicians are also interested in trying nonpharmacological therapies outside the conventional medical spectrum, particularly so as to avoid adverse drug effects of which older people are at high risk. Such measures have various degrees of benefit and are outlined below.

Bed Rest

There is limited quality research into bed rest as a treatment for lower back pain but current evidence suggests that bed rest should not be recommended for acute low back pain as this may delay recovery and potentially harm patients with complications such as deep vein thrombosis or pressure sores. Enforced bed rest should not be replaced, however, with enforced activity (Allen *et al.*, 1999).

Type of Mattress

Physicians are commonly asked by patients with lower back pain to advise on the type of bed or mattress that may relieve symptoms. In a randomized double-blinded controlled multicenter study which included patients up to 82 years, it was shown that a mattress of medium firmness improved pain and disability among patients with chronic nonspecific low back pain possibly by promoting sleeping in the fetal position or distributing body weight more evenly (Kovacs *et al.*, 2003).

Lumbar Supports

A restriction of trunk motion for flexion–extension and lateral bending as well as a reduction in required back muscle forces in lifting are proposed as mechanisms of action of lumbar supports. They have been used as both primary and secondary preventative measures for lower back pain. There is, however, no evidence that they are effective in the latter while there is moderate evidence that they are no more effective than no intervention, in the former (Jellema *et al.*, 2000).

There is still a requirement for high quality randomized controlled trials with inclusion of older people to address their value if any, while aid compliance will also need to be fully ascertained in such work. There are also valid concerns that prolonged use of such supports may lead to increased trunk muscle weakness and atrophy which may in turn exacerbate the underlying problem.

Massage

Advocates of massage therapy claim that it can minimize pain and disability, as well as speed up return to normal function. A systematic review of various massage treatments concluded that massage might be beneficial for patients with subacute and chronic nonspecific lower back pain, particularly when combined with exercise treatment and patient education. Patients included in the trials examined were predominantly a younger population. In this group acupuncture massage appears to be more effective than classic massage but more studies including older participants are required to confirm this as well as determining its cost-effectiveness (Furlan *et al.*, 2002). In elderly institutionalized individuals back massage has been shown to reduce anxiety levels but effects on pain control have not been examined(Fraser and Kerr, 1993). The effects of massage therapy for nonspecific neck pain are not clearly established yet.

Exercise Therapy

Exercise is a widely prescribed treatment for chronic low back pain aiming to improve performance in activities of daily living by improving impairments in back flexibility, strength, and endurance. Exercise also aims to reduce the intensity of back pain and associated disability by challenging established fears and attitudes patients might have. Tailored exercise programs addressing the specific needs and abilities of individual patients have been found to be a safe and effective way of reducing pain and functional dependency. In a systematic review there was strong evidence that exercise helps individuals with chronic low back pain to return to normal activities of daily living, but is not more effective for acute low back pain than inactive or other active treatments (Van Tulder *et al.*, 2000a).

Acupuncture

Both acupuncture and electroacupuncture are used worldwide as alternative medical therapies mainly for the treatment of acute and chronic pain. Endogenous opioid peptides in the central nervous system play an essential role in mediating their analgesic effect. In a systematic review acupuncture appears to be superior to various control interventions but there is insufficient evidence to establish its superiority to placebo (Tulder *et al.*, 2000). In a subsequent randomized controlled study, electroacupuncture was specifically examined in older patients over 60 years of age with chronic low back pain and was found to be a safe and effective adjunctive treatment in the intervention group (Ernst *et al.*, 2002).

Spinal Manipulation Therapy (SMT)

Spinal manipulation therapy (SMT) acts on the various components of the vertebral motion segment. It distracts the facet joints and with faster separation a cracking sound is heard. Relaxation of the paraspinal muscles occurs when they

are forcibly stretched although the mechanisms of this are unclear. SMT is often used for both back and neck pain. In a systematic review incorporating 39 randomized controlled trials it was concluded that there is no evidence that SMT is superior to other treatments such as general practitioner care, analgesia, physiotherapy, exercise, or back schools for acute or chronic low back pain (Assendelft *et al.*, 2003). There is limited evidence that SMT is superior to general practitioner management for short-term pain reduction in chronic neck pain but no long-term benefit is gained. This is especially so when compared to more multidisciplinary rehabilitation exercise programs (Bronfort *et al.*, 2004). The safety profile of SMT in older patients has not been fully established particularly for the treatment of acute or chronic neck pain.

Transcutaneous Electrical Nerve Stimulation (TENS)

Transcutaneous electrical nerve stimulation (TENS) therapy was introduced in the 1970s as an alternative therapy to drug treatments for chronic pain. It is a noninvasive modality that is used for pain relief by electrically stimulating peripheral nerves via electrodes placed on the skin. Its mode of action is based on the gate-control theory of pain which proposes that the TENS mechanism generates neuroregulatory peripheral and central effects that modulate pain transmission. In a systematic review there was no evidence to support the use of TENS in the treatment of chronic low back pain although the meta-analysis lacked data on how TENS effectiveness is affected by the type and site of electrode applications or treatment durations, frequencies, and intensities (Milne *et al.*, 2004).

Behavioral Treatment

Behavioral interventions are commonly used in the treatment of disabling chronic low back pain. These are based on the rationale that psychosocial factors, patient attitudes and beliefs, as well as illness behavior are just as important in chronic low back pain syndromes as somatic disease (Waddell,1987).

Cognitive therapy aims to identify and modify patients' thoughts regarding their pain and disability. This can be done directly by cognitive restructuring techniques such as imagery or attention diversion, or indirectly by changing maladaptive beliefs and thoughts (Turner and Jensen, 1993).

A systematic review concluded that behavioral therapies appeared to be an effective treatment for patients with chronic low back pain, but it was unclear what type of patients would benefit while the reviewed trials predominantly examined younger populations (Van Tulder *et al.*, 2000b).

Biopsychosocial approaches have not been examined in older adults but in a working age population there is moderate evidence that multidisciplinary rehabilitation is effective for subacute low back pain (Karjalainen *et al.*, 2004a) but not for neck pain (Karjalainen *et al.*, 2004b). Routine physiotherapy for patients with mild to moderate low back pain may be no more effective in the long term than advice given by a physiotherapist (Frost *et al.*, 2004).

Back Schools

These have been predominantly studied in younger age-groups where a systematic review concluded that they may be effective for patients with recurrent and chronic low back pain in occupational settings. Their cost-effectiveness has not been established. The trials examined did not include older patients as participants (Van Tulder *et al.*, 2000c).

Neuroreflexology

Neuroreflexology is characterized by temporary implantation of a number of epidermal staples into trigger points in the back and into referred tender points in the ear. It is a separate entity to acupuncture as different zones of the skin are stimulated. It is performed without anaesthesia and takes about 60 minutes for the staples to be implanted. These remain in place for up to 90 days in the back and up to 20 days in the ear. A systematic review showed that it appears to be a safe and effective short-term treatment for chronic nonspecific low back pain, but further multinational randomized controlled trials are needed to confirm this (Kovacs *et al.*, 2002).

Radiofrequency Denervation

Radiofrequency current is a clinical tool used for creating discrete thermal lesions in neural pathways in order to interrupt transmission. Such currents can be used to block nociceptive pathways at various sites. It can be considered as a minimally invasive alternative to open surgery in suitably selected older patients. The technique was first developed in the 1970s and has been used as a palliative treatment in conditions such as trigeminal neuralgia and nerve root avulsion. It is a highly technical procedure, which requires a skilled operator and is not without its complications. In a systematic review, there was limited evidence that it provides short-term benefits in patients with lumbar zygapophysial joint pain and conflicting evidence in favor of a short-term benefit in cervical zygapophysial joint pain Niemisto *et al.* (2003).

Other Treatments

Other alternative treatments that have been tried for lower back pain include herbal medicines, homeopathy, balneotherapy, prolotherapy, heat and cold therapies, but evidence for their efficacy is limited.

Pharmacological Interventions

Readers are referred to **Chapter 84, Control of Chronic Pain** on pain management, particularly stepwise treatment

of pain along the pathway of the standard analgesic ladder. A number of systematic reviews have addressed the benefits and problems of different category analgesics especially for nonspecific causes of back pain. Again it must be emphasized that pharmacological treatments beyond simple analgesia such as paracetamol, should be preferably avoided given the usually inevitable association with adverse effects in older people.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are the most frequently prescribed medications worldwide. Their potential for adverse effects including gastrointestinal, cardiovascular, and renal function, particularly in older people is well documented. It remains unclear whether or not they are more effective than simple analgesia such as paracetamol (Van Tulder *et al.*, 2000d).

Muscle Relaxants

Both benzodiazepines and nonbenzodiazepines have been evaluated in treating low back pain. The latter have greater efficacy than the former in treating acute pain, but the relatively high occurrence of adverse effects including gastrointestinal and central nervous system effects such as drowsiness and dizziness, of which older people may be more vulnerable to, suggests they should be used with great caution. Most studies have been performed in a relatively younger population where the nonbenzodiazepine drugs particularly carisoprodol have been shown to have most efficacy for acute lower back pain (Van Tulder *et al.*, 2004)

Antidepressants

Antidepressant drugs have been extensively used for chronic pain syndromes including chronic low back pain. Their efficacy has been postulated to be due to a combination of their antidepressant, sedative, and analgesic properties. Both tricyclic and tetracyclic antidepressants produce a moderate effect on symptom reduction in patients with chronic low back pain, independently of depression status. Selective serotonin reuptake inhibitors do not appear to have the same effect. It is unclear whether patient functional status improves though (Staiger *et al.*, 2003).

Neck Pain

Neck pain is second only to low back pain as the most common musculoskeletal disorder in population surveys and primary care with a point prevalence of 22% (Cote *et al.*, 2000). As such, it too represents a major cause of morbidity and health-care expenditure. Like low back pain it can be a difficult symptom to assess as often the pain is poorly localized and important symptoms and signs are often located peripherally. The aging neck is also prone to many of the degenerative processes described earlier, particularly as it is a relatively more mobile structure than the thoracic or lumbosacral spine. Cervical disk, vertebrae, as well as cord pathology can all produce symptoms and signs located elsewhere. Pain may be purely mechanical such as in spondylosis, myelopathy, or disk herniation, but other pathologies must also be considered, especially as these tend to occur more frequently in older people. These include:

rheumatological disorders such as rheumatoid and psoriatic arthritis, ankylosing spondylitis, fibromyalgia, polymyalgia rheumatica, and giant cell arthritis;

neurological disorders such as the neuropathies, brachial plexitis, and causes of meningeal irritation including subarachnoid hemorrhage;

neoplastic disease including primary and metastatic disease and multiple myeloma;

infective causes such as osteomyelits and diskitis as described previously. Herpes zoster infections may only become apparent with the appearance of the characteristic vesicular rash;

gastrointestinal disease including oesophageal spasm, gastro-oesophageal reflux disease, and pharyngeal pouch pathology;

trauma including both direct and indirect injuries;

referred pain including cardiovascular sources such as angina or arterial dissection.

Clinical Approach

A similar assessment process incorporating many of the features in assessing back pain will help guide appropriate investigations and treatment. Many of the specific causes of neck pain are addressed elsewhere in this textbook.

Cervical Spondylosis

This is usually caused by degenerative disk disease and is a very common cause of chronic neck pain in older people. Whiplash injuries in earlier adult life may also result in premature secondary cervical spondylosis. It can affect all levels of the cervical spine with degenerative disease evident in the intervertebral disks, vertebral body osteophytosis, and facet and laminal arch hypertrophy. Pain associated with cervical spondylosis may be local or referred elsewhere or both. Typical pain syndromes include that which develops at the back of the neck radiating to the occiput, shoulder, and upper limb if there is cervical root pressure from osteophytes or cervical disk disease. Pain responds variably to activity modification, neck immobilization, exercise programs, and appropriate analgesia.

Cervical spondylotic myelopathy is the most serious and disabling complication of the disease (*see* **Chapter 85, Cervical and Lumbar Spinal Canal Stenosis**). Simple neck immobilization can result in improvement in up to 50% of patients, while surgical intervention should be considered in patients presenting with severe or progressive

neurological signs. However, there is no definite conclusion on the benefit/risk ratio of surgery (Fouyas *et al.*, 2002). Fortunately, neurological symptoms are uncommon, tending to occur more often in patients with associated congenital spinal stenosis.

KEY POINTS

- Back and neck pain are very common symptoms in older people.
- The incidence of serious pathology is much more common than in younger age-groups.
- "Red flag" symptoms and signs demand thorough investigation.
- Serious disease should be managed using the expertise of all appropriate specialists.
- Restoration of function and abolition of pain are the mainstays of management of nonspecific low back pain.

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PART III

Medicine in Old Age

Section 10

Endocrine and Metabolic Disorders

Water and Electrolyte Balance in Health and Disease

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INTRODUCTION

The major constituent of all body fluids is water and the major solutes are electrolytes. The body water is divided into major fluid compartments, which are the intracellular and extracellular spaces, and the extracellular space is further separated into plasma and interstitial components. Intracellular solutes are very different from those found in extracellular fluid. However, osmotic equilibrium dictates that the chemical potential of water must be the same in intra- and extracellular fluid. Since all cell membranes are readily permeable to water, osmolality throughout the body fluids is essentially the same, with only a few exceptions (renal medulla, CSF (cerebrospinal fluid)).

The volume and composition of both the intracellular and extracellular fluid may be altered by a variety of circumstances. In order for normal metabolic activity to be carried out, there must be maintenance of an optimal body fluid osmolality in both the extracellular and intracellular fluid. Homeostatic mechanisms are therefore constantly at work to maintain such an environment. Most major metabolic activities do not occur in the extracellular fluid, so there can be substantial alteration in its osmolality without causing any adverse effects.

Extracellular fluid serves to transmit substances (electrolytes, metabolites, nutrients) between cells and the various organ systems. It regulates both intracellular volume and ionic composition. Because of the requirement for osmotic equilibrium between the cells and the extracellular fluid, any alteration in extracellular fluid osmolality is accompanied by identical changes in intracellular osmolality, often with a concomitant change in cell volume. The brain, on the other hand, appears to regulate its osmolality primarily by alteration of intracellular solute content rather than by changes in cell volume (Ayus *et al.*, 1996; Arieff *et al.*, 1995). The ability of the extracellular fluid to transmit substances from plasma to organs and cells requires maintenance of a near-normal extracellular fluid volume. Maintenance of an intact plasma volume is also necessary to maintain cardiovascular stability and adequate tissue oxygen delivery. This chapter will describe the normal and abnormal regulation of body water, intracellular and extracellular volume, antidiuretic hormone (ADH), sodium, potassium, and osmolality. Abnormalities of sodium, osmolality, water, potassium, and ADH, as well as their management, will be described.

TOTAL BODY WATER AND PLASMA VOLUME

Total body water (TBW) varies as a function of age, sex, and weight. Body water in hospitalized adults who do not have abnormalities of fluid and electrolyte balance is about 43–54% of body weight. The relative water content of the body is highest in infants and children and decreases progressively with aging. The water content also depends on the percent of body fat, which is greater for women and obese individuals. The frequently quoted figure for TBW as 60% of body weight applies primarily to healthy young males. The percent of TBW varies widely as a function of age, sex, and body habitus, with a range of 42% (obese elderly women) to 75% (young children), while the mean figure for hospitalized adults is about 50% of body weight. The percent body water as a function of age, gender, and weight has recently been determined in a large number of subjects by radioisotope studies (Chumlea *et al.*, 2001). The intracellular volume is estimated from TBW and extracellular volume, but the extracellular volume can be measured directly by use of various chemical markers (insulin, sucrose, sulfate, Cl^-, CNS^-, Br^-). Measurement of TBW by various dilution techniques is relatively reproducible, but measurement of the extracellular volume is technically difficult, because there is no material that is known to distribute exclusively in

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extracellular fluid. Thus, depending on the type of marker used, the extracellular volume will vary from 27–45% of TBW (Oh and Carroll, 1995).

Brain Cell Volume Regulation

Disorders of body water and electrolytes exert their most severe manifestations upon the brain. In general, hypoosmolar states tend to result in brain swelling, while hyperosmolar states lead to brain shrinkage. To understand how these conditions can affect the central nervous system, it is first necessary to understand how the brain can defend itself against alterations in body water and electrolytes. The principal osmotically active constituents of brain consist of both organic and inorganic solutes. Substantial evidence exists, both in humans and experimental animals, that there are several clinical situations where changes in plasma osmolality occur, but the apparent net loss or gain of cellular water and solute in brain does not account for the apparent change in tissue osmolality (McManus *et al.*, 1995). In these instances, there may be (1) inactivation of intracellular solute; (2) a gain in solute that is not the same as the usual commonly measured substances (urea, glucose, sodium, potassium, lactate). This undetermined solute has been called *idiogenic osmoles*. Furthermore, it is now known that the brain undergoes osmotic adaptation to hyperosmolar states in a manner that is distinctly different from that of most other mammalian tissues.

In clinical situations characterized by hypoosmolality, the brain minimizes swelling by lowering its intracellular osmolality with extrusion of sodium, potassium, chloride, and, possibly, amino acids (Arieff *et al.*, 1995; Vexler *et al.*, 1994a). The decrement of brain intracellular sodium and potassium is largely mediated by the effects of Na–K ATPase (Fraser and Arieff, 2001). The lowering of brain osmolality in this manner prevents the influx of water, which would lower brain osmolality at the expense of a gain in brain cell volume. In several different mammalian species, when hyponatremia is produced over periods of days to weeks, brain water content is normal to only slightly increased, and there is a markedly reduced cell content of both sodium and potassium (Arieff *et al.*, 1995).

Hyperosmolar States

The response of the brain to hyperosmolality has been extensively studied, with hyperosmolality produced using either NaCl, glucose, sodium, mannitol, glycerol, ethyl alcohol, or urea (Arieff *et al.*, 1977). It has been shown that the brain response depends on the type of solute accumulated. When hyperosmolality is caused by endogenous solutes, such as in hypernatremia or hyperglycemia, the increase in intracellular solute content necessary for osmotic equilibrium is largely accounted for by the osmoles of unknown nature (idiogenic osmoles) and, to a lesser extent, by increases in Na, K, and Cl, and amino acids (Ayus *et al.*, 1996). Other potential idiogenic osmoles present in the brain of animals with hypernatremia include myoinositol, betaine, phosphocreatine, and glycerophosphorylcholine (GPC), creatine, other methylamines, choline, sorbitol, and other polyols (Lien *et al.*, 1990). However, the osmotic contribution of any of these organic compounds has not been determined. It is possible that idiogenic osmoles arise from the osmotic activation of some solutes normally bound to polyvalent anions and released in response to the increase in ionic strength. The speed of brain volume regulation in hyperosmolality seems to vary with the type of solutes that cause the hyperosmolality. It appears that the speed of volume regulation is similar during hyperglycemia and hypernatremia. In glucose-induced hyperosmolality (in rabbits), the brain volume is restored to normal within 4 hours (Arieff *et al.*, 1977), similar to the findings after 4 hours of NaCl-induced hyperosmolality (Ayus *et al.*, 1996). Rapid infusion of urea can cause brain dehydration because the equilibration of urea in the brain is relatively slow. Although it takes less than 1 hour for urea to equilibrate in skeletal muscle, it takes 4–10 hours to reach equilibrium in the brain. In chronic uremia, despite the absence of a urea concentration gradient, there is substantial accumulation of idiogenic osmoles, suggesting that shrinkage of brain cells is not required for the formation of idiogenic osmoles. In contrast to chronic uremia, there is no accumulation of idiogenic osmoles in experimental acute uremia (Fraser and Arieff, 1997a).

HORMONAL AND PHYSICAL EFFECTS ON BRAIN ADAPTATION

The ability of the brain to adapt to either hyperosmolar or hypoosmolar states is markedly influenced by the effects of both hormones and physical factors (water content, ratio of brain size to skull size) (Fraser and Arieff, 2001). The most important of these hormones are vasopressin, estrogens, androgens, progesterone, and atriopeptin. The most important effects of physical factors on brain adaptation are the progressive alterations between the ratio of brain size to skull capacity, which occurs with the aging process (Gur *et al.*, 1991), and the gender differences between men and women (Arieff *et al.*, 1995). Recent studies demonstrate that physical factors are primarily responsible for the differences in brain adaptation between immature versus adult laboratory animals, as hormonal factors are not different (Fraser and Arieff, 2001).

VASOPRESSIN

Most studies of hyponatremia in both children and adults demonstrate that virtually all hyponatremic patients have increased blood levels of the hormone arginine vasopressin (Anderson *et al.*, 1985). There are multiple cerebral effects of

vasopressin (Arieff *et al.*, 1993). Vasopressin administration in rodents, acting through cerebral V1 (Vasopressin 1) receptors, results in water movement into brain in the absence of hyponatremia, a significant decline in brain synthesis of ATP, decreased brain blood flow and CSF production, and impairment of several possible pathways for sodium efflux during hyponatremia (Kanda and Arieff, 1994; Kanda *et al.*, 1992). The decline of ATP synthesis in female rats after vasopressin administration may be related in part to brain ischemia from cerebral vasoconstriction. The vascular reactivity of vasopressin, a potent vasoconstrictive agent, is significantly greater in female rats than in males (Kozniewska *et al.*, 1995). Following blood loss, plasma vasopressin levels are significantly higher in female rats than in males. When hyponatremia is induced with either water alone or water plus a vasopressin analogue, desmopressin (DDAVP, which has no effect on the brain V1 receptor), the aforementioned cerebral effects of vasopressin are absent, demonstrating the importance of vasopressin in the pathogenesis of hyponatremic encephalopathy (Arieff *et al.*, 1995).

ESTROGEN, PROGESTERONE, AND ANDROGENS

The important mechanisms of early adaptation of brain to hyponatremia include extrusion of sodium from brain cells by several pathways (Fraser and Swanson, 1994; Vexler *et al.*, 1994b). Hyponatremic male laboratory animals are better able to extrude sodium to decrease brain cell osmolality than are females, resulting in significantly less brain swelling in males than in females both *in vivo* and *in vitro* (Fraser and Swanson, 1994). Following an initial fall in cerebral blood flow and loss of CSF via bulk flow, extrusion of sodium is the most important early defense of the brain against hyponatremia (Vexler *et al.*, 1994a). The major reasons for the increased morbidity and mortality in females compared to males include a diminished ability of the female brain to adapt to hyponatremia by limiting the amount of brain swelling. There is increasing evidence that these effects of gender may be mediated in part through the actions of certain steroid and peptide hormones, including estrogen, progesterone, and testosterone (Fraser and Swanson, 1994). In addition, there is substantial evidence that estrogen stimulates vasopressin release, whereas androgens suppress it (Arieff *et al.*, 1995). In addition to effects on vasopressin release, estrogen may antagonize brain adaptation via the Na^+-K^+ ATPase system while androgens may enhance such adaptation (Fraser and Swanson, 1994).

Atrial Natriuretic Peptide (*see* Chapter 49, Mechanisms of Heart Failure)

Atrial natriuretic peptide (ANP) in the central nervous system appears to play an important role in the regulation of brain water content in several pathologic states characterized by cerebral edema. During the regulatory volume decrease observed with hyponatremia, an important initial response in the brain is a loss of sodium (Arieff *et al.*, 1995). ANP may act to decrease cell volume by effecting a net decrease of the intracellular sodium concentration in nerve cells (Kanda *et al.*, 1992). By decreasing sodium uptake in pathological states, the net effect of ANP would be a decrease in intracellular sodium, as it continues to be pumped out by Na^+-K^+ ATPase. The effect of ANP in brain appears to be opposite to that of vasopressin (Del Bigio and Fedoroff, 1990). ANP also affects the regulation of CSF production and hence its pressure.

PHYSICAL FACTORS

There are two important factors that impact the physical elements of brain adaptation. The first is the aging process, which is marked by progressive alterations between the ratio of brain size to skull capacity. This ratio is highest at birth and progressively decreases with age. The second factor is gender. For reasons yet unknown, the ratio between skull size and brain size is different between adult men and women (Gur *et al.*, 1991). Other physical factors include CSF volume and brain water and electrolyte content. Physical factors may play an important role in adaptation to hyponatremia, particularly in small children and the elderly. In humans and laboratory animals, brain water content is more than 2.5 times higher in the young, decreasing progressively with advancing age (Gur *et al.*, 1991). In children, the ratio of brain to skull size is such that there is less room for expansion of the pediatric brain in the skull than there is in the adult (Gur *et al.*, 1991). Adult brain size is reached at about age six, while full skull size is not reached until about age 16. Additionally, the intracerebral volume of CSF is more than 10% greater in the adult than in the young (Gur *et al.*, 1991). When brain swelling occurs, the intracerebral loss of CSF increases the available volume in which the brain can expand. Since the percentage of CSF in the brain increases with age, adults have more room in the rigid skull for the brain to expand than do children (Gur *et al.*, 1991). In neonatal rats and dogs with hyponatremia, the ability of the brain to adapt to hyponatremia is impaired (Arieff *et al.*, 1995). The net result of the aforementioned physical factors is manifest in prepubescent children and menstruant women with hyponatremia (Arieff *et al.*, 1992). When symptomatic hyponatremia occurs in either group, the morbidity and mortality are very high, largely because of the effects of physical factors and decreased ability of the brain to adapt (Arieff *et al.*, 1992). In postoperative hyponatremia, a prospective study of 77 000 patients revealed that menstruant women are far more susceptible to brain damage from hyponatremia than are either men or postmenopausal women (Ayus *et al.*, 1992), a finding confirmed many times over (Steele *et al.*, 1997; Nzerue *et al.*, 2003).

Thirst and its Regulation

The sensation of thirst is an important general regulator of the body's water balance. The afferent stimuli for thirst sensation include both increases in plasma osmolality and decreases in extracellular volume. Increases in either plasma or CSF sodium concentration will also stimulate thirst and cause ADH to be released. At a normal plasma osmolality of approximately 285 mOsm/kg water, the circulating plasma ADH level is approximately 2 pg ml^{-1}, which is the level needed to produce a half maximal urine concentration of approximately 600 mOsm/kg. Normal individuals do not usually experience thirst at this level of plasma osmolality. With dehydration, thirst is first expressed only when plasma osmolality reaches approximately 294 mOsm/kg water. This level of plasma osmolality represents a 2% increase above normal and is generally referred to as the *osmolar threshold* for thirst. At this level of plasma osmolality, ADH is maximally stimulated (usually above 5 pg ml^{-1}) and is sufficient to achieve maximally concentrated urine (above 1000 mOsm/kg in young adults). A number of pharmacologic agents increase thirst, including tricyclic antidepressants and antihistamines. Certain hormones increase thirst, including ADH and angiotensin II.

A patient with defective thirst mechanism and intact osmolar regulatory center will appropriately release ADH in response to volume contraction and hypertonicity, but will become increasingly dehydrated because of the lack of thirst sensation. Such patients will not experience the desire to drink and have to be taught to drink water on a routine basis. They also have to learn to increase water intake with increased ambient temperature and physical activity. Such patients are classically described as having "essential hypernatremia" as their ability to normalize their serum sodium depends entirely on the ability to take in sufficient amounts of oral fluids. On the contrary, patients with intact thirst mechanism and decreased circulating ADH (diabetes insipidus) can often exist quite normally because of voluntary water intake stimulated by thirst. These patients may get into trouble only if access to water is prevented, as in the case of incapacity.

The afferent stimuli for the sensation of thirst include both osmolar and volume signals. However, it is not clear how these signals are transmitted to the thirst center. For example, increases in either plasma or CSF sodium concentrations can stimulate thirst (and ADH release); but it is not clear which is more important, or if changes in tonicity or sodium concentration are the primary stimuli. As is true for ADH release, it is clear that "effective" osmoles (those that are relatively restricted to the extracellular fluid, such as sodium salts or mannitol) are effective thirst stimuli. The cellular mechanisms by which changes in osmolality are translated into thirst are also unknown, although changes in brain cell volume have been proposed (McKinley *et al.*, 1988). Changes in intracellular volume seem more important in regulating thirst than changes in intracellular osmolality (without a change in intracellular volume), or changes in extracellular volume (without a change in intracellular volume) (McKinley *et al.*, 1988).

Complex roles for enkephalins and other opiate mediators in thirst regulation have recently been proposed, and the roles for prostaglandins and other neuroactive substances are also being explored. ADH may also have central dipsogenic effects (McKinley *et al.*, 1988). Thirst may also alter ADH distribution and metabolism, and substances such as isoproterenol may affect it by altering angiotensin II levels. Angiotensin II has substantial dipsogenic properties within the brain, but it does not cross the blood-brain barrier as does angiotensin I. Angiotensin I readily crosses the blood-brain barrier, and the brain has its own angiotensin converting enzyme (ACE) system, which converts angiotensin I to angiotensin II. The exact biochemical mechanism by which angiotensin II activates the cerebral thirst center is unknown. Such mechanisms are similar to those proposed for osmolar stimuli, suggesting that there may be a final common pathway for the two normal (physiologic) thirst stimuli (McKinley *et al.*, 1988).

Primary hypodipsia is a "pure" deficit in the thirst mechanism, requiring all other aspects of osmoregulation to be normal. The results of such a "pure" deficit in thirst may then be predicted as follows. The loss of thirst would result initially in decreased water intake and a tendency both to hyperosmolality and to effective arterial blood volume depletion. Both changes would stimulate ADH release and thereby increase renal water conservation. If water conservation is sufficient to offset the decrease in water intake (if plasma osmolality and blood volume are returned to near normal), the thirst deficit may go unrecognized by the patient. On the other hand, if renal water conservation is insufficient to compensate for the decreased water intake, symptoms of hyperosmolality and hypovolemia would supervene.

A meaningful evaluation of thirst deficits is difficult because drinking behavior is influenced by many stimuli that are unrelated to osmoregulation or volume regulation (Zerbe and Robertson, 1994). Definitive testing for thirst deficits should include both osmolar and volumetric stimuli, but only the former is usually evaluated. The test subject must be alert, oriented, and able to indicate whether or not thirst sensation is present. When studies of osmolar thirst stimuli are performed, the subject should be euvolemic (normal blood volume), and other dipsogenic stimuli (hyperthermia, exercise) should be minimized. A commonly used testing method is the administration of intravenous hypertonic NaCl (514 mM NaCl) solution at a rate sufficient to elevate the plasma osmolality from baseline to some arbitrary level that is at least 10% above baseline. The plasma osmolality should be determined at the baseline and at 30-minute intervals until the sensation of thirst is reported, or until the plasma osmolality has increased by at least 10% (Zerbe and Robertson, 1994). This technique will increase both blood volume and plasma osmolality, and the increased blood volume will tend to decrease hypovolemia-induced thirst. Moreover, the conclusion of the test is arbitrary if thirst is not elicited; thus, total absence of thirst (dipsia) can never be defined with certainty.

AGE-RELATED CHANGES IN SODIUM AND WATER HOMEOSTASIS

Hypernatremia is a frequent problem in older patients (Palevsky *et al.*, 1996). Thus, changes that may occur in the physiological responses of the elderly to hypernatremia may be of particular interest in understanding the pathogenesis of hypernatremia in the elderly. If healthy elderly men are compared to younger controls, there are differences in the response to 24 hours of water deprivation (Lindeman *et al.*, 1985). In the older men, there are deficits in both the intensity and threshold of the thirst response to specific stimuli, and in the subsequent water intake that follows the thirst. The ability to produce a concentrated urine during water deprivation also declines with advancing age. This may be related to a relative increase in renal medullary blood flow, which washes out medullary tonicity; increases in solute load per nephron (because of nephron dropout) resulting in an obligate osmotic diuresis; or impairment of renal tubular responsiveness to osmolality-mediated vasopressin release. Although there is an enhanced responsiveness to osmolality-mediated vasopressin release, there may be impaired responsiveness of vasopressin release to volume and pressure stimuli (Phillips *et al.*, 1984). In addition, there is a high prevalence of bacteriuria in elderly patients, which may impair urinary-concentrating ability. Finally, there is both a decline in glomerular filtration rate (GFR) and an increased incidence of renal disease with advancing age, both of which may contribute to impaired ability to conserve water (Lindeman *et al.*, 1985).

THIRST AND WATER METABOLISM IN THE ELDERLY

There are several alterations of water metabolism that have been described in elderly individuals. After 24 hours of water deprivation, elderly men (age above 67 years) exhibited greater increases in plasma osmolality, serum sodium and plasma vasopressin levels than did younger men (age below 31 years) (Phillips *et al.*, 1984). In addition, after 24 hours of water deprivation, elderly men were less thirsty, and their maximal urine osmolality was less, than observed in younger men (Phillips *et al.*, 1984). For a given serum osmolality, the plasma vasopressin levels are higher in older men than in their younger counterparts. Although there is thus an enhanced responsiveness to osmolality-mediated vasopressin release in older men, there may be impaired responsive volume stimuli. In addition, there is a high prevalence of bacteriuria in elderly patients, which may impair urinary-concentrating ability, and with increasing age, there is a decline of GFR, which may contribute to impaired ability to conserve water (Lindeman *et al.*, 1985; Palmer and Levi, 1997).

Despite the fact that maximal urine osmolality is less in elderly individuals, hyponatremia is the most common electrolyte abnormality encountered in the elderly, although hypernatremia is almost as frequent. Unlike the situation with hyponatremia, hypernatremia in the elderly carries a very poor prognosis, with a mortality in excess of 40%, seven times that observed in age-matched controls (Palevsky *et al.*, 1996; Snyder and Arieff, 1992). An important cause of hypernatremia is diabetes insipidus, which can be congenital (Bichet *et al.*, 1997), related to stroke, tumor, other causes of brain damage (Bichet, 1997), or as a complication of neurosurgery (Bichet, 1997; Arafah *et al.*, 1996a; Arafah *et al.*, 1996b).

REGULATION OF VASOPRESSIN

Arginine vasopressin (antidiuretic hormone, ADH) is the principal hormone responsible for the regulation of body water. ADH is synthesized in the hypothalamus and is carried in cortical CSF to portal blood flowing to the pituitary capillaries (Arieff *et al.*, 1993). The hormone is also secreted (from the hypothalamus) into the CSF of the third ventricle, where it binds to V1 receptor sites on neurons and blood vessels where its cerebral effects are mediated by intracellular second messengers (Faraci *et al.*, 1990). From the pituitary, vasopressin is then secreted into the bloodstream (Zerbe and Robertson, 1994). Neither ADH nor most other hormones that have effects on the brain have access to the brain parenchyma. These substances bind to brain cells and exert their effects inside the brain by means of second messengers. For ADH in brain, the second messengers include calcium, inositol triphosphate (IP3), and nitric oxide, and a linkage has been demonstrated between IP3 and vasopressin V1 receptors in the brain.

There are two primary stimuli for the release of ADH: (1) increased plasma osmolality; and (2) decreased intravascular volume (Share, 1996). Extracellular volume becomes important in the control of vasopressin elaboration only when there is a decrease of about 5%. With ADH release, ingested water is retained abnormally, which lowers plasma osmolality and repletes plasma volume. As these parameters are satisfied, ADH release is inhibited and any excess intake of water is eliminated in the urine. If a patient with normal kidneys takes in a normal daily solute load (1000 mosmoles), and is able to produce a maximally dilute urine (50 mOsm/kg), he will theoretically be able to ingest up to 20 l of water/day without becoming hyponatremic. However, in patients with poor nutrition (solute load of 250 mOsm/day), as in the case of beer potomania (Fenves *et al.*, 1996), water intake in excess of 5 l could lead to the development of hyponatremia. A similar situation would exist with a diet low in both NaCl and protein, combined with a water intake of less than 5 l per day, either as beer or other fluids (Goldman *et al.*, 1997). Similar cases have been reported after water intoxication associated with use of the recreational drug ecstasy (Balmelli *et al.*, 2001; Ben-Abraham *et al.*, 2003). A number of factors other than elevated plasma osmolality and hypovolemia can cause ADH release and override the effects of osmolality and volume. These include many medications,

tumors, pulmonary lesions, intracranial processes, emesis, nausea, stress, hypoxia, and even anxiety and fear. Elevation in ADH levels secondary to these entities, along with a clinical syndrome consisting of a normal to increased intravascular volume, with hypoosmolality, urine osmolality above 100 mOsm/kg, and decreased plasma levels of sodium, urea, uric acid, and creatinine is known as the *syndrome of inappropriate secretion of antidiuretic hormone* (*SIADH*). The patient must have no other reason for increased ADH, such as volume depletion or hyperosmolality, or any of the nonosmotic stimuli for vasopressin release (Verbalis, 2001).

DIABETES INSIPIDUS

The absence of ADH effect upon the kidney results in diabetes insipidus. Diabetes insipidus is a clinical condition characterized by the decreased or absent renal effects of the hormone vasopressin, and it can be either nephrogenic or central in origin. Vasopressin is synthesized by the hypothalamus and is both stored and secreted by the posterior pituitary gland. In central diabetes insipidus, there is an impairment of either synthesis or release of vasopressin into the circulation. In nephrogenic diabetes insipidus, vasopressin is usually present in the circulation but the kidney response to the hormone is impaired or absent. Criteria for the diagnosis of diabetes insipidus include the presence of polyuria (urine output above 250 ml hour^{-1}) with hypotonic urine (urine osmolality below 100 mOsm/kg) in the absence of osmotic diuresis (plasma osmolality is below about 300 mOsm/kg without elevations in plasma levels of impermiant solutes, such as glucose, mannitol, urea). The diagnosis of central diabetes insipidus can be established by the above findings plus the following: (1) before the onset of polyuria, patients were able to excrete a hypertonic urine (urine osmolality above 300 mOsm/kg); (2) after several days of polyuria, when plasma is concentrated, the urine osmolality should remain below 100 mOsm/kg. At this time, vasopressin stimulation should be maximal and urine intensely concentrated; (3) no drugs have been administered, nor was there any medical condition present, which would predispose the patients to the development of nephrogenic diabetes insipidus; and (4) findings by radiologic evaluation or autopsy should demonstrate hypothalamic/pituitary damage but normal kidneys and renal tubular function. Both central and nephrogenic diabetes insipidus can lead to hypernatremia and permanent brain damage (Vin-Christian and Arieff, 1993).

In the syndrome of central diabetes insipidus, ADH is either not synthesized at all or not released into the circulation in quantities sufficient to maintain normal water balance. Complete diabetes insipidus is the inability to produce urine of greater osmotic concentration than that of plasma under an appropriate osmotic stimulus. Patients with partial diabetes insipidus include those who can produce a urine hypertonic to plasma but whose ADH production is below normal. Conscious patients with diabetes insipidus do not become dehydrated unless they also have a thirst defect, a combination that may occur with stroke, hypothalamic disease or after hypothalamic surgery. Renal function is normal in pituitary diabetes insipidus. Mild serum hyperosmolality and increased sodium concentration may be the only laboratory abnormalities detectable. Unconscious patients manifest polyuria and hypernatremia with worsening dehydration (Trivedi and Nolph, 1994).

If ADH is absent but thirst is normal, the patient will drink sufficient water to prevent the serum sodium from rising but will manifest polyuria and polydipsia as well. If ADH secretion is normal and thirst is absent, the patient will become progressively dehydrated with hypernatremia and small volumes of concentrated urine unless he drinks deliberately (primarily hyodipsia). If ADH and thirst are both absent, the patient will become very dehydrated and will manifest hypernatremia. The extreme dehydration will eventually lead to a reduction of GFR and the production of small volumes of concentrated urine. If ADH is partially deficient and thirst is normal, the patient will have a water diuresis with a normal plasma osmolality, leading to an eventual increase of plasma osmolality. This will provoke thirst and polydipsia (incomplete pituitary diabetes insipidus). If thirst is absent, the patient with partial diabetes insipidus will lose water and will not drink. The loss of water will raise serum sodium and osmolality to such a level that the quantity of ADH released is sufficient to permit the excretion of concentrated urine. This condition, sometimes described as "essential hypernatremia", is usually caused by a hypothalamic lesion (Zerbe and Robertson, 1994).

With nephrogenic diabetes insipidus, there is no impairment of the ability to secrete vasopressin, but there is rather an impairment of the ability of the hormone to affect the kidney. Arginine vasopressin binds to the vasopressin V2 receptor in the renal distal tubule (thick ascending limb of the loop of Henle) and collecting tubules. The V2 receptor is coupled to an adenylate cyclase, which generates cyclic AMP when stimulated. A number of pharmacological agents can lead to nephrogenic diabetes insipidus, and these include lithium, demethylchlortetracycline, methoxyflurane, and certain hypoglycemic agents such as glyburide (Morrison and Singer, 1994). Hyperparathyroidism with hypercalcemia can lead to nephrogenic diabetes insipidus, as can a number of renal interstitial disorders (Vin-Christian and Arieff, 1993).

Diabetes insipidus is most commonly of undetermined cause and is occasionally familial. The familial form, which is probably due to atrophy of the nerve cells in the area of the hypothalamus where ADH is synthesized, may present at any age. When the etiology is known, it most often results from metastatic tumors (breast or lung), granulomas (including sarcoidosis) in the areas of the sella or hypothalamus, surgical interruption of the hypothalamic-neurohypophyseal system, skull fractures, or cerebral vascular accidents. Among the most common causes of acute diabetes insipidus is head trauma associated with either falls or auto accidents (Trivedi and Nolph, 1994; White and Likavec, 1992). Cerebral hypoxema is another cause of diabetes insipidus, where patients have cerebral encephalomalacia associated with

severe brain damage secondary to clinical circumstances as asphyxia, drug-induced respiratory failure, cardiac arrest, or shock. Diabetic insipidus has been infrequently reported after cerebral herniation complicating symptomatic hyponatremia (Fraser and Arieff, 1990), or cerebral edema associated with diabetic ketoacidosis or nonketotic hyperosmolar coma. In rare situations, clinical diabetes insipidus may not be apparent if both anterior and posterior pituitary cease to function, because glucocorticoid secretion may be impaired secondary to ACTH deficiency (Morrison and Singer, 1994). The diabetes insipidus will become apparent only when glucocorticoid replacement therapy is given (Arieff, 2003).

Diabetes insipidus is a well-recognized complication of blunt head trauma. Delay in diagnosis can occur when head trauma does not appear to be severe or when the patient is admitted to a service other than neurosurgery. Detailed assessment of anterior pituitary function in patients with traumatic diabetes insipidus usually requires a delay until the patient is medically stable. Generally, these patients are initially treated with adrenal steroid therapy for cerebral edema, and detailed evaluation of endocrine function is often difficult to obtain. The diabetes insipidus caused by head trauma may persist for several years, and may become permanent if the patient does not recover within 4–6 months (Arieff, 2003).

HYPONATREMIA

While diabetes insipidus generally occurs because of the absence of ADH effect upon the kidney, hyponatremia is usually associated with elevated plasma levels of ADH. Hyponatremia can be succinctly defined as an abnormally low plasma sodium concentration. Although the kidney is important in the pathogenesis of hyponatremia, the target organ for changes that produce morbidity and mortality is the brain. Hyponatremia has few important sequelae or clinical manifestations other than those associated with the central nervous system. Hyponatremia is the most common electrolyte abnormality seen in a general hospital population, with an incidence and prevalence of about 1.0 and 2.5%, respectively (Ayus *et al.*, 1992). The incidence of hyponatremia is similar among men and women, but brain damage occurs predominantly in young (menstruant) females and prepubertal individuals (Arieff *et al.*, 1992; Ayus *et al.*, 1992; Arieff, 1998). Brain damage from hyponatremia is generally uncommon in men but does occur in older (postmenopausal) women (Ayus and Arieff, 1999).

It is now clear that brain damage from hyponatremia can be associated with either hyponatremic encephalopathy or improper therapy of symptomatic hyponatremia. However, even with improper therapy of symptomatic hyponatremia, brain damage is exceedingly rare, occurring in less than 4% of such cases (Ayus and Arieff, 1996). More recent evidence strongly suggests that virtually all of the brain damage associated with hyponatremia is due to hypoxia (Nzerue *et al.*, 2003; Knochel, 1999). Clinical evidence suggests that the vast majority of brain damage from hyponatremia is associated with untreated hyponatremic encephalopathy, and occurs primarily in a limited number of clinical settings. These include (1) the postoperative state; (2) polydipsia-hyponatremia syndrome; (3) pharmacologic agents; (4) congestive heart failure; (5) acquired immunodeficiency syndrome (AIDS); hepatic insufficiency; and (6) malignancy (Figure 1).

Clinical Manifestations of Hyponatremia

The clinical signs and symptoms of hyponatremia are directly related to the development of cerebral edema, increased intracellular pressure, and cerebral hypoxia. Neurological manifestations of hyponatremia may be observed when the plasma sodium is below 130 mM. Early symptoms of hyponatremia from any cause may include apathy, weakness, muscular cramps, nausea, vomiting, and headache. The type of symptoms varies enormously among individuals, and no individual is likely to have any or all ascribed symptoms. More advanced clinical manifestations are shown in Table 1. In general, symptoms are more severe and occur at a higher level of serum sodium in younger women (age 16–49 years) than in either men or older women (Figure 2; Fraser and Arieff, 1997b).

Patients with chronic hyponatremia have been said to have less severe symptoms and a lower mortality. However, this has been shown to be incorrect, with the overall

Table 1 Objective and subjective manifestations of hyponatremic encephalopathy

Objective findings
Anorexia
Headache
Nausea
Emesis
Muscular cramps
Weakness
Subjective findings
Impaired response to verbal stimuli
Impaired response to painful stimuli
Bizarre (inappropriate) behavior
Hallucinations (auditory or visual)
Asterixis
Obtundation
Incontinence (urinary or fecal)
Respiratory insufficiency
Advanced subjective findings
Decorticate and/or decerebrate posturing
Bradycardia
Hypertension
Altered temperature regulation (hypo- or hyperthermia)
Hyperglycemia (secondary to central diabetes mellitus)
Dilated pupils
Seizure activity (usually grand mal)
Coma
Respiratory arrest
Cardiac arrest
Polyuria (secondary to central diabetes insipidus)

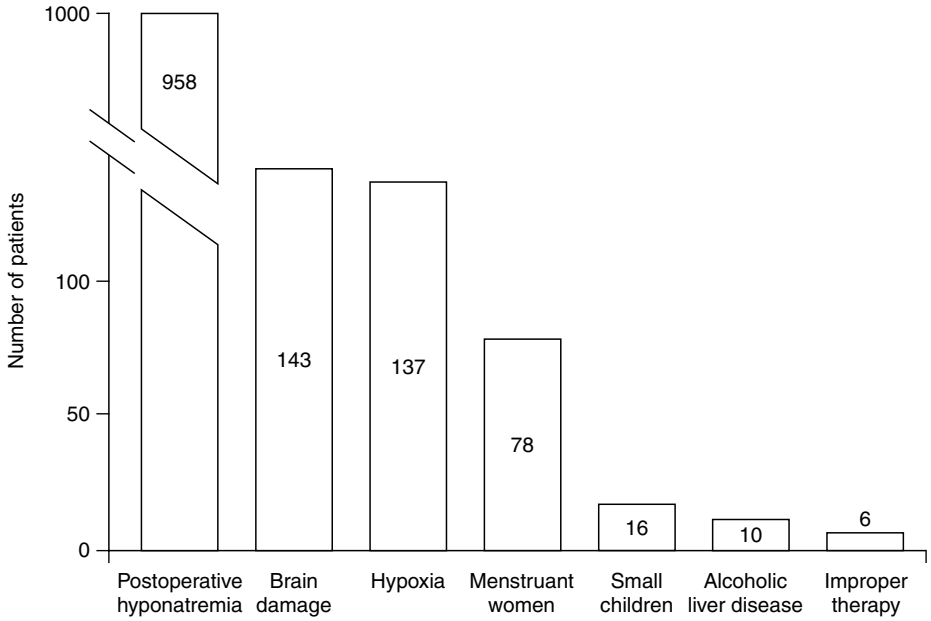

Figure 1 The major risk factors associated with permanent brain damage among hospitalized patients with hyponatremia (serum sodium below 128 mmol l^{-1}). Most patients (96%) suffered a hypoxic episode because of failure to initiate active therapy in a timely manner. In only 4% of patients suffering permanent brain damage could improper therapy for hyponatremia be implicated in the outcome. The incidence of hyponatremic encephalopathy in 11 published series from our laboratory comprising 958 hospitalized patients with hyponatremia was 23% (143/958). Among patients with hyponatremic encephalopathy, the overall morbidity was 15%

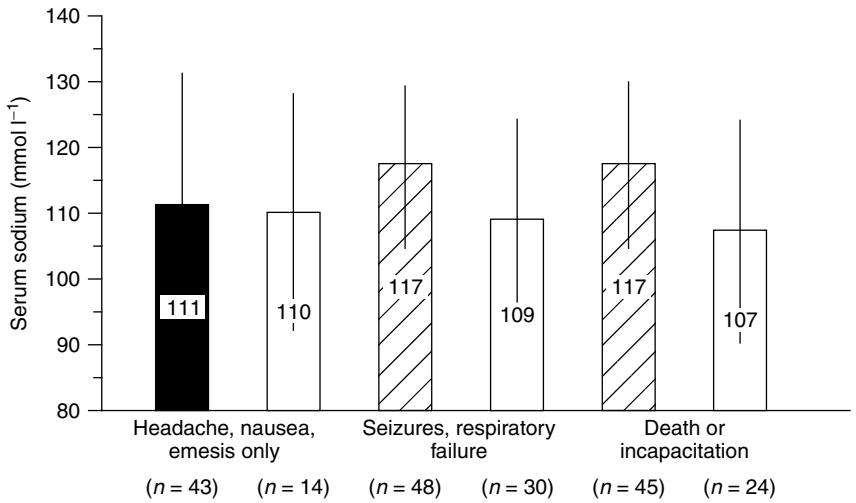

Figure 2 The plasma sodium in 136 patients with hyponatremic encephalopathy. The men and postmenopausal women with headache, nausea, and emesis only did not progress to respiratory failure. We have observed less than 10 menstruant women with headache, nausea, and emesis who did not progress to respiratory failure, and these are not included because of the small sample. The plasma sodium in menstruant women who progressed to respiratory failure or permanent brain damage was significantly higher ($p < 0.001$) than that of postmenopausal women who progressed to respiratory failure or permanent brain damage. The plasma sodium in menstruant women who progressed to respiratory failure or permanent brain damage was also significantly higher ($p < 0.001$) than that of either men or postmenopausal women who had headache, nausea, and emesis only ($p < 0.01$). We have observed less than 10 men (all age-groups) with headache, nausea, and emesis who progressed to either respiratory failure, death, or permanent brain damage, and these are not included because of the small sample size. The data is presented as the mean ±2 standard deviations (±2SD)

mortality from chronic hyponatremia being about 25% (Ayus and Arieff, 1999). However, in most clinical situations, it is very difficult to determine the duration of the hyponatremia, and the separation may in fact be largely artificial. Since chronic hyponatremia is more common in both men and elderly women, the less severe symptoms may be due not so much to the duration of hyponatremia as to the age, sex, and hormonal status of the patients. Young women are not prone to many of the disorders that may be associated with chronic hyponatremia, such as long-term diuretic use,

congestive heart failure, and hepatic insufficiency. An important but poorly recognized cause of chronic hyponatremia is polydipsia in elderly women. The incidence is not known, but there have been many reported deaths (Ayus and Arieff, 1999; Posner *et al.*, 1967; Ashraf *et al.*, 1981).

Postoperative Hyponatremia (*see* Chapter 137, Perioperative and Postoperative Medical Assessment)

Postoperative hyponatremia is a common clinical problem in the United States and Western Europe, with an occurrence of about 1% (Ayus *et al.*, 1992; Ayus and Arieff, 1996), or about 250 000 cases per year, with an overall morbidity of approximately 5%. In the vast majority of cases, the patients tolerated the surgery without complications, being able to walk, talk, and eat after surgery before symptoms of encephalopathy developed. Initial symptoms are usually quite mild (Table 1). Because these symptoms are somewhat nonspecific, they are often mistakenly attributed to routine postoperative sequelae. However, if the symptoms are due to hyponatremia and left untreated, the patient may progress to more advanced manifestations (Table 1) (Fraser and Arieff, 1990; Arieff, 1986). Thus, symptomatic hyponatremia in postoperative patients is particularly dangerous and should be promptly treated. In this setting, premenopausal women are particularly at risk of developing hyponatremic encephalopathy and respiratory insufficiency when compared to men and postmenopausal women (Ayus *et al.*, 1992; Figure 3). Additionally, respiratory arrest occurs at a significantly higher plasma sodium (±SD) in menstruant women ($117 \pm 7\,\text{mmol}\,l^{-1}$; range $104-130\,\text{mmol}\,l^{-1}$) than in postmenopausal women ($107 \pm 8\,\text{mmol}\,l^{-1}$; range $92-123\,\text{mmol}\,l^{-1}$) (Figure 2). Although the frequency of permanent brain damage from hyponatremia following elective surgery is not known, recent studies suggest a morbidity of about 20% in patients with encephalopathy (Ayus *et al.*, 1992; Ayus and Arieff, 1996; Figure 3).

Polydipsia

Another common setting in which symptomatic hyponatremia can occur is with polydipsia. The polydipsia-hyponatremia syndrome (frequently known as *psychogenic polydipsia*) occurs primarily in individuals who have either schizophrenia, bipolar disorder, or certain eating disorders (Demitrack *et al.*, 1992; Vieweg, 1996). The average daily solute intake is about $1000\,\text{mmol}\,\text{day}^{-1}$, and if the kidney can elaborate a maximally dilute urine (below 100 $\text{mOsm}\,\text{kg}^{-1}$), the normal individual should theoretically be able to excrete in excess of $20\,\text{l}\,\text{day}^{-1}$. To lower plasma sodium below $120\,\text{mmol}\,l^{-1}$ requires retention of more than $80\,\text{ml}\,\text{kg}^{-1}$ of water, so that to develop hyponatremia in the absence of elevated plasma levels of ADH requires ingestion of over $20\,\text{l}\,\text{day}^{-1}$ in a 60-kg adult. Most patients with polydipsia-hyponatremia syndrome have actually ingested less water than that theoretically required. Instead, they have less fluid intake but both abnormal urinary diluting capacity and elevated plasma ADH levels (Vieweg, 1996; Goldman *et al.*, 1988). Beer potomania is a variation of polydipsia-hyponatremia syndrome, where the hyponatremia is associated with poor nutrition and massive ingestion of beer instead of water (Fenves *et al.*, 1996).

Primary polydipsia has been reported in almost all age-groups, from the very young to the elderly. Many such patients have histories of psychiatric disorders (usually schizophrenia, bipolar disorder, or bulimia nervosa) (Demitrack *et al.*, 1992; Vieweg, 1996). Symptoms of drug-induced primary polydipsia can often be mistaken for symptoms stemming from nonrelated psychiatric disorders (confusion, hallucinations, bizarre behavior). Accurate diagnosis

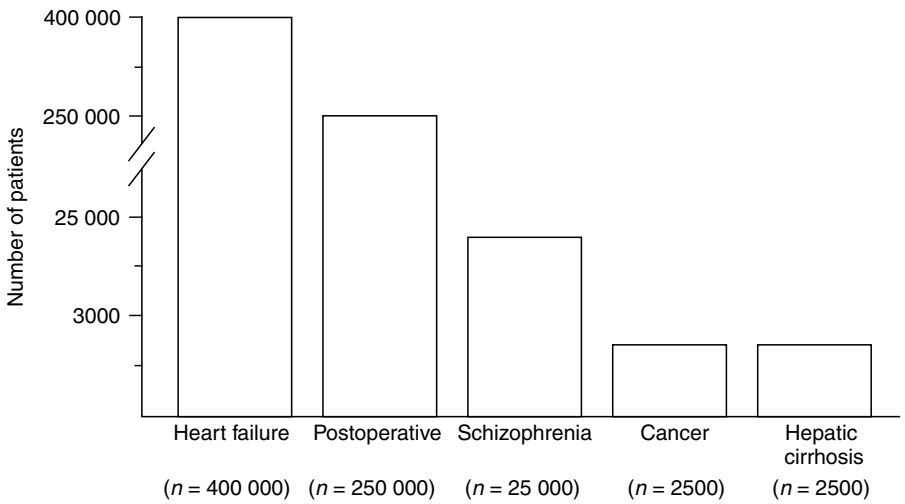

Figure 3 The clinical causes of hyponatremia that are likely to be associated with death or permanent brain damage. Of the five causes, only in the case of postoperative hyponatremia is there solid epidemiologic data. The other causes are estimated from the current literature. There is not enough data in the current literature to estimate the incidence of hyponatremia associated with AIDS, diuretic therapy, or hyponatremia-polydipsia syndrome

of symptoms stemming from drug-induced polydipsia and symptomatic hyponatremia may therefore be challenging. The clinical picture may be further complicated when the patient is taking phenothiazines or tricyclic antidepressants, which may increase ADH release, or diuretics, which can interfere with renal water excretion (Sandifer, 1983). Such patients may ingest excessive quantities of water, which can lead to symptomatic hyponatremia. Absent any medication, patients who are compulsive water drinkers disorders may also be at risk for both symptomatic hyponatremia and fatal water intoxication (Cheng *et al.*, 1990).

The mainstay of therapy of polydipsia is water restriction and treatment of underlying reversible causes of the disease. Such causes include drugs, certain psychiatric or neurologic disorders, hypercalcemia, and potassium depletion (resulting in nephrogenic diabetes insipidus). However, these patients are very adept at obtaining water, even under well-controlled circumstances, and their psychiatric disturbances may not easily be amenable to therapy.

Congestive Heart Failure (*see* Chapter 50, Heart Failure in the Elderly)

The most common cause of hyponatremia in the United States is congestive heart failure with an incidence of about 400 000 per year (Figure 1) (Lee and Packer, 1986). The pathogenesis of the hyponatremia is complex and may include activation of vasoconstrictor hormones, thirst stimulation, diuretic therapy, impaired renal water excretion, high plasma ADH levels, and elevated plasma renin activity. The one year mortality among patients with congestive heart failure exceeds 50%, although an undetermined number of these actually die from hyponatremia. Although the mortality from hyponatremia among patients with heart failure is thus difficult to estimate, there are many reported deaths and low plasma sodium is of major prognostic importance. Recent studies suggest that the renin-angiotensin system is of major importance in the pathogenesis of hyponatremia in patients with heart failure, and that both the hyponatremia and long-term outcome can be improved by converting-enzyme inhibition (Lee and Packer, 1986). However, converting-enzyme inhibition also improves survival in patients with heart failure without hyponatremia (SOLVD, 1991), and addition of furosemide is often required.

Pharmacologic Agents

A number of pharmacologic agents may interfere with the ability of the kidney to excrete free water. Included are large numbers of sedatives, hypnotics, analgesics, oral hypoglycemic agents, tranquilizers, narcotics, antineoplastic drugs, antidepressant agents, and diuretics (DeFronzo and Arieff, 1995). In most such instances, there is excessive net retention of ingested or infused free water. Those diuretics most commonly associated with hyponatremia are thiazides and "loop" diuretics (furosemide). In patients with thiazide-associated hyponatremia, there may be an idiosyncratic reaction to the drug, resulting in massive acute losses of sodium and potassium in the urine, often with associated polydipsia.

Acquired Immunodeficiency Syndrome (AIDS)

AIDS is a major cause of hyponatremia in the United States (Vitting *et al.*, 1990). The hyponatremia in patients with AIDS may be secondary to SIADH; volume deficiency with hypotonic replacement fluids; or adrenal insufficiency (Vitting *et al.*, 1990; Grinspoon and Bilezikian, 1992). Even in the presence of mineralocorticoid deficiency, glucocorticoid function may be intact, resulting in a normal ACTH stimulation test. Adrenal insufficiency is particularly suspect in hyponatremic AIDS patients who have disseminated cytomegalovirus or tuberculosis. Therapy with Florinef (fludrocortisone acetate) is indicated only if adrenal insufficiency is documented in hyponatremic patients with renal salt-wasting (Grinspoon and Bilezikian, 1992). Current data strongly suggest that patients who have AIDS and hyponatremia have both a higher mortality and longer duration of hospitalization than those who are normonatremic. However, with such a virulent disease as AIDS, it is difficult to determine the exact role of hyponatremia in the associated morbidity.

Hepatic Insufficiency (*see* Chapter 33, Liver and Gall Bladder)

Hyponatremia is a common disorder in patients with liver disease and it is almost always associated with excessive retention of free water. Regardless of the volume status in such patients, the total body exchangeable cation (potassium + sodium) is "diluted" by relatively greater amounts of TBW (Papadakis *et al.*, 1990). Even in the setting of hypoosmolality, ADH levels, which are normally suppressed, are not.

Hyponatremia is a major risk factor among patients with hepatic insufficiency, although it is unclear if the hyponatremia actually increases the mortality, or is merely a marker for more severe degrees of hepatic insufficiency. The best therapy for hyponatremia in patients with liver disease is prevention by judicious monitoring of serum electrolytes, fluid balance, and response to diuretic therapy. Discontinuation of diuretics and restriction of water intake will improve hyponatremia, but the response is generally slow, usually less than $2\,\text{mmol}\,l^{-1}$ per day. Among patients with hepatic insufficiency who have undergone liver transplantation, postoperative hyponatremia carries a prohibitive mortality (Singh *et al.*, 1994). Cerebral demyelinative lesions are frequent in such patients, and appear to be related to upward changes in the plasma sodium concentration. Thus,

patients with hepatic insufficiency, particularly those who have undergone liver transplantation, are at greatly increased risk for development of cerebral demyelinative lesions (Ayus *et al.*, 1987).

There is not a consensus of opinion regarding the optimal method or rate of correction of symptomatic hyponatremia in patients with liver disease. There is substantial clinical evidence that correction of severe symptomatic hyponatremia to mildly hyponatremic levels in nonalcoholic patients does not usually result in cerebral demyelinating lesions, such as central pontine myelinolysis. However, there is only limited data available in patients with liver disease, and data in patients who have undergone liver transplantation suggest that any increment of plasma sodium, whether such patients are hyponatremic or not, is potentially dangerous (Singh *et al.*, 1994). However, it has recently been shown that a substantial percent of patients with liver disease who have not been hyponatremic will have central pontine myelinolysis, which is asymptomatic (Sullivan and Pfefferbaum, 2001). Such data strongly support the concept that central pontine myelinolysis is common in alcoholic subjects and has nothing to do with hyponatremia.

Recent studies suggest that the major determinants of the occurrence of permanent brain damage in patients with liver disease and hyponatremia include at least four factors (Papadakis *et al.*, 1990; Ayus *et al.*, 1987): (1) the occurrence of a hypoxic episode (arterial pO_2 below 75 mmHg); (2) correction of serum sodium above 128–132 mmol l^{-1} within the initial 48 hours of therapy; (3) elevation of serum sodium by more than 25 mmol within the initial 24–48 hours of therapy; (4) the presence of hypernatremia (serum sodium above 145 mmol l^{-1}) in patients with liver disease receiving lactulose. The mortality in patients who have both liver disease and serum sodium below 120 mmol l^{-1} accompanied by central nervous symptoms is probably above 40% (Papadakis *et al.*, 1990). Therapy of the hyponatremia found in patients with liver disease should soon change. There are several vasopressin V2 receptor-blocking agents that are in various stages of clinical testing. These agents have proven effective in the therapy of hyponatremia associated with liver disease, and may soon be commercially available (Decaux, 2001; Gross *et al.*, 2001).

Malignancy-associated Hyponatremia (*see* Chapter 129, Oncological Emergencies and Urgencies)

A major group of patients with asymptomatic hyponatremia and normal to slightly expanded extracellular volume are those who have a malignancy that secretes a peptide having actions similar to antidiuretic hormone (arginine vasopressin, ADH), although some tumors actually secrete arginine vasopressin (Bartter and Schwartz, 1967). The most common of such malignancies associated with SIADH is lung cancer, particularly oat cell or bronchogenic carcinoma, although a large number of malignancies may be associated with elaboration of ADH. It is difficult to even estimate the mortality of hyponatremia associated with malignancy because most patients eventually die of the primary disease.

Management of Hyponatremia

The management of hyponatremia may be broadly divided into three groups: (1) active (usually hypertonic NaCl intravenously); (2) passive (usually water restriction); (3) supportive modalities (respiratory support, diuretics, intubation); (4) antagonism of effects of ADH on the kidney (declomycin, lithium); and (5) vasopressin V2 receptor antagonists. The most important decision is whether to treat a patient in a passive manner (water restriction being the cornerstone of such therapy) or if there is a need for active therapeutic intervention (infusion of hypertonic NaCl (500–850 mM NaCl), either with or without a loop diuretic). The decision should be primarily based upon the presence or absence of neurologic symptomatology.

In patients whose hyponatremia is asymptomatic, neither active therapy (with hypertonic NaCl) nor supportive measures are indicated. If the patient is volume-depleted, isotonic (154 mM) NaCl is usually the fluid of choice. If there is a hormone deficiency (adrenal, thyroid), appropriate replacement is indicated. If the patient has received a drug that may interfere with renal handling of sodium or water, the drug should be discontinued whenever possible. Although water restriction can theoretically be of benefit in some of these disorders, practical considerations diminish its usefulness. There are several medical regimens for the long-term management of patients with stable asymptomatic hyponatremia. Demeclocycline, a tetracycline antibiotic, in doses above 600 mg day^{-1} can be effectively used to produce a state of nephrogenic diabetes insipidus and has been successful in treating patients with SIADH (DeFronzo and Arieff, 1995).

The most important measures for the management of at-risk patients are prophylactic. Every hospitalized patient in the six groups discussed above should be considered at risk for the development of hyponatremia, and appropriate measures undertaken. The most important measure is the avoidance of intravenous hypotonic fluid to hospitalized patients. Other important procedures include monitoring of daily electrolytes, weight, and strict input and output. Symptomatic hyponatremia is a medical emergency, with a morbidity in excess of 15% (Ayus and Arieff, 1996). In patients with hyponatremic encephalopathy, the preponderance of clinical evidence demonstrates that correction by water restriction results in an unacceptable morbidity and mortality (Ayus and Arieff, 1999). Patients with hyponatremic encephalopathy should be constantly monitored, preferably in an intensive care unit. The first step in management of such patients is a secure airway with assisted ventilation if required. Therapy should be initiated with intravenous hypertonic sodium chloride (514 mmol l^{-1}) using an

infusion pump, with the infusion designed to raise plasma sodium at a rate of about 1 mmol l^{-1} per hour. If the patient is actively seizing or has other clinical evidence of increased intracranial pressure, then the rate of hypertonic fluid administration should be adjusted to elevate plasma sodium by about 4–5 mmol l^{-1} $hour^{-1}$ over the first hour. Therapy with hypertonic NaCl should be discontinued when: (1) the patient becomes asymptomatic; (2) the patient's plasma sodium has increased by 20 mmol l^{-1}; or (3) the plasma sodium reaches a value in the range of 120 to 125 mmol l^{-1}. While active correction of symptomatic hyponatremia is in progress, monitoring of plasma electrolytes should be carried out every 2 hours, until the patient has become neurologically stable. In addition to hypertonic NaCl, therapy should include supportive measures when required. The plasma sodium should never be acutely elevated to hyper- or normonatremic levels, and should not be elevated by more than 25 mmol l^{-1} during the initial 48 hours of therapy (Ayus *et al.*, 1987). The technique has been described in detail elsewhere (DeFronzo and Arieff, 1995).

The patient's TBW, which varies as a function of age, sex, and body habitus, with a range of 42% (obese elderly women) to 75% (young children), should be estimated (Chumlea *et al.*, 2001). Correction of the plasma sodium should be initially planned using intravenous 514 mM NaCl, often combined with a loop diuretic (furosemide) (DeFronzo and Arieff, 1995) Infuse the 514 mM NaCl at a rate calculated to increase plasma sodium at a rate of 1 mmol l^{-1} per hour. The plasma sodium must be monitored at least every 2 hours, with appropriate adjustments in the infusion rate to reach the desired level.

There are possible complications of the therapy of hyponatremia. Therapy is usually not an important factor in the genesis of permanent brain damage in hyponatremic patients (Nzerue *et al.*, 2003; Ayus and Arieff, 1999; Figure 3). It had been suggested that the development of cerebral demyelinating lesions might somehow be related to the correction of hyponatremia (DeFronzo and Arieff, 1995). However, a number of studies have shown that cerebral demyelinating lesions develop only when patients with hyponatremia (1) are inadvertently made hypernatremic during treatment; (2) have an absolute increase in plasma sodium, which exceeds 25 mmol l^{-1} in the first 24–48 hours of therapy; (3) suffer an hypoxic event; (4) have severe liver disease (Singh *et al.*, 1994; Ayus *et al.*, 1987; Tien *et al.*, 1992). On the other hand, there is overwhelming evidence that treatment of symptomatic hyponatremia with hypertonic NaCl is associated with recovery and survival (Ayus and Arieff, 1999; DeFronzo and Arieff, 1995).

HYPERNATREMIC STATES

Hypernatremia is defined as an abnormally high concentration of plasma sodium. Because sodium with its accompanying anions comprises the great majority of osmoles in the plasma, hypertonicity always accompanies hypernatremia. However, a hyperosmolar state can exist in the absence of hypernatremia if another solute (such as glucose or urea) is present in excessive amounts. The subjects of uremia (Fraser and Arieff, 1997a) hyperglycemic nonketotic hyperosmolar coma and diabetic ketoacidosis are discussed in detail elsewhere and will not be covered here (Halperin *et al.*, 1995).

Brain Adaptation to Hypernatremia

Adaptation of the brain to hypernatremia determines survival, and a rapid increase of plasma sodium without the brain having an opportunity to adapt can lead to permanent brain damage. The response of excitable cells (central nervous system) to a hyperosmolar external fluid can be described as follows. Initially the cells shrink owing to osmotic water abstraction, but ultimately the cells nearly regain the water content they had in the control state by virtue of a combination of net solute uptake and generation of solute *de novo*. Several important differences exist in the response of brain cells versus those of other tissues, such as skeletal muscle and kidney. These are mainly in the types and quantity of solutes that accumulate within the cells as well as the mechanisms by which they accumulate (Strange and Morrison, 1992).

Previous studies have shown that there is some uptake of electrolytes (sodium and potassium) during adaptation of the brain to hypernatremia in rat brain (Ayus *et al.*, 1996). However, while regulatory increases in brain cell volume occur largely due to increases in brain cell content of monovalent cations, these are not the only solutes that accumulate during regulatory increases in brain cell volume. Recent studies have provided good support for the notion that a number of organic compounds account for some of the increase in total brain osmoles (Ayus *et al.*, 1996; Lien *et al.*, 1990). Studies of hypernatremia have shown that over the course of 7 days, water content of the brain decreases by approximately 10% but ultimately recovers to within 98–99% of control (Ayus *et al.*, 1996). This is largely accompanied by an increase in brain solute content. Most of this increase is accounted for by inorganic ions (Na^+, K^+, Cl), amino acids, and undetermined solute (idiogenic osmoles). The increase in undetermined solute (idiogenic osmoles) begins after only about 1 hour of hypernatremia and changes very little during 4 hours to 1 week of hypernatremia (Ayus *et al.*, 1996). The increase in undetermined solute serves to protect brain cell volume from further dehydration. However, this initial protective effect may eventually become deleterious during correction of hypernatremia if the plasma sodium is somehow decreased at a more rapid rate than the brain is able to dissipate the idiogenic osmoles. During treatment of experimental hypernatremia, brain edema may develop despite a significant decrease in brain content of (sodium + potassium), due to failure of amino acids and idiogenic osmoles to dissipate (Ayus *et al.*, 1996).

Causes of Hypernatremia

The causes of hypernatremia in children and adults have recently been reviewed (Arieff, 1995). There are a number of medical conditions that are commonly associated with hypernatremia, the etiology of which is quite different in children and adults. In infants, gastroenteritis with diarrhea is the most common cause while in elderly individuals, hypernatremia is often associated with infirmity and inability to freely obtain water, leading to gradual desiccation (Snyder and Arieff, 1992). Small children may also become hypernatremic after accidental administration of a high solute load, particularly accidental substitution of NaCl for sugar in preparation of formula or improper dilution of concentrated formulas (Finberg *et al.*, 1963). Children commonly develop hypernatremia after dehydration from diarrhea or emesis associated with common illnesses (Mocharla *et al.*, 1997; Moritz and Ayus, 1999).

In adults, causes of hypernatremia include nasogastric hyperalimentation, nonketotic hyperosmolar coma, acute renal failure, renal tubular damage, improper mixture of dialysis fluid, dehydration secondary to either fever or elevated ambient temperature, $NaHCO_3$ administration, and diabetes insipidus. Generally, diabetes insipidus is associated with hypernatremia only under circumstances where the patient is unable to freely obtain water or when the lesion responsible for the diabetes insipidus results in a decrease in thirst. Excessive administration of hypertonic solutions of $NaHCO_3$ to critically ill patients suffering cardiac arrest or lactic acidosis has been associated with a dangerously elevated plasma osmolality and infrequent survival. Severe hypernatremia has also been occasionally observed in patients inadvertently receiving intravenous hypertonic NaCl for therapeutic abortion.

Clinical Manifestations of Hypernatremia

The signs and symptoms of hypernatremia are variable. In experimental hyperosmolality, findings include nystagmus, myoclonic jerking of the extremities, severe weight loss, decreased food intake, and, ultimately, respiratory failure and death (Ayus *et al.*, 1996). In human subjects, preexisting abnormalities of mental status may make it difficult to detect any new neurological findings. In addition, since hypernatremia frequently occurs in the setting of a coexistent pathologic process, it may be difficult to ascribe any particular symptom or group of symptoms to hypertonicity *per se*. In children, there may be alternating periods of lethargy and irritability; tachypnea is frequently present. A history compatible with gastroenteritis is frequently obtained and may be the cause of the hypernatremia; conversely, nausea and vomiting are often seen even in the absence of diarrhea. Seizures are common and roughly correlate with the degree of hypernatremia. Associated abnormalities include metabolic acidosis, hyperglycemia, and weight loss (Moritz and Ayus, 1999).

In the elderly, some important differences exist (Snyder and Arieff, 1992). When considering only patients who were hypernatremic at the time of hospital admission, women were predominant. Although nearly half the hypernatremic patients had a febrile illness, other associated conditions assume more prominence than in infants. These include the postoperative state, diuretic administration, excessive intravenous solute administration (including nutritional supplements), and diabetes mellitus as the leading causes. Depression of the sensorium is frequently present and is highly correlated with the degree of hypernatremia. Altered mental status is also an independent predictor of subsequent mortality at any level of hypernatremia (Palevsky *et al.*, 1996; Snyder and Arieff, 1992).

Morbidity and Mortality of Hypernatremia

Hypernatremia is associated with considerable long-term morbidity and mortality both in children and adults. Most studies in children report morbidity and mortality figures of about 15%, with survivors of hypernatremia having a 10–15% likelihood of having permanent neurological deficits (Banister *et al.*, 1975) (Moritz and Ayus, 1999). In adults, the figures are similar. The mortality in elderly patients with hypernatremia was found to be 42% in one study, and neurological morbidity as assessed by changes in level of care was present in 38% of the survivors (Snyder and Arieff, 1992). One especially noteworthy finding in this series was the fact that mortality was higher in patients with hypernatremia developing in the hospital. These findings have recently been confirmed (Palevsky *et al.*, 1996; Long *et al.*, 1991). Authors have attributed this finding to a more complicated clinical setting and delayed recognition of hypertonicity in hospitalized subjects.

Essential Hypernatremia

The initial descriptions of the syndrome of essential hypernatremia included the following elements: (1) asymptomatic chronic hypernatremia, (2) clinical euvolemia, (3) hypodipsia, (4) partial central diabetes insipidus, and (5) absence of nephrogenic diabetes insipidus. In more physiologic terms, essential hypernatremia is a disorder of osmoregulation where the regulatory systems (ADH and thirst) are at least partially responsive to osmolar and volumetric stimuli. In the steady state, patients are hypernatremic, euvolemic (by the usual clinical evaluation), and asymptomatic (absence of thirst) (Goldberg *et al.*, 1967). By definition, if the plasma osmolality is substantially elevated, this steady state represents an upward resetting of the osmolar set point for ADH release and probably of the osmolar threshold for thirst perception (if the steady state plasma osmolality is above about 294 mOsm/kg H_2O). Volumetric stimuli for ADH release and for thirst perception must operate at normal or near-normal settings to maintain clinical euvolemia.

Thus, the syndrome of essential hypernatremia is the hyperosmolar counterpart of the syndrome of "reset osmostat". In the latter syndrome, asymptomatic euvolemic hyponatremia is maintained with a decreased osmolar set point for ADH release and a decreased osmolar threshold for thirst.

Hypernatremia and Liver Disease

A group of adult patients in whom the entity of hypernatremia with its attendant sequelae is not appreciated are chronic alcoholic subjects with end stage liver disease who present with fulminant liver failure and hepatic encephalopathy (Fraser and Arieff, 1985). Such patients are often treated with oral lactulose as therapy for their hepatic encephalopathy. Hypernatremia may complicate such therapy (Fraser and Arieff, 1985). Patients with lactulose-associated hypernatremia had a mortality of 87 versus 60% in those patients who did not develop hypernatremia.

Hypernatremia in patients with severe liver disease may be quite a common occurrence after therapy with intravenous osmotic diuretic agents and/or oral lactulose (Fraser and Arieff, 1985). The hypernatremia is associated with a high mortality and appears to be directly related to a negative free water balance (Arieff and Papadakis, 1988). Patients with liver disease who have undergone hepatic transplantation and then develop hypernatremia are particularly susceptible to the development of cerebral demyelinating lesions (Ayus *et al.*, 1987; Estol *et al.*, 1989; Wszolek *et al.*, 1989).

Treatment of Hypernatremia

The goal of therapy in hypernatremia is the reduction of plasma osmolality toward normal by the administration of free water in excess of solute. Hypernatremia is uncommonly associated with administration of excessive quantities of NaCl, but when such a situation is present, removal of solute must be considered. Removal of solute is usually accomplished by dialysis. When water administration is planned, the major therapeutic questions are the type and quantity of fluid to be given. In adult patients with hypernatremia, although 280 mM dextrose in water (5% dextrose in water, D5W) has commonly been utilized, this therapeutic modality has recently come into question.

Patients with hypernatremic dehydration should be treated with fluid that provides free water in excess of electrolytes. In both children and adults, fluid therapy is usually calculated so as to be administered over a period of about 48 hours. Despite such recommendations, little data in humans or animals is available as to the ideal rate of fluid administration. Fatal cases of cerebral edema, as well as permanent brain damage, have occurred when hypernatremia was completely corrected within 24 hours, while seizures with cerebral edema occur in more than 50% of hypernatremic rabbits when plasma sodium is reduced from 185 to 142 $mmol\,l^{-1}$ in 4 hours. The pathophysiology of cerebral edema complicating rapid (less than 24 hours) correction of experimental hypernatremia (in rabbits) has recently been described (Ayus *et al.*, 1996). These studies highlight the dangers of overly rapid correction of hypernatremia. In addition, recent information suggests that therapy of hypernatremia with glucose-containing solutions (280 mM glucose/H_2O) may lead to cerebral intracellular lactic acidosis (Sheldon *et al.*, 1992), although this has not been confirmed in humans. Current recommendations for treatment of chronic hypernatremia in adults, when the hypernatremia is primarily due to water loss, are:

1. If there is evidence of circulatory collapse, the patient should receive initial resuscitation with colloid, such as plasma or a plasma substitute (such as isotonic NaCl), rapidly enough to correct shock and stabilize the circulatory system.
2. Fluid deficit should be estimated on the basis of serum sodium, body weight, and TBW. The deficit should be given over a 48-hour period, aiming for a decrement in serum osmolality of approximately 1–2 mOsm per liter per hour. Maintenance fluids, which include replacement of urine volume with hypotonic fluid, are given in addition to the deficit.
3. Hypotonic fluid should be administered. The usual replacement fluid will be 77 $mmol\,l^{-1}$ NaCl. In general, solutions containing glucose should be avoided if possible.
4. Plasma electrolytes should be monitored at frequent intervals, usually about every 2 hours. It should be stressed that many adult patients with hypernatremia have serious underlying systemic illness, such as stroke, dementia, infection, or head trauma. Many such patients appear to die of their underlying illness rather than of hypernatremia *per se*. Close attention should be given to the treatment of associated medical conditions.
5. If the hypernatremia is secondary to excessive loss of other body fluids, the replacement fluid should be similar to the fluid actually lost.

The ideal treatment of hypernatremia represents a balance between free water administration and solute (sodium) excretion. Sodium removal can be accomplished with diuretics or dialysis. Infusion of glucose-containing fluids can be associated with intracellular lactic acidosis, and they should be avoided if possible. Overzealous correction can be accompanied by rehydration seizures that are probably due to acute cerebral edema from brain cellular water uptake.

DISORDERS OF POTASSIUM

Disorders of the plasma potassium concentration are almost as common as are those of sodium, but otherwise there are few similarities. Unlike sodium, most potassium is located intracellularly, primarily in skeletal muscle. Abnormalities of plasma or total body potassium do not affect the brain. The factors that regulate plasma potassium concentration

consist primarily of the kidney and the hormones insulin, aldosterone, the renin-angiotensin system, and epinephrine (DeFronzo, 1994). Although the kidney is responsible for most abnormalities of plasma potassium, the primary target organs are the heart and skeletal muscle. Although a linear relationship was once suggested between plasma potassium and metabolic acidosis, such a causal relationship is now known not to exist, as in most conditions associated with metabolic acidosis, plasma potassium is not elevated. In the original study, virtually all of the patients with hyperkalemia had either diabetic ketoacidosis or acute renal failure (Burnell *et al.*, 1956). It is now known that patients with acute renal failure tend to have both metabolic acidosis and hyperkalemia independently. Among patients with diabetic ketoacidosis, breakdown of skeletal muscle as substrate for gluconeogenesis accounts for the hyperkalemia. Hyperkalemia is not generally present with other forms of metabolic acidosis.

Hyperkalemia

Hyperkalemia may develop from a shift of potassium from intracellular to extracellular compartments, from tissue (muscle) breakdown, or it can be secondary to decreased renal potassium excretion. An important cause of hyperkalemia has only been described in the past 5 years. ACE inhibitors have been prescribed in increasing quantities for the treatment of congestive heart failure (Juurlink *et al.*, 2004) and the prevention of diabetic nephropathy (Lewis *et al.*, 2001; Palmer, 2004). Among hospitalized patients, the major concerns relating to alterations of potassium homeostasis are effects on the heart, which is particularly vulnerable to increases in the serum potassium. The electrocardiographic (ECG) changes associated with hyperkalemia have previously been described (Altmann, 1995). In brief, the earliest change associated with hyperkalemia is a symmetrical increase in the amplitude or "tenting" of the T waves, which is best observed in the precordial leads. Such ECG changes usually cannot be appreciated on a "rhythm strip" generated from a cardiac monitor. These changes usually become manifest when the serum potassium reaches levels of $5.5-6.0\,\text{mmol}\,l^{-1}$. As the serum potassium concentration rises further ($6.0-7.0\,\text{mmol}\,l^{-1}$), conduction through the conducting system and ventricles becomes delayed. This is reflected by a lengthening of the PR interval and widening of the QRS complex. With potassium concentrations of 7.0 to 7.5, atrial muscle conduction becomes impaired and there is a progressive flattening of the P wave; there is continued widening of the QRS complex and a further delay in A-V conduction. When the potassium concentration exceeds $8\,\text{mmol}\,l^{-1}$, atrial conduction ceases and the P waves disappear. As the QRS complex widens further, it merges with the T wave, producing a sine wave pattern. If these changes go unrecognized and appropriate therapy is not begun, ventricular fibrillation or asystole will follow. In addition to the classic sequence of events outlined above, virtually any type of arrhythmia or conduction disturbance may be seen in hyperkalemic patients. The first symptoms include paresthesias and weakness in the arms and legs. These may be followed by a symmetrical flaccid paralysis of the extremities that ascends toward the trunk and may involve the muscles of respiration, causing hypoxemia, and carbon dioxide retention.

Treatment of Hyperkalemia

Treatment of the hyperkalemic patient is dependent upon the severity and etiology of the hyperkalemia. Whether or not aggressive therapy should be instituted will depend both upon the degree of hyperkalemia and the presence of cardiac or neuromuscular manifestations. If a specific cause for the increase in serum potassium concentration can be identified, it should be eliminated. Regardless of etiology, there will be certain patients in whom the hyperkalemia is life threatening and rapid correction is indicated. If the serum potassium concentration has risen acutely to levels above $6.0\,\text{mmol}\,l^{-1}$, or if ECG changes of hyperkalemia are present, treatment should be initiated immediately. There are several possible therapeutic regimens for hyperkalemia, which are explained in detail elsewhere (Smith and DeFronzo, 1995).

Calcium has no effect on the serum potassium level, but its intravenous infusion will immediately antagonize the effects of hyperkalemia on the heart. Although calcium does not affect the resting membrane potential, it increases the threshold potential at which excitation occurs.

Sodium bicarbonate will increase plasma bicarbonate and arterial pH, shifting potassium into cells, thus lowering serum potassium. Sodium bicarbonate is administered intravenously as a 50 mmol bolus over 5 to 10 minutes. The onset of action is 5 to 10 minutes, with the effect lasting about 2 hours.

Insulin stimulates potassium uptake by extrarenal cells, primarily skeletal muscle. This is the result of a direct effect of insulin on the cell membrane and is independent of glucose transport or intracellular glucose metabolism. Glucose is administered only in order to prevent hypoglycemia. Ten units of insulin with 50 gm of glucose are administered over 1 hour. The onset of action occurs in about 30 minutes, with the effect lasting for 4 to 6 hours. The plasma potassium should decrease by $0.5-1.2\,\text{mmol}\,l^{-1}$ within 1 to 2 hours.

None of the therapeutic maneuvers discussed above will result in a net removal of potassium from the body. These maneuvers serve as temporizing measures until more definitive therapy can be initiated. Hyperkalemia is frequently encountered in patients with renal failure, where little can be done to enhance renal potassium excretion. Nebulized albuterol may be effective in such patients (Allon *et al.*, 1989). However, in the patient with intact kidney function, measures that enhance urine flow and sodium delivery to the distal tubular sites of potassium secretion will augment renal potassium excretion. Such measures include diuretics, which act proximal to the potassium secretary sites, such as furosemide (40–80 mg intravenously).

Cation-exchange resins, such as sodium polystyrene sulfonate (Kayexalate), decrease the plasma potassium concentration by exchanging sodium for potassium in the

gastrointestinal tract. Each gram of Kayexalate removes 0.5–1 mmol of potassium in exchange for 2–3 mmol of sodium. The usual dose of Kayexalate is 25 g either orally or as a retention enema. Since the resin is constipating, it should always be given with sorbitol or mannitol (15–30 ml of 70% sorbitol or mannitol every 30 minutes) to induce osmotic diarrhea, which can be sustained by administering additional doses every 6–8 hours. If the patient cannot tolerate oral administration, 50 g of Kayexalate with 50 g of sorbitol can be added to 200 ml of 10% dextrose in water and given per rectum.

Both peritoneal and hemodialysis are very effective in removing potassium from the body. If acute reduction of the serum potassium concentration is indicated, hemodialysis is the therapy of choice. Using a potassium-free dialysate, the plasma potassium begins to fall within minutes and one can remove about 30–40 mmol of potassium during the first hour, assuming an initial plasma potassium of 7 mmol l^{-1}. The hypokalemic effect persists as long as dialysis is continued. Peritoneal dialysis is also effective in removing potassium from the body but the rate of removal is much slower than can be accomplished with either hemodialysis or cation-exchange resins. Using standard 2 l exchanges with one exchange per hour will remove only about 5 mmol of potassium per hour.

HYPOKALEMIA

Hypokalemia is discussed in substantial detail elsewhere (Smith *et al.*, 1995) and can result from (1) redistribution of potassium from the extracellular to intracellular space, (2) dietary deficiency of potassium, (3) extrarenal (mainly gastrointestinal tract) losses, or (4) renal losses. The plasma potassium concentration has only an approximate relationship to total body potassium stores. In circumstances where there is movement of potassium out of cells (such as diabetic ketoacidosis), substantial potassium depletion can be masked by a relatively normal plasma concentration.

Alkalemia is a well-known cause of hypokalemia. The most important mechanism contributing to hypokalemia is enhanced urinary excretion of potassium. When alkalemia has been present for more than a few minutes, urinary excretion accounts for substantially more potassium loss than does sequestration within cells, a mechanism that has little effect upon serum potassium. Hypokalemia commonly accompanies gastrointestinal disease (when emesis is present). Since renal potassium conservation develops slowly when intake is reduced, a significant potassium loss may develop on this basis alone. The normal gastrointestinal tract secretes more than 6 l of fluid daily, which has an average potassium concentration of 5–10 mmol l^{-1}. Significant quantities of this gastrointestinal fluid may be lost owing to vomiting, nasogastric suctioning, diarrhea, external fistulae, or sequestration within an aperistaltic segment ("third spacing"). Depletion of hydrochloric acid by removal of gastric juices will result in metabolic alkalosis (for each H^+ ion lost from the GI tract, a bicarbonate has been generated and retained), sequestration of potassium within cells, and urinary potassium wasting. Similarly, when chronic metabolic acidosis develops due to diarrhea, loss of potassium in the urine is common. It should be emphasized that although gastrointestinal fluids contain significant quantities of potassium, the major route of potassium loss in patients with diarrhea or vomiting is often renal. The concentration of potassium in gastric juice is about 10–15 mmol l^{-1}. Hypokalemia in patients with vomiting or nasogastric suction could result directly from loss of potassium-rich gastric fluid. However, these factors tend to promote urinary potassium wasting to such an extent that this usually accounts for the majority of the total potassium deficit among patients with extensive emesis or nasogastric suction.

Since the concentration of potassium in bile and pancreatic juice is similar to that of plasma, external drainage of these secretions will not usually directly cause hypokalemia. However, any accompanying decrease in the extracellular volume will activate mechanisms for renal potassium excretion, such as secondary aldosteronism and metabolic alkalosis.

The potassium concentration in stool water is normally about 75 mmol l^{-1}. Since daily stool output contains only 100 ml of water, very little potassium is normally excreted by this route. However, stool volume in severe diarrheal illness can exceed 10 l per day. If the potassium concentration in these circumstances resembled basal values, the obligatory potassium wasting would rapidly deplete body stores. However, potassium concentration in diarrheal stool falls sharply in inverse proportion to daily stool volumes. With stool losses above 3 l day^{-1}, the stool potassium concentration is usually similar to that of plasma.

Treatment of Hypokalemia

Hypokalemia is usually defined by a serum potassium concentration below 3.5 mmol l^{-1}. Prior to initiation of therapy, one should estimate the potassium deficit. There is no exact relationship between serum potassium and intracellular potassium. In muscle tissue, which constitutes most of body bulk, the intracellular potassium is about 130 mmol kg^{-1} H_2O. A decrease in the serum potassium concentration of 1 mmol l^{-1}, from 4.0–3.0 mmol l^{-1}, corresponds to approximately a 10% reduction (about 300 mmol) in total body potassium content. Such deficits are not usually associated with clinical manifestations and can usually be corrected with oral potassium replacement. A decline in the serum potassium concentration from 4.0–2.0 mmol l^{-1} implies a 15–20% or greater decrease in total body potassium stores (about 600 mmol), and potassium may have to be replaced more rapidly, depending on the presence of clinical manifestations. When the serum potassium level drops to below about 2.0 mmol l^{-1}, it is difficult to estimate the true potassium deficit because the relationship between serum potassium concentration and total body potassium content becomes less linear. With serum potassium levels below 2.0 mmol l^{-1}, small additional decreases may be associated with huge deficits in total body potassium. The treatment

for hypokalemia consists of potassium replacement, usually in the form of KCl. How rapidly potassium is replaced and whether the potassium is given intravenously or orally will depend upon both the absolute serum potassium concentration and attendant clinical manifestations.

In general, treatment of a low serum potassium concentration is not an emergency. Symptoms tend to be more severe in patients with acute hypokalemia than when the disorder is more protracted. Whenever possible, potassium replacement should be given orally. The best guide to the adequacy of potassium replacement is sequential monitoring of serum potassium. Although changes in total body potassium content are roughly reflected by changes in the serum potassium concentration, there is substantial variation among patients.

Potassium can be administered intravenously as chloride, phosphate, or bicarbonate salt, depending on the accompanying electrolyte and acid–base disturbance. Evidence of cardiac or neuromuscular dysfunction, the presence of severe hypokalemia (below 2.0–2.5 mmol l^{-1}), and the inability to administer potassium orally (postsurgery, emesis) are indications for intravenous potassium. In general, a maximum of 40 mmol of potassium chloride in 1 l of IV fluid should be administered per hour. Infusion of 0.75 mmol potassium/kg over 1–2 hours will increase plasma potassium from 3–4.5 mmol l^{-1}. Although this might lead to ECG changes, it would be unlikely to cause life-threatening arrhythmia. Furthermore, when potassium is given to patients with more profound hypokalemia (below 2.0–2.5 mmol l^{-1} with body potassium deficits of 15–20%) a greater percent of the administered potassium will enter cells. Consequently, the increase of plasma potassium will be less than the 1–1.5 mmol l^{-1} observed in normokalemic patients or mildly hypokalemic subjects. Thus, 0.75 mmol kg^{-1} of body weight administered over 1–2 hours is a safe means of replacing potassium intravenously. If hypokalemia is severe (2.0 mmol l^{-1} or less) and associated with cardiac arrhythmias such as premature ventricular contractions or ventricular tachycardia, potassium replacement must be more rapid, with as much as 80 mmol infused during the first hour.

KEY POINTS

- Hyponatremia is the most common electrolyte disorder in hospitalized patients; the symptoms are often dramatic, and if not managed properly, can lead to death or permanent brain damage.
- Hypernatremia affects about 3% of hospitalized elderly patients; the symptoms are very subtle, and the overall mortality when plasma sodium exceeds 150 mmol/l is in excess of 50%.
- The most common causes of hypernatremia in hospitalized elderly patients are administration of hypotonic intravenous fluids to hospitalized postoperative patients and inappropriate use of diuretics.
- Total body water varies as a function of age, gender, and body mass, with a range of 42% (elderly women) to 75% (young children) and an average of 50% in hospitalized adults.
- Hyperkalemia is most common in patients with renal insufficiency and in those taking aldactone plus ACE inhibitors for the treatment of heart failure. It can lead to fatal arrhythmia if not properly managed.

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Endocrinology of Aging

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INTRODUCTION

Hormones flow from the ductless glands into the circulation and regulate the metabolism of the body. With aging there is a decline in the circulating levels of a number of hormones. Deficiency of some of these hormones produces symptoms and signs similar to the changes seen with aging. This has led different authorities to suggest that aging is due to an endocrinopause, and that replacement of one or more hormones will result in a reversal of the aging process. Thus, it has been claimed that the aging process is due to the somatopause, adrenopause, menopause, or andropause. However, hormonal replacement has been as likely to produce negative effects as it has to lead to rejuvenation. Aging is also associated with changes at the receptor or postreceptor level that can alter hormonal responsiveness.

HORMONAL REGULATION AND AGING

Hormones are regulated by a classical negative feedback system. Each peripheral hormone is regulated by a central system consisting of the hypothalamic-pituitary unit. The hypothalamus produces releasing hormones (and occasionally inhibitory hormones) that create a feedforward system that regulates the pulsatility and the circadian rhythm of hormone release. These releasing hormones regulate the release of anterior pituitary hormones, which in return result in the release of endorgan hormones. The endorgan hormones then feed back at the pituitary and the hypothalamic level to inhibit further release of pituitary hormones (Figure 1). When disease occurs in the endorgan hormone, it leads to failure of the endorgan and, therefore, negative feedback with an increase in the pituitary hormone (HYPO-disease) or increased activity of the endorgan with suppression of pituitary hormone release (HYPER-disease). When this occurs, the disease is considered to be primary endorgan disease, for example, primary hypothyroidism. Alternatively, failure can occur in the hypothalamic-pituitary unit leading to a decrease in both the pituitary and the endorgan hormone and this is known as *secondary disease*, for example, secondary hypogonadism. Finally, excess production of either a hypothalamic releasing hormone or pituitary hormone can occur. An example of this central form of HYPER-disease would be Cushing's Syndrome.

Aging has effects on all levels of the hypothalamic-pituitary-gonadal axis. The circadian rhythm is controlled by the suprachiasmatic nucleus, which feeds information to the hypothalamus. The hypothalamic releasing hormones are responsible for maintaining the pulsatility of hormone release, which is essential for optimal hormonal action. With aging, the pulse generator leads not only to a decline in maximal hormone production, but also to an irregular or "chaotic" production of hypothalamic releasing hormones. This is amplified at the pituitary level where there is a decrease in the ability to respond to the hypothalamic signal. In addition, the endorgan itself has decreased responsiveness to the stimulus from the pituitary hormone (Veldhuis and Bowers, 2003; Veldhuis, 1999; Korenman *et al.*, 1990; Harman and Tsitouras, 1980; Matsumoto, 2002) (Figure 2).

In addition, with aging changes in hormonal binding to its receptor and postreceptor responsiveness can also occur. An example of this is the posterior pituitary hormone, arginine vasopressin (AVP) or antidiuretic hormone (ADH). There is a decline in the renal responsiveness to AVP with aging. This leads to an increase in basal secretion of AVP with aging. A small further increase in AVP then puts the older person at high risk of developing hyponatremia and syndrome of inappropriate ADH (Miller *et al.*, 1995). There is also an attenuation of the normal increase in AVP that occurs at night. This increase is important for reabsorption of fluid during sleep and, therefore, its attenuation with aging leads to increasing nocturia (Moon *et al.*, 2004).

Classically, endocrinologists have interpreted circulating hormone levels in the absence of an understanding of

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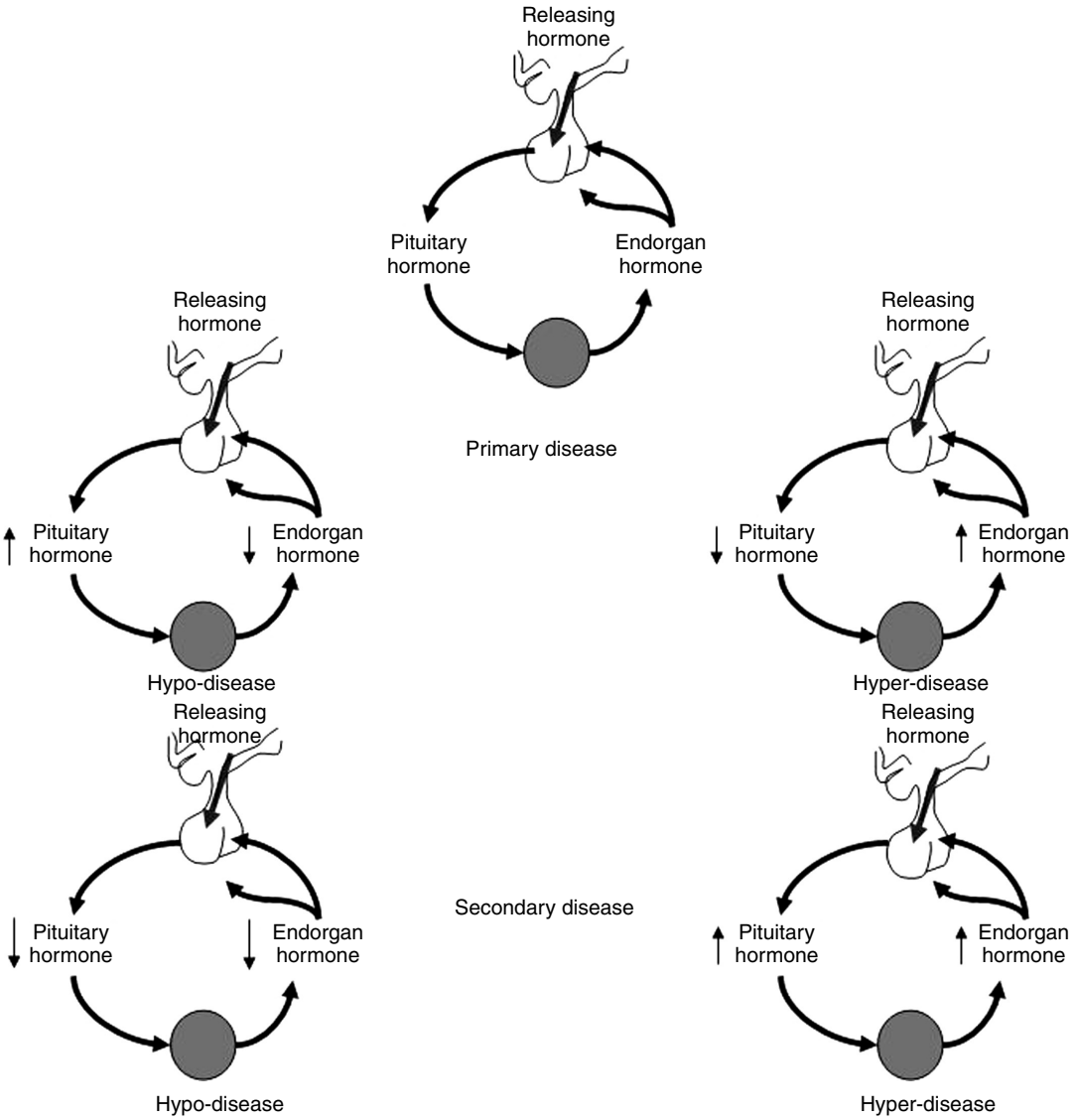

Figure 1 The normal hypothalamic-pituitary-endorgan and the effects of disease processes on it

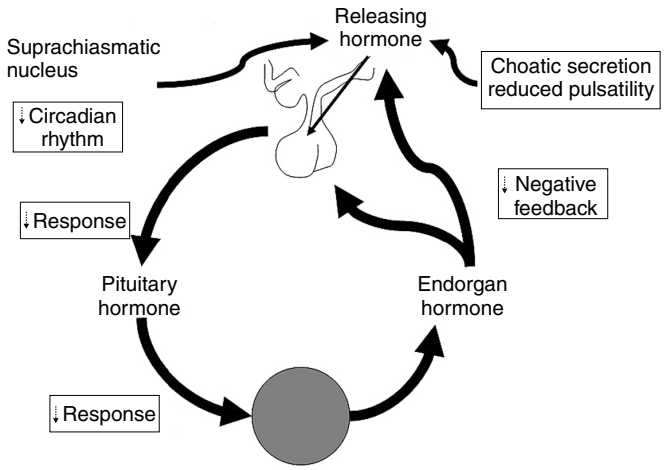

Figure 2 Effects of aging on the hypothalamic-pituitary-endorgan axis

the functioning of the receptor. This is becoming less acceptable as was shown recently by the example of the testosterone receptor and prostate cancer. The testosterone receptor contains a number of CAG repeats. The more the repeats, the less responsive the receptor is to testosterone. Prostate cancer occurs less often in males with a higher number of CAG repeats (Linja and Visakorpi, 2004).

Table 1 lists the hormonal changes seen with aging. The levels of circulating hormones are determined by their production and clearance rates. Thus, the level of thyroxine remains normal because both the production and clearance rates decrease equally. Cortisol levels are slightly increased as there is a greater decrease in clearance rates. Cholecystokinin levels increase markedly due to the decline in clearance rate (MacIntosh *et al.*, 2001).

It is generally believed that free hormone or tissue available hormone levels determine the effectiveness of the

Table 1 Hormonal changes associated with aging

Decreased	Normal	Increased
Growth hormone	Estrogen (men)	ACTH
Insulin Growth Factor-I	Luteinizing hormone (men)	Cholecystokinin
Testosterone	Thyroxine	Insulin
Estrogen (women)	Pancreatic polypeptide	Amylin
Dehydroepiandrosterone	Gastric inhibitory peptide	Luteinizing hormone (women)
Pregnenolone	TSH	FSH
Triaodothyronine	Glucagon-releasing peptide	Vasoactive intestinal peptide
25 $(OH)_2$ Vitamin D	Epinephrine	Cortisol
1,25(OH) Vitamin D	Prolactin	Parathyroid hormone
Aldosterone		Norepinephrine
Calcitonin		Glucagon

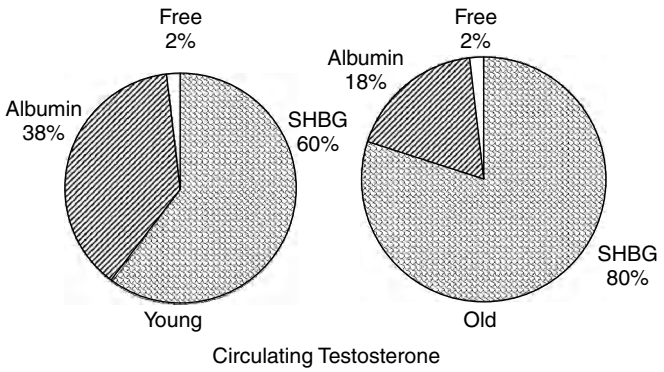

Figure 3 The effect of altered binding proteins with aging on the effect of tissue available hormones: the example of testosterone

hormone. Thus, in the case of testosterone in males there is a marked increase in sex hormone binding globulin (SHBG) with aging. The testosterone bound to SHBG is not thought to be available to tissues (Figure 3). The rest of the testosterone is free or bound to albumin, which is thought to be tissue available. Thus, measurement of the bioavailable testosterone gives a more accurate reflection of the true testosterone level than does a total testosterone measurement (Morley *et al.*, 2002). Similarly, a number of growth hormone binding proteins can produce marked changes in the ability of growth hormone to access its receptor.

EFFECTS OF AGING AND RELATED DISEASES ON ENDOCRINE DISEASES

With aging, there is a blurring of the boundaries between health and disease. The age-related decline in many hormone levels results in difficulties in making the biochemical diagnoses of endocrine disorders. The decreased functional reserve of endocrine organs that occurs with aging increases the propensity for older persons to develop endocrine deficiency disorders. With aging there is a decrease in T-suppressor lymphocytes and an increase in autoantibodies. Many endocrine disorders are due to autoimmune disease, and these changes amplify the possibility of an older person developing hypoendocrine disease in old age. There is also an increased likelihood of the development of polyglandular failure syndromes (Morley, 2001).

The decline in receptor and postreceptor responsiveness that occurs with aging often leads to atypical presentations. Apathetic thyrotoxicosis is, in part, due to the decreased postreceptor responsiveness for ß-adrenergic receptors that occurs with aging. The classical changes of apathetic thyrotoxicosis include depression, weight loss, atrial fibrillation, heart failure, blepharatosis, and proximal myopathy. Apathetic thyrotoxicosis occurs only in about 7% of older persons with hyperthyroidism. The presentations of endocrine disease in older persons are further confused by the fact that they often present with nonspecific symptoms, for example, delirium, fatigue, falls, weight loss, cognitive decline, or depression. These symptoms are common in older persons and can lead to delayed diagnosis. For example, Addison's disease can present with weight loss, fatigue, abdominal pain, diarrhea, and hyponatremia. The increase in cancer with aging can lead to ectopic hormone production with an increase in endocrine disorders such as the syndrome of inappropriate ADH.

Polypharmacy is common among older persons. This can lead to (1) interference with hormonal and metabolic measurements, for example, Vitamin C interferes with the measurement of glucose; (2) altered circulating hormone levels, for example, phenytoin and thyroxine; (3) decreased hormonal responsiveness, for example, spironolactone and aldosterone; (4) altered requirement for appropriate hormonal replacement dose, for example, rifampin increases the thyroxine replacement dose; (5) precipitation of latent disease, for example, thyrotoxicosis by iodine-containing medicines; (6) drug-hormone interaction, for example, coumadin and oral hypoglycemics to produce hypoglycemia; (7) production of metabolic abnormalities, for example, Vitamin A in megadoses produces hypercalcemia; (8) poor compliance with endocrine replacement therapies, and (9) adverse drug reactions.

Hypothyroidism represents a classical example of an endocrine condition that has major overlap with symptoms commonly seen in older persons. These include cold intolerance, slowed pulse, constipation, fatigue, cognitive changes, erectile dysfunction, dry skin, dry, brittle hair, and high blood pressure.

There are a number of endocrine disorders that occur virtually exclusively in older persons. These include osteoporosis, andropause, Paget's disease, and endotheliomainduced hypertension.

INSULIN RESISTANCE SYNDROME AND AGING

There is increasing awareness that insulin resistance syndrome is a cause of an accelerated aging process (Morley, 2004b). This condition is produced by a genetic propensity interacting with overeating and lack of exercise, that is, the couch potato syndrome (Figure 4). It is classically associated with visceral obesity, that is, an increase in intra-abdominal fat. This leads to an increased production of tumor necrosis factor α and leptin and a decrease in adiponectin (a hormone that decreases insulin resistance). The insulin resistance syndrome consists of hyperinsulinemia, diabetes mellitus, hypertension, hyperuricemia, hypertriglyceridemia, hypercholesterolemia, increased small, dense low-density lipoprotein (LDL) molecules, alterations in coagulation status, myosteatosis (fat infiltration into muscle), cognitive decline, and nonalcoholic steatohepatitis. Hypertriglyceridemia is a key in the development of the myosteatosis and the cognitive decline. Persons with insulin resistance have an increased incidence of myocardial infarction and stroke. The insulin resistance syndrome is associated with frailty, disability, and increased mortality.

Recent studies have suggested that a major component of the pathogenesis of the insulin resistance syndrome is accumulation of triglycerides and free fatty acids within muscle cells. This can occur either because of a failure of mitochondria leading to decreased utilization of intracellular fatty acids (primary syndrome) or because of excess circulating triglycerides and fatty acids (secondary syndrome). Accumulation of fatty acids within the cell leads to decreased activity of the insulin receptor substrate and therefore, a decrease in GLUT-transporter activity (Lowell and Shulman, 2005).

THE HORMONAL FOUNTAIN OF YOUTH

The parallel decline of many hormones with aging and age-related symptoms has led to the suggestion that the hormonal decline may be a central component in the pathogenesis of aging (Morley, 2004a). Unfortunately, with the exception of the role of vitamin D in age-related loss of bone mineral density there is little evidence to support this premise. In this section, each of the hormones that has been suggested to play a role in the aging process will be briefly discussed.

Vitamin D

Vitamin D has been shown to decline with aging in a longitudinal study (Perry *et al.*, 1999). There is clear evidence that vitamin D (800 IU) together with calcium decreases the rate of hip fracture in older persons (Chapuy *et al.*, 1994). This is associated with a decline in mortality. Vitamin D replacement in persons who have clear vitamin D deficiency improves muscle strength and decreases falls (Bischoff-Ferrari *et al.*, 2005; Bischoff-Ferrari *et al.*, 2004). Vitamin D deficiency should be suspected in any older person with a borderline low

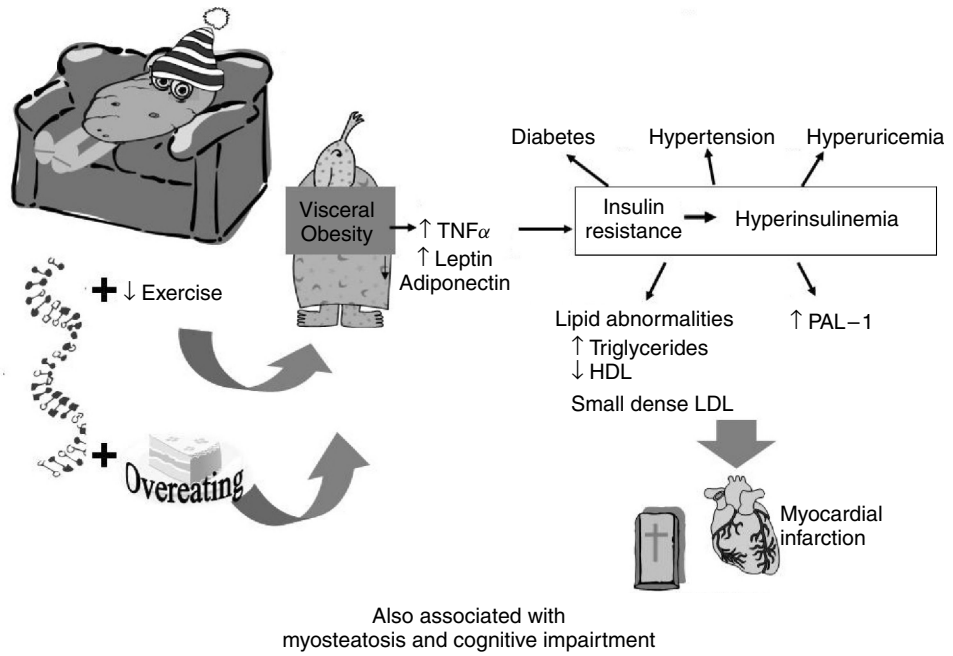

Figure 4 Metabolic syndrome: the deadly quintet (Camus, 1966; Reaven, 1993)

calcium level and an elevated alkaline phosphatase. Increased exposure to sunlight may be as efficacious in increasing Vitamin D levels as using Vitamin D replacement. However, there is some evidence that old skin when exposed to ultraviolet light is less effective than young skin, at manufacturing cholecalciferol.

Testosterone

Testosterone levels decline both in males and females with aging. The effects of testosterone replacement in males and females with aging is shown in Table 2. Testosterone replacement at relatively high doses in older males has been shown to increase muscle mass, strength, functional status, and bone mineral density (Page *et al.*, 2005; Matsumoto, 2002). Testosterone increases libido in both males and females. In males, testosterone increases erectile strength, volume of ejaculation and visuospatial cognition. The major side effect is an excessive increase in hematocrit. The effects of long-term testosterone replacement on benign prostate hypertrophy and prostate cancer are unclear at present. Testosterone can cause gynecomastia, produce water retention, and may worsen sleep apnea in a few individuals. The lack of long-term safety data for testosterone is a major concern. At present, testosterone should be considered a quality of life drug in both men and perhaps women (*see* **Chapter 11, Sexuality and Aging**; **Chapter 121, Ovarian and Testicular Function**). The development of selective androgen receptor modulators (SARMs) is under way in an attempt to avoid some of the potential side effects of testosterone. Nandrolone has been shown to be a potent anabolic agent in older persons.

Growth Hormone

The concept that growth hormone may be able to rejuvenate older men was given impetus by a publication of Rudman *et al.*, (1990) in the New England Journal of Medicine. Unfortunately, since this original publication, numerous studies have failed to demonstrate any major positive effects of growth hormone (Table 3; Morley, 1999). In addition, growth hormone has been shown to have a variety of side effects when administered for more than 3 months to older persons. There is some evidence that growth hormone may improve weight gain and function in malnourished older persons (Chu *et al.*, 2001; Kaiser *et al.*, 1991).

Studies in animals have suggested that growth hormone deficient animals live longer than growth hormone sufficient animals (Bartke, 2005). In addition, in a human study, persons with the highest levels of growth hormone had the highest mortality rate. At present, there is no evidence to support the use of growth hormone to slow aging or improve the quality of life of older persons.

Table 2 Effects of testosterone in older males and in postmenopausal females

Old males	Postmenopausal females
Increased muscle mass	Increased muscle mass
Increased strength	Increased bone mineral density
Increased function	Increased libido
Increased bone mineral density	Decreased mastalgia
Increased hematocrit	
Increased visuospatial cognition	
Increased libido	
Increased strength of erection	
Increased volume of ejaculation	

Table 3 Lesson from growth hormone studies in older persons

Growth hormone increases nitrogen retention
Growth hormone produces weight gain
Growth hormone increases muscle mass
Growth hormone possibly increases Type-II muscle fibers
Growth hormone does not increase strength
Growth hormone is associated with multiple side effects
Growth hormone may improve function in malnourished older persons

Insulin Growth Factor-1 (IGF-1)

Insulin Growth Factor-1 (IGF-1) is produced in peripheral tissues in response to growth hormone. In human studies, it has tended to produce hypoglycemia and minimal positive effects. In animals, it accelerates the growth of tumor cells. In muscle, three different forms of IGF are produced. One of these is mechanogrowth factor (MGF). MGF levels increase in response to resistance exercise. Stem cell replacement of MGF has reversed the muscle atrophy seen in older rats.

Ghrelin

Ghrelin is produced in the fundus of the stomach and released into the circulation. It causes the release of growth hormone and increases food intake (Table 4). MK-771, a ghrelin analog, while increasing growth hormone, has failed to produce major positive effects in older humans.

Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) is an adrenal hormone whose levels decline markedly with aging. It has been touted as the "mother hormone" by antiaging charlatans. DHEA has

Table 4 Ghrelin and aging

Ghrelin is produced in the fundus of the stomach
Ghrelin is slightly decreased with aging
Ghrelin increases food intake
Ghrelin releases growth hormone from pituitary
Ghrelin increases body mass
Ghrelin enhances memory
Ghrelin produces its food and growth hormone effects through nitric oxide synthase stimulation
MK-771 (a ghrelin agonist) had minimal effects in older humans

remarkable effects on the immune system and cognition in rodents. Unfortunately, a year long study of 50 mg, showed no effects on muscle mass or strength and only a small increase in libido in women over 70 years and some positive effects on the skin (Percheron *et al.*, 2003; Baulieu *et al.*, 2000; Berr *et al.*, 1996). It may have some small effects on insulin resistance. At doses of 100 mg, it has been reported to have effects on humans, but at this dose it is converted into substantial amounts of circulating testosterone.

Pregnenolone

Pregnenolone is produced by the adrenals from cholesterol. It is the true "mother hormone" as it is the precursor of DHEA. In mice, it is the most potent memory enhancer yet to be discovered (Flood *et al.*, 1992). Unfortunately, it has not been shown to have positive effects in humans.

Estrogen

Estrogens were originally touted as hormones that would make women "feminine forever". The Women's Health Initiative (WHI) has shown that premarin in older postmenopausal women increases breast cancer, pulmonary embolism, heart disease, and Alzheimer's disease while decreasing hip fracture and colon cancer (Sherwin, 2005; Goldzieher, 2004; Seelig *et al.*, 2004). While there are still scientists pursuing a better (safer) estrogen which will have the positive effects in women without the negative effects, estrogens should be avoided in women over the age of 60 at present. The use at the time of the menopause represents a quality of life decision.

Melatonin

Melatonin is synthesized from tryptophan in the pineal gland. Melatonin levels increase at night and fall to very low levels during the day. Melatonin has been used with minor success to enhance sleep in older persons. It does not alter the normal sleep structure. It may have a role in the treatment of seasonal affective disorder. Extravagant claims for the utility of melatonin have been based primarily on animal studies and include life extension, enhanced immune function and decreased tumor growth. Studies in humans to support these claims are virtually nonexistent. The rate of decline of melatonin with age is less than was originally thought.

KEY POINTS

- It has been suggested that multiple hormonal changes occur with aging which may play a role in the pathophysiological process associated with aging.
- Many hormones decline with aging but their replacement does not necessarily reverse aging effects.
- The role of melatonin and dehydroepiandrosterone in aging is unknown.
- The insulin resistance syndrome can be considered a cause of the accelerated aging process.
- Testosterone and other hormones may play a role in the treatment of sarcopenia, which is an important proximate occurrence in the development of functional decline in older persons.

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The Pituitary Gland

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INTRODUCTION

The pituitary gland is the master endocrine gland as it detects and integrates multiple sources of information to regulate physiologic functions (Figure 1). The name pituitary originated from the Latin *pituita*, which means mucus. It was believed that the pituitary excreted mucus from the brain through the nose. Understanding age-related changes in this gland and the manifestations of pituitary disease in the elderly is becoming increasingly important as the population ages. The magnitude of these age-related changes is highly variable, and the confounding effect of illness on these changes must be appreciated. Interpreting age-associated changes in pituitary function must also take into account the rates and pulsatile secretion of hormones, the rapid changes in the levels of some hormones due to physiologic states such as stress, the binding of hormones to plasma proteins, the hormone clearance rates from the plasma, and the altered target tissue sensitivity to hormones. The comorbidity often seen in older persons can mask the usual presentation of pituitary disease and make the diagnosis and treatment of these disorders challenging.

This chapter will review the pertinent changes in the pituitary gland that occur with aging and the diseases that affect this gland and are relevant to the care of the older individual.

ANATOMY

The pituitary gland is functionally divided into an anterior lobe, a posterior lobe, and an intermediate lobe. It is located at the base of the brain within the sella turcica and is covered by the diaphragm sella. The pituitary stalk exits through the diaphragm sella to connect with the hypothalamus. The adult pituitary gland weighs 600 mg and measures 13 mm (transverse) $\times 6-9$ mm (vertical) $\times 9$ mm (anteroposteriorly) (Melmed and Kleinberg, 2003). The optic chiasm is located anterior to the pituitary stalk and is directly above the diaphragm sella, making the optic tracts vulnerable to compression by an expanding pituitary mass. The hypothalamus contains neurons that synthesize releasing and inhibiting hormones as well as the hormones arginine vasopressin and oxytocin of the posterior pituitary. The five cell types that secrete hormone in the anterior pituitary gland are listed in Table 1.

In the elderly, the pituitary gland is moderately decreased in size and contains areas of patchy fibrosis, local necrosis, vascular alterations, and cyst formation. Extensive cellular deposits of lipofuscin and regional deposits of amyloid are also seen. There are not any prominent age-associated alterations in the relative proportions of different types of pituitary secretory cells. The LH and FSH contents are somewhat increased in older people, but there are no age-related changes in the pituitary content of GH, PRL, and TSH (Blackman, 1987).

Blood Supply

The blood supply to the anterior pituitary is through a rich vascular network. The superior hypophyseal arteries (from the internal carotid arteries) supply the hypothalamus and form a capillary network and portal vessels from this network supply the anterior pituitary. These vessels form the conduit for the releasing and inhibiting hormones of the hypothalamus to the anterior pituitary cells. Inferior hypophyseal arteries from the posterior communicating and internal carotid arteries supply the posterior pituitary. Drainage is into the cavernous sinus and internal jugular veins.

Anterior Pituitary Disorders – Clinical Manifestations

Pituitary tumors are very common occurring at postmortem in 20–25% of persons (Costello, 1936). Microadenomas

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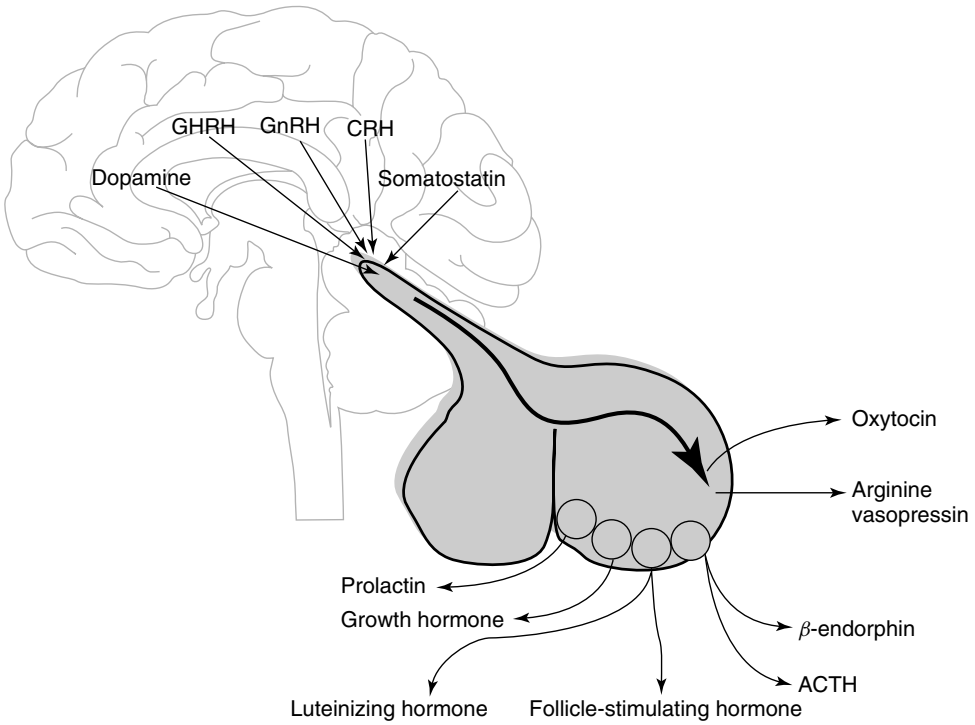

Figure 1 Hormones produced by the anterior pituitary and its hypothalamic controlling factors

Table 1 Pituitary cell type, their hormone, and their percentage

Cell type	Hormone	Stimulators	Inhibitors	Percentage of anterior pituitary cells
Corticotroph	POMC including ACTH	Corticotropin-releasing hormone, vasopressin, cytokines	Glucocorticoids	15–20
Somatotroph	GH	GH-releasing hormone, GH secretagogues	Somatostatin, IGF	50
Thyrotroph	Alpha subunit and beta subunit (thyrotropin)	TRH	T_3, T_4, dopamine, somatostatin, glucocorticoids	<10
Gonadotroph	FSH and LH	Gonadotropin-releasing hormone	Sex steroids, inhibin	10–15
Lactotroph	PRL	Estrogen, TRH	Dopamine	10–25

POMC, pro-opiomelanocortin peptides; ACTH, adrenocorticotrophic hormone; GH, growth hormone; FSH, follicle-stimulating hormone; LH, leuteinizing hormone; PRL, prolactin; TRH, thyrotropin-releasing hormone; IGF, insulin-like growth factor; T_3, triode thyronine; T_4, thyroxine.

are more common in men than in women and over half the tumors in older persons have immunoreactive prolactin staining in their cytoplasm. Despite the frequency of this occurrence, pituitary tumors in the elderly are a neglected subject in the literature. Outcome studies on the prevalence and treatment of the various types of pituitary adenomas are confounded by lack of long-term follow-up, comorbidity, and a referral bias toward younger patients (Turner and Wass, 1997). Pituitary tumors in persons over 60 years of age account for 3–13.4% of all brain tumors (Kleinschmidt-DeMasters *et al.*, 2003). Pituitary lesions present with a variety of manifestations, including pituitary hormone hypersecretion and hyposecretion, enlargement of the sella turcica, and visual loss. In the general adult population, hypersecreting pituitary adenomas are the most common cause of pituitary dysfunction, and the earliest symptoms are due to endocrinologic abnormalities. Visual loss and headache are later manifestations and are due to sellar enlargement. These later symptoms are seen only in patients with large tumors on extension above the sella (Aron *et al.*, 2004). Early visual symptoms include the hemifield slide phenomenon, that is, images floating apart from one another, and the inability to focus on two points at the same time, for example, the inability to do needlework. The classical visual sign of pituitary tumors is bitemporal hemianopsia. In older persons, this sign can be difficult to detect as some degree of bitemporal hemianopsia occurs as a normal part of the aging process.

In contrast, most clinically relevant pituitary tumors in the elderly are nonfunctioning and do not present with features of hormonal hypersecretion. Patients are more likely to be

diagnosed with visual field deficits or as incidentalomas (Turner and Wass, 1997). In a study by Cohen *et al.* (1989) 73% of 22 pituitary tumors diagnosed in patients over 70 years of age were nonfunctioning. Cushing's disease was diagnosed in one, prolactinoma in one, and acromegaly in three. In the series by Kleinschmidt-DeMasters *et al.* (2003), of the 13 tumors one was a prolactinoma with subarachnoid hemorrhage and apoplexy and two secreted growth hormone. The other 10 were nonfunctioning.

Of the hormones hypersecreted by pituitary adenomas, prolactin (PRL) is the most common. Measuring PRL is an important part of the evaluation of patients with suspected pituitary disorders and should be performed in older patients presenting with gonadal dysfunction, secondary gonadotropin deficiency, or sella turcica enlargement. The characteristic syndromes of acromegaly and Cushing's disease are due to the hypersecretion of GH and ACTH, respectively, but are rare presentations of pituitary disease in the older population. The characteristic symptoms of acromegaly are given in Table 2. Even more rarely, ectopic GH-releasing hormone causing somatotroph hyperplasia leading to acromegaly and corticotropin-releasing hormone to Cushing's disease can be due to abdominal or chest tumors.

Hypopituitarism is another manifestation of a pituitary adenoma. The clinical presentation of hypopituitarism depends on which hormones are affected, the acuteness or chronicity of the disorder, and the severity of the hormone deficiencies (Table 3).

In adults, hypogonadism is the earliest clinical manifestation of an adenoma and is secondary to elevated PRL, ACTH and cortisol, or GH. The hypogonadism is due to impaired secretion of gonadotropin-releasing hormone rather than anterior pituitary distinction. Older persons with hypopituitarism may present with recurrent falls (Johnston *et al.*, 1996), hyponatremia (Mansell *et al.*, 1993), postural hypotension, and hypothyroidism with an inappropriately suppressed TSH (Belchetz, 1985). Tayal reported pituitary adenomas as the most common cause of hypopituitarism in 12 patients aged 63–89 years (Tayal *et al.*, 1994). The presenting features in this series were lethargy, hypotension, weakness, falls, weight loss, drowsiness, confusion, immobility, and urinary incontinence. Other symptoms of hypopituitarism in older adults include changes in body composition (abdominal obesity and loss of muscle leading to decreased exercise tolerance and fatigue – due to GH loss), decreased sexual function (owing to gonadotropin loss), hypoglycemia and hypocortisolism (caused by loss of ACTH), and polyuria and polydipsia (due to deficits in vasopressin). Other causes of hypopituitarism are given in Table 4.

Pituitary apoplexy, resulting from hemorrhage or infarction of the pituitary gland, usually occurs as a sudden crisis in a patient with a known or previously unrecognized pituitary tumor, but may occur in a normal gland. The risk factors for this condition are common in the elderly. Symptoms at presentation include the sudden onset of headache, stiff neck, oculomotor disturbances, and confusion (Turner and Wass, 1997).

An enlarged sella turcica is another presentation of pituitary disease. The enlargement is usually noted on X rays performed for other indications such as trauma, sinusitis, or mental status changes. Patients with an enlarged sella usually have a pituitary adenoma or empty sella syndrome as

Table 3 Symptoms of hypopituitarism in older adults

Insufficient thyroid-stimulating hormone production
- Confusion
- Cold intolerance
- Weight gain
- Dry skin
- Constipation
- Hypertension
- Fatigue

Insufficient growth hormone production
- Fatigue
- Decreased strength

Insufficient gonadotropin production
- Fine wrinkled skin
- In males worsening libido

Insufficient corticotropin production (very rare)
- Fatigue
- Hypoglycemia
- Hypotension
- Intolerance of stress

Table 2 Symptoms of acromegaly in older persons with pituitary secreting tumors

Fatigue
Weakness
Swelling of hands and feet
Coarse facial features
Increased head size
Increased perspiration
Deepening of voice
Enlargement of lip, nose, and tongue
Joint pain
Snoring
Cardiomyopathy
Headaches
Visual loss

The diagnosis can often be made by looking at serial photos taken over the lifetime to detect the physical changes that occurred.

Table 4 Causes of hypopituitarism

Primary hypopituitarism
- Pituitary tumors
- Hemosderosis
- Infections
- Sarcoidosis
- Radiation therapy
- Tuberculosis
- Hypophysitis (autoimmune disease)
- Surgery
- Impaired vascular supply

Secondary hypopituitarism
- Hypothalamic tumors
- Head injuries
- Multiple Sclerosis
- Inflammatory disease

the cause (Aron *et al.*, 2004). In the elderly, carotid artery aneurysms would also be in the differential diagnosis, while craniopharyngiomas and lymphocytic hypophysitis seen in younger populations would be less likely. Pituitary function in the empty sella syndrome is usually normal, although some patients have hyperprolactinemia. MRI confirms the diagnosis.

An increased suspicion of a pituitary/hypothalamic disorder should occur if patients present with unexplained unilateral or bilateral visual field deficits including bitemporal hemianopsia or visual loss. Vision changes were the most common presentation of pituitary adenomas in Cohen's series of 22 patients aged 70 years and over (Cohen *et al.*, 1989). These patients should have a neuro-ophthalmologic evaluation, MRI, and a serum prolactin as well as an assessment for hypopituitarism. Additional concerns of large pituitary lesions are that they may have lateral extension into the cavernous sinus leading to diplopia caused by dysfunction of the third, fourth, or sixth cranial nerve. These large tumors may also extend in an inferior direction through the sphenoid sinus and roof of the palate and lead to cerebrospinal fluid leakage. Seizures and personality changes can result from invasion of the temporal or frontal lobe. Hypothalamic encroachment can lead to hypogonadism, diabetes insipidus, and disorders of temperature regulation, appetite, and sleep. Headaches can be due to stretching of the dural plate and do not necessarily correlate with size or extension of the mass.

ANTERIOR PITUITARY DISORDERS – TREATMENT

Nonfunctioning Pituitary Tumors

The clinical features of these tumors are usually due to mass effects. Hypopituitary and hyperprolactinemia (caused by impingement on the pituitary stalk and interference with tonic inhibition of lactotroph cells by dopamine secreted by the hypothalamus) are usually present in varying degrees. Less than one-third of the time there is an elevation of follicle-stimulating hormone (FSH), LH, or their subunits.

There is no effective medical therapy. Nonfunctioning microadenomas ($\leq$10 mm) have a benign natural history and can be followed with annual visual acuity and visual field testing and neuroimaging in the asymptomatic patient. Surgery and radiotherapy appear to be very effective in producing control of symptomatic nonfunctioning pituitary tumors. In Cohen's series (Cohen *et al.*, 1989), transsphenoidal surgery was performed in 64% of the 16 patients and was well tolerated with few postoperative complications. Vision was significantly improved in seven and unchanged in one. Temporary visual deterioration occurred in one patient and permanent deterioration occurred in another. In Brada's population aged 60 years and over, 79% of patients treated with radiotherapy had a diagnosis of nonfunctioning pituitary adenoma and, after 10 years of follow-up, only one showed evidence of tumor progression (Brada *et al.*, 1993). In the United States, 5497 pituitary surgery operations were performed between 1996 and 2000. There was a 0.6% death rate and a 3% discharge to long-term care. Age was a significant predictor of mortality and a worse outcome at hospital discharge (Barker *et al.*, 2003). Surgeons with a higher case load had much better outcomes.

Prolactinomas

In addition to symptoms caused by mass effects, postmenopausal women may present with galactorrhea and men can present with hypogonadism including decreased libido. Excluding medications, hypothyroidism, and other causes of hyperprolactinemia is an important step in the initial approach to this problem. In general, treatment consists of medical therapy with a dopamine agonist. The available dopamine agonists include bromocriptine, lisuride, pergolide, and cabergoline. Dopamine agonists can produce orthostans and delirium with hallucinations and delusions. Surgery is used for those intolerant or resistant to dopamine agonist therapy. Surgery is also indicated for those patients who require urgent decompression of the sella turcica for visual field deficits. Treatment is recommended for microprolactinoma ($\leq$10 mm) to prevent osteoporosis, the infrequent occurrence of tumor progression, and the effects of prolonged hypogonadism.

The management of prolactinomas in the elderly is hindered by the lack of data. Several reviews include no elderly patients (Ciccarelli *et al.*, 1990; Soule *et al.*, 1996; Bevan *et al.*, 1992), so extrapolation from data in younger populations and individualizing treatment decisions is necessary.

Cushing's Disease

The diagnosis of Cushing's disease may be more challenging in the elderly because symptoms (weight gain, hypertension (HTN), diabetes mellitus (DM)) may be nonspecific and because elevated urinary cortisol exertion can be seen with Alzheimer's disease and multi-infarct dementia (Maeda *et al.*, 1991). Lack of cortisol suppression after low-dose dexamethasone is seen with depression and Alzheimer's disease as well as Cushing's disease and further complicates the diagnosis. In addition, up to 50% of ACTH tumors are not visible on MRI and require inferior petrosal sinus sampling and CRH-provocative testing.

Treatment of ACTH-producing tumors is by transsphenoidal resection. A higher relapse rate has been seen in younger patients versus older patients (Bochicchio *et al.*, 1995; Robert and Hardy, 1991). Metyrapone has also been used to treat Cushing's disease in the elderly (Donckier *et al.*, 1986).

Acromegaly

The predominant cause of acromegaly is GH-producing tumors, and the effects of GH are medicated by IGF-1

(produced by the liver). Symptoms are those of acromegaly as well as those caused by mass effects of the tumor. The best screening test for this disease is an IGF-1 level. Because the secretion of GH is pulsatile, random levels are not helpful with the diagnosis. The treatment of choice for a GH-secreting tumor is excision. Pharmacologic therapy with octreotide or radiotherapy can be considered if disease persists after excision.

Acromegaly in older patients appear to be a milder disease than in younger patients (Klijn *et al.*, 1980), and it has been suggested that treatment can be more conservative in this group (Clayton, 1993). It appears that elderly individuals respond well to both transsphenoidal surgery and medical treatment with somatostatin agonists (Turner and Wass, 1997).

Thyrotropin (TSH)-Secreting Tumors

About 2% of all pituitary tumors are TSH-secreting. They can present with symptoms of thyrotoxocosis. Among 25 patients with TSH-producing tumors, one was 60, one 63, and one 80 years old (Brucker-Davis *et al.*, 1999). There are few data for treatment in any age-groups for this rare tumor. Octreotide appears to be a safe and effective treatment (Charson *et al.*, 1993). However, in the older patients tumors tend to be large, requiring surgery and radiation. Often some tumor remnant remains in these patients.

Gamma-knife Radiosurgery

Gamma-knife radiosurgery is a new option for the management of pituitary tumors. The gamma-knife is a device that allows radiation to be delivered from outside the head to a precise position within the brain. It requires no incision. Multiple radiation beams are aimed at the pituitary. Each individual beam is too weak to damage the brain tissue it passes through, with the tissue destruction only happening at the place in the pituitary where the beams meet. Accuracy is to within a fraction of a millimeter: Occasionally, gamma-knife therapy can cause local swelling 2–12 months following the procedure. Otherwise, it is relatively side effect–free.

Empty Sella Turcica

Empty sella turcica has been diagnosed in men and women in their 60s and 70s. It is characterized by enlargement of the bony structure enclosing the pituitary together with loss of pituitary tissue. It occurs most commonly in overweight women with high blood pressure. Symptoms include cephalgia, hypopituitarism, or a runny nose. Most empty sellas are diagnosed incidentally during a radiological procedure of the head.

Table 5 Changes reported in hormones

Hormone	Increase	Decrease	None
Adrenocorticotrophin hormone	−	+	−
Follicle-stimulating hormone	+	+	−
Luteinizing hormone	+	+	−
Growth hormone	−	+	−
Thyroid-stimulating hormone	−	+	+
Prolactin	+	+	+

Anterior Pituitary Hormone Secretion – Functional Changes with Age

Functional changes in anterior pituitary hormone secretion occur with increasing age. Table 5 summarizes some of the changes that have been reported in these hormones (Rehman and Masson, 2001).

Gonadotropins (LH and FSH)

Blood concentrations of both LH and FSH abruptly and universally increase in about the sixth decade in women as ovarian secretion of estrogens decreases. These values gradually decline after age 75 years (Vaninetti *et al.*, 2000). Serum FSH and LH rise approximately twofold in men aged 75–85 years, and then decline gradually, as pituitary gonadotropic secretory capacity is reduced with advancing age. This is suggested by a decrease in the amplitude of LH and/or FSH responses to gonadotropin-releasing hormone (Harman *et al.*, 1982). There is a widespread of values at these ages, suggesting primary hypogonadism in some men and secondary (central) hypogonadism in others. Secondary hypogonadism may be the rule rather than the exception with aging (Kaiser and Morley, 1994). The mean LH pulse amplitude and the maximal pulse amplitude are lower in elderly than in younger males (Vermeulen, 1994).

The changes in the LH response to aging may be due to the effects of aging on the catecholamine responses in the hypothalamus. The estrous cycle in old female rats is reinstated by drugs that stimulate brain catecholamine neurotransmitters (Quadri *et al.*, 1973). Naloxone administered to old rats partially restores the LH surge. This suggests that opiates from the hypothalamus may be partly responsible for reduction in LH secretion (Allen and Kalra, 1986).

Prolactin (PRL)

Unlike other pituitary hormones, hypothalamic control of prolactin is mainly inhibitory through dopamine. Other than stimulating lactation in the post partum period, prolactin has no significant physiologic function. Hyperprolactinemia suppresses sex steroid production.

There is no consensus on the effects of aging on prolactin secretion. Investigators have reported decreases, increases, or no change in prolactin levels (Blackman, 1987). Sawin's analysis of prolactin levels from the Framingham cohort showed no significant difference in the prolactin levels between the age-matched sexes. The mean prolactin level in men for ages 40–49 years was $6.4 + 1 - 3.1\,\mathrm{mg\,ml^{-1}}$ compared with $8.4 \pm 3.8\,\mathrm{mg\,ml^{-1}}$ for ages 80–89 years. In age-matched women, the values of 6.9 ± 3.1 and $8.8 \pm 5.3\,\mathrm{mg\,ml^{-1}}$ corresponded to the same age groups as described for the men (Sawin *et al.*, 1989). Alterations of PRL in humans are probably of small magnitude and unlikely to affect sexual function in the older adult, but more likely the causes hyperprolactinemia in this population are medications and prolactinomas which should be evaluated (Harman and Blackman, 2000).

Growth Hormone

Both aging and sex effect growth hormone secretory dynamics. Young women have twice as high daily growth hormone production as young men. The fall in growth hormone over the life span is from $1200\,\mu\mathrm{g\,m^{-2}}$ in adolescents to $60\,\mu\mathrm{g\,m^{-2}}$ in older individuals (Veldhuis and Bowers, 2003). The fall in growth hormone secretion with aging is due both to a decrease in the orderly production of growth hormone releasing hormone from the hypothalamus and an increase in somatostatin production from the hypothalamus. The fall in growth hormone secretion leads to a decline in insulin-growth-factor-1.

Circulating growth hormone is bound to growth hormone binding proteins. With aging there is a decline in growth hormone binding proteins. The level of growth hormone binding proteins is approximately half that in nonagenarians compared to the 60-year-olds (Maheshwari *et al.*, 1996).

In older women, estrogen increases growth hormone secretion. In older men only high doses of aromatizable form of testosterone (200 mg) increased basal and the mytohemeral growth hormone production (Gentili *et al.*, 2002).

Overall aging is associated with multiple changes of the hypothalamic-growth hormone – insulin growth factor-1 axis and their binding proteins. Interactions with sex hormones further complicate these effects. However, studies with growth hormone or ghrelin analog replacement have failed to demonstrate physiologically important effects of these changes on the aging process.

POSTERIOR PITUITARY GLAND

The posterior pituitary gland is neural tissue and consists only of the distal axons of the hypothalamic magnocellular neurons. The cell bodies of these axons are located in the supraoptic and paraventricular nuclei of the hypothalamus. The axon terminals contain neurosecretory granules in which are stored the hormones oxytocin and vasopressin (antidiuretic hormone (ADH)). Diseases of the posterior pituitary (diabetes insipidus, syndrome of inappropriate ADH) modulate water homeostasis. Persons with diabetes insipidus (insufficient production of vasopressin) present with excessive thirst, polyuria, and dehydration. The major causes of diabetes insipidus are listed in Table 6.

Table 6 Causes of diabetes insipidus

- Hypothalamic malfunction or damage
- Brain injury including cerebrovascular accidents
- Tumors
- Meningitis and encephalitis
- Sarcoidosis
- Tuberculosis

Water excretion in the elderly is affected by physiologic changes of the aging process and leads to an increased risk of both hyponatremia and hypernatremia (Stout *et al.*, 1999; Davies, 1987). Multiple diseases common in elderly persons and the treatments for these diseases can further affect water balance. In addition, body water is reduced in the elderly. By age 75–80, total body water declines to 50% of the level in young adults and complicates studies of responses to dehydration, volume stimulation, and osmolar stimulation (Fulop *et al.*, 1985).

There is a reduced responsiveness of the renal collecting duct to vasopressin in older as compared with younger individuals, the consequences of which is an increased vulnerability to water deprivation (Davis and Davis, 1987). This decreased renal sensitivity to ADH is thought to be due to a decreased ability of vasopressin to stimulate aquaphorin-2 levels in the kidney, and results in a chronic increase in vasopressin secretion and an eventual depletion in posterior pituitary hormone stores. This may cause a decreased visualization of the bright spot on T-1 weighed MRI scans in elderly people (Terano *et al.*, 1996). The bright spot in the sella on MRI is due to stored hormone in neurosecretory granules in the posterior pituitary.

Vasopressin levels have a greater range of normal in older persons and do not correlate as directly with plasma osmolality (Johnson *et al.*, 1994; Favll *et al.*, 1993). Changes in vasopressin levels in response to osmotic stimulation are either normal (Stachenfeld *et al.*, 1996) or increased (Stachenfeld *et al.*, 1996; Ayos and Arieff, 1996), while the vasopressin response to volume depletion (mediated by baroreceptors) is increased (Phillips *et al.*, 1984).

Older persons also have a decrease in thirst in response to osmotic stimulation. As a result of the decrease in thirst and in the responsiveness of the kidney to vasopressin, it is easy for older patients to become dehydrated and hypernatremic despite an increase in vasopressin secretion (Weinberg and Minaker, 1995). Even when recovering from dehydration, older people drink less fluid to return their volume to normal (Phillips *et al.*, 1991).

Excreting a water load is also limited in the elderly. Decreases in glomerular filtration rate and a decreased suppression of vasopressin contribute to this phenomenon. Vasopressin is not shut off in the elderly as well as in the

young in response to drinking and oral-pharyngeal receptor stimulation. Those older patients with increased levels of ADH secretion in response to a particular osmotic level have a downward alteration in their osmotic set point. This inability to execute a water load can lead to an increased tendency toward hyponatremia in the elderly. Almost 75% of patients with the syndrome of inappropriate ADH secretion are over 65 years of age (Harman and Blackman, 2000).

Given the issues raised above by numerous studies, healthy older adults probably exhibit normal secretion of vasopressin but do have a decreased thirst appreciation and a decreased ability to maximally concentrate the urine to retain water or to maximally dilute the urine to excrete water. Both hyponatremin (Roberts, 1993) and hypernatremia (Hoffman, 1991), to which older people are susceptible due to the physiologic changes noted above, can cause increased morbidity and mortality especially in the frail elderly and therefore warrant vigilance for their occurrence.

KEY POINTS

- Nonfunctioning pituitary tumors are extremely common in older persons.
- With aging there is a decline in anterior pituitary function.
- Diabetes insipidus is due to insufficient production of vasopressin and leads to excessive thirst and polyuria.
- Treatment for pituitary tumors includes medical, surgery and most recently gamma-knife radiation.

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Thyroid Disorders

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INTRODUCTION

Changes in thyroid gland anatomy and function occur with aging. However, distinguishing physiologic processes of normal aging from pathologic processes associated with disease is difficult. For example, clinical diagnosis of thyroid disease in the elderly is obscured by the presence of many signs and symptoms of hypothyroidism in euthyroid elderly persons, and the absence of many signs and symptoms that represent disease in hyperthyroid elderly persons. An understanding of the changes in thyroid gland anatomy, thyroid hormone economy, and thyroid hormone actions that occur with aging is important for accurate diagnosis and therapy.

CHANGES IN THYROID GLAND ANATOMY AND HISTOLOGY

Thyroid gland anatomy and histology change with aging. Grossly, thyroid weight may be increased, unchanged, or decreased (Denham and Wills, 1980; Mariotti *et al.*, 1995). Increased thyroid weight occurs with the development of a nodular goiter, which occurs more commonly in the elderly (Mariotti *et al.*, 1995). Thyroid nodularity may be related to iodine deficiency (Laurberg *et al.*, 1998), and so may not be attributed to the aging process alone. Microscopically, there is lymphocytic infiltration, fibrosis, reduction in follicle size, and flattening of follicular epithelium (Mariotti *et al.*, 1995). While the presence of thyroid nodules carries a risk for autonomous function and hyperthyroidism, and the presence of lymphocytic infiltrates in a patient with antithyroid antibodies suggests autoimmune thyroiditis and a risk for hypothyroidism, anatomic and histologic changes that occur with aging do not always correlate with abnormalities in thyroid function. Still, in one survey of thyroid glands from elderly patients obtained at postmortem examination, there was a statistically significant increased incidence of abnormal function in nodular versus normal thyroid glands. Microscopic changes, however, occurred in both nodular and normal thyroid glands (Denham and Wills, 1980).

CHANGES IN THYROID HORMONE ECONOMY

There are also changes in thyroid hormone economy with aging. These occur at various levels of the hypothalamus-pituitary-thyroid gland axis (Table 1). Beginning at the hypothalamus, there may be a reduction in thyrotropin-releasing hormone (TRH) concentration, as less TRH was released *in vitro* by hypothalamic tissue from older as compared to younger rats (Pekary *et al.*, 1987). There is no reduction in either the pituitary content of thyrotropin-stimulating hormone (TSH) or serum TSH concentration with aging. A comparison of serum TSH concentrations in a large group of older persons in the community-based Framingham Heart Study to their middle-aged offspring showed no significant difference in serum TSH concentrations among individuals without known thyroid disease (Hershman *et al.*, 1993). Although serum TSH concentration does not change with age, studies have demonstrated decreased pituitary sensitivity to TRH. The TSH response to TRH stimulation is proportional to the basal TSH concentration. Some, but not all studies have found that the peak TSH response to exogenous TRH is lower in the elderly. In one study, the TSH response was lower only in older women (Kaiser, 1987). In two other studies (Erfuth *et al.*, 1984; Snyder and Utiger, 1972), TSH response was lower in older men, while one study did not find any significant reduction in TSH response to TRH in older men (Harman *et al.*, 1984).

Another change in the hypothalamic-pituitary axis is demonstrated by a decrease in the pulse amplitude of nocturnal TSH secretions, although the pulse frequency is unchanged; the circadian variation of serum TSH concentrations in 78- to 83-year-old men was smaller compared with the TSH oscillation in younger subjects (Hermann *et al.*,

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Table 1 Age-related changes in thyroid economy

No change	No change or ↓	↓	↑
TSH	Thyroid sensitivity to TSH	Production of T4, T3	Serum half-life of T4
Pituitary concentration of TSH	TSH response to exogenous TRH	Degradation of T4, T3	
T3	Diurnal variation in	Pulse amplitude of	
rT3	TSH secretion	nocturnal TSH	
TBG			
T4 and FT4		Thyroid gland uptake of iodine	
		TSH rise 2^0 to decreasing T4	

Source: Adapted from Mooradian, 1995 and Case and Mooradian, 2000.

1981). While the pituitary content of TSH and serum TSH concentrations may be unaltered, the reduced pituitary sensitivity to TRH and reduced pulse amplitude of TSH secretions could signal reduced biologic activity of TSH. Reduced biological activity of TSH may occur without a change in immunoreactive mass of TSH, since biologic activity is dependent on proper glycosylation of TSH, a process that is modulated by TRH.

Changes in the set point of pituitary-thyroid axis with aging are unclear. A cross-sectional study of euthyroid subjects showed that the slope of the curve correlating TSH and free thyroxine (FT4) is not altered in elderly subjects (Friedman *et al.*, 1992). However, a more direct estimate of pituitary sensitivity to thyroid hormone, measured by the pituitary response to thyroxine (T4) that is suppressed with exogenous iodide, shows a significant reduction in pituitary sensitivity to T4 in the elderly (Ordene *et al.*, 1983). In other words, the increase in TSH rise in the face of the decrease in T4 was blunted in elderly subjects. The latter observation can alternatively be interpreted as increased effectiveness of T4 in suppressing the TSH during hypothyroxinemia. Similar changes are seen in aging rat models (Mooradian, 1993; Mooradian and Wong, 1994). These changes could be partially attributed to either increased thyroid hormone receptors in the pituitary, or more importantly, increased conversion of T4 to triiodothyronine (T3) through increased activity of 5′ deiodinase type II (Donda *et al.*, 1987; Donda and Lemarchand-Beraud, 1989). Extrapolation of these results to humans is difficult, however, because of interspecies differences in thyroid hormone economy (Reymond *et al.*, 1992).

Finally, in humans, thyroid response to TSH may be reduced or remain unaltered. In one study, T3 responses to exogenous TSH in younger and older subjects were similar. However, these results are questioned because exogenous TSH was administered in very high doses (Van Coevorden *et al.*, 1989). There is also a decreased production of thyroid hormone with age such that T4 production decreases from 80 to 60 $\mu g\,day^{-1}$, and T3 production decreases from 30 to 20 $\mu g\,day^{-1}$ (Mooradian, 1995; Case and Mooradian, 2000). While this appears to be a compensatory response to decreased thyroid hormone clearance, it may also be a function of reduced thyroidal sensitivity to TSH, as well as altered TSH secretory kinetics and TSH bioactivity (Choy *et al.*, 1982). Decreased T3 production also reflects decreased peripheral conversion of T4 to T3, as a result of decreased T4 production and possibly secondary to reduced activity of 5′ deiodinase type I. In general, thyroid hormone clearance is reduced in the elderly, with an increase in the half-life of T4 from 6.7 days in the third decade to 9.1 days in the seventh decade (Gregerman *et al.*, 1962). Finally, thyroidal uptake of iodine is reduced in the elderly (Gaffney *et al.*, 1982), reflecting decreased thyroid hormone production.

CHANGES IN THYROID HORMONE ACTION

Thyroid hormone acts by modulating gene expression, and specific gene products are positively or negatively regulated biomarkers of thyroid hormone action (Mooradian and Wong, 1994). Age-related changes in thyroid hormone action are reflected in changes in these gene products (Table 2). For example, there is a decrease in Na^+-K^+ ATPase activity in renal cortical and hepatic cells with age; this may be responsible for the decline in thyroid-induced thermogenesis (Mooradian *et al.*, 1994b). There is a decrease in malic enzyme activity; this may be responsible for a decline in thyroid-induced lipogenesis (Mooradian *et al.*, 1991; Mooradian and Albert, 1999). In addition to lipogenic enzymes, a

Table 2 Age-related changes: Thyroid hormone responsiveness of various markers of thyroid hormone action

Serum
Angiotensin-converting enzyme
Liver
ApoA1 Mrna
Malic enzyme activity
Malic enzyme mRNA
Fatty acid synthase
Spot14 (encodes liver protein which may be involved in lipogenesis)
Red blood cells
Na^+-K^+ ATPase
Ca^{++} ATPase
2-Deoxy-glucose transporter
Kidney
Na^+-K^+ ATPase
Thymocyte
2-Deoxy-glucose transporter
Heart
Isoproterenol-stimulated adenyl cyclase
Sarcoplasmic Ca-ATPase mRNA
α-Myosin heavy chain
β-Myosin heavy chain (negatively regulated biomarkers)
Pituitary
TSH sensitivity to T4 (negatively regulated biomarkers)
Cerebral cortex
Synaptosomal adrenergic transmission
THRP
NAT-1

Source: Adapted from Mooradian and Wong, 1994 and Case and Mooradian, 2000.

slue of biomarkers of thyroid hormone action in the liver, such as apoliprotein AI (Shah *et al.*, 1995; Mooradian *et al.*, 1996) and S14 (Mooradian *et al.*, 1994a), shows reduced responsiveness to thyroid hormones. The response of a serum marker of thyroid hormone action, namely angiotensin-converting enzyme, is also altered in aging (Mooradian and Lieberman, 1990). Similar alterations in thyroid hormone action have been observed in cardiac muscle. In this tissue, the response of myosin heave chain and calcium ATPase response to thyroid hormone is reduced in aged animals. There is also a decrease in isoproterenol-stimulated adenyl cyclase activity that may play a role in reduced thyroid-induced cardiac chronotropic activity (Mooradian and Scarpace, 1989). In addition, response of glucose transport isoforms (Mooradian *et al.*, 1999) and malondialdehyde modification of proteins (Chehade *et al.*, 1999) are altered in aged rats.

The effect of age on the thyroid hormone responsiveness of the cerebral cortex is not well studied as there are only few biomarkers of thyroid hormone action in the brain of mature animals (Haas *et al.*, 2004). The thyroid hormone responsiveness of adrenergic neurotransmission in synaptosomal membranes is reduced in aged rats (Mooradian and Scarpace, 1993). Two novel markers of thyroid hormone action in the brain, namely thyroid hormone responsive protein (THRP) (Shah *et al.*, 1997; Haas *et al.*, 2002; Mooradian *et al.*, 1998) and novel translational repressor (NAT-1) (Shah *et al.*, 1999), also show significant reduction to thyroid hormone responsiveness in senescent rats. The precise biological implications of these observations are not clear. However, THRP is identified as an important mediator of thyroid hormone–induced neurotoxicity in primary neauronal cultures (Haas *et al.*, 2005). Thus, an age-related decline in THRP responsiveness may have a neuroprotective role.

Possible mechanisms for changes in thyroid hormone action with age include impaired transport of T3 across plasma membranes, impaired tissue metabolism of thyroid hormone, and alterations in postreceptor processes modulating gene expression. Transport of T3 across plasma membranes is a carrier-mediated process that has been shown to be reduced by 50% in the liver of old rats, leading to a decrease in the number of nuclear receptors occupied by T3 while receptor affinity for T3 (Ka) measured *in vitro* is unchanged (Mooradian, 1990a,b). Second, tissue metabolism of the thyroid hormone is impaired as a result of a decrease in the deiodination rate of T4 to T3 (Gregerman *et al.*, 1962; Jang and Distefeno, 1985). Finally, there may be alterations in postreceptor processes that modulate gene expression; these could be related to alterations in transcription factors or secondary to structural changes of the gene. Changes in the activity of S14 gene expression in response to T3 reflect both age-related alterations in transcription factors and gene structure. A transcription factor P-1 binds S14 DNA and represses gene transcription, while another transcription factor, PS-1, binds S14 DNA and stimulates gene transcription. Aging is associated with decreased levels of P-1 (Mooradian *et al.*, 1994a), resulting in an age-related increase in basal expression of S14 gene. Also, there is an age-related demethylation of the S14 gene, reflecting structural changes that result in the increased expression of this gene with age (Wong *et al.*, 1989). Despite increased basal expression of this gene, its thyroid hormone responsiveness is reduced with age.

Overall, it appears that the thyroid hormone responsiveness of a host of biomarkers of the thyroid hormone action is blunted in aging. This age-related "relative" resistance to the thyroid hormone action may partly explain the myriad symptoms and signs of hypothyroidism that older subjects exhibit despite normal plasma levels of thyroid hormones. Alternatively, it can also account for the paucity of symptoms or signs of excess thyroid hormone in patients with apathetic hyperthyroidism.

CLINICAL IMPLICATIONS OF AGE-RELATED CHANGES IN THE THYROID

The clinical presentations of hypothyroidism and hyperthyroidism change in the elderly. In addition, because of age-related changes in thyroid hormone kinetics and alterations in drug effects and tolerability, the management of thyroid disease in the elderly can be challenging.

Hypothyroidism

Clinical diagnosis of hypothyroidism is difficult, as many signs and symptoms associated with hypothyroidism are present in euthyroid elderly individuals (Table 3). For example, slow mentation, fatigue, constipation, hair loss, dry skin, and delayed relaxation phase of deep tendon reflexes occur in both hypothyroid patients and euthyroid elderly individuals (Case and Mooradian, 2000) (Table 3). In healthy outpatient subjects followed in the Framingham Heart Study, the prevalence of clinically unrecognized hypothyroidism in subjects at the age of 60 and older was found to be approximately 2.5% (Sawin *et al.*, 1985). While hypothyroid patients and euthyroid elderly individuals may share

Table 3 Signs and symptoms of hypothyroidism commonly found in older euthyroid subjects

Signs	Dry skin
	Delayed deep tendon reflexes
	Gynecomastia
	Bradycardia
	Hypertension
Symptoms	Slow mentation
	Muscle fatigue
	Hair loss
	Decreased appetite
	Constipation
	Cold intolerance
	Decreased libido
	Depression

Source: Adapted from Case and Mooradian, 2000.

many of the same signs and symptoms, it is interesting that overall the elderly hypothyroid patient exhibits fewer number of signs and symptoms, and also fewer of the classical signs. In a study comparing clinical signs and symptoms of hypothyroidism between elderly patients and younger patients, indeed the most frequent clinical features in elderly patients were the nonspecific findings of fatigue and weakness. However, the mean number of clinical signs per patient was significantly smaller in the elderly patients, and also four classical signs of hypothyroidism, cold intolerance, paresthesias, weight gain, and cramps occurred significantly less frequently in elderly patients (Trivalle *et al.*, 1996).

Even more challenging is the diagnosis of secondary hypothyroidism. In these patients, serum TSH levels may be normal or subnormal and the free T4 levels are low. This condition is particularly common in people over the age of 85 (Sundbeck *et al.*, 1991). Many people with this set of thyroid function tests are also taking medications known to interfere with TSH and T4 levels, making the diagnosis of hypothyroidism particularly difficult.

Once hypothyroidism is diagnosed, treatment strategies must be tailored to the elderly patient. When initiating thyroid hormone replacement for hypothyroidism, dosages should be low (no more than $25\,\mu g\,day^{-1}$), and increased slowly, as the consequent increase in myocardial oxygen demand may precipitate coronary syndrome or congestive heart failure in patients with organic heart disease. The maintenance dose of thyroid hormone replacement will also be reduced in the elderly hypothyroid patient as compared to the younger patient; the mean daily dose of thyroid hormone replacement required to attain a euthyroid state in the elderly is $110\,\mu g\,day^{-1}$, while in younger subjects it is $130\,\mu g\,day^{-1}$ (Silverberg and Mooradian, 1998; Case and Mooradian, 2000). This is the result of alterations in thyroid hormone economy with aging, specifically, a decrease in the clearance rate of thyroid hormone. Should a hypothyroid elderly patient begin to require increasing doses of thyroid hormone replacement therapy, the possibility of decreased drug absorption should be considered. Several drugs including bile acid sequestrants (i.e. colestipol, cholestyramine), aluminum hydroxide, ferrous sulfate, calcium carbonate, and sucralfate can decrease absorption of exogenous oral thyroid hormone, rendering the patient hypothyroid again (Surks and Sievert, 1995). Finally, in any patient in whom secondary hypothyroidism is suspected, thyroid hormone replacement is withheld until adrenal insufficiency is excluded or glucocorticoid replacement therapy is initiated.

Treatment of subclinical hypothyroidism (isolated elevation of TSH levels) is generally recommended when the TSH is over $10\,mU\,ml^{-1}$, but may also be considered at TSH levels of $5–10\,mU\,ml^{-1}$ in the presence of antithyroid antibodies, as these patients are more likely to progress to overt hypothyroidism (2–3% vs. 4–5% annual rate) (Samuels, 1998). In addition to the development of overt hypothyroidism, subclinical hypothyroidism carries an increased risk of aortic atherosclerosis and myocardial infarction (Hak *et al.*, 2000), hyperlipidemia (Biondi *et al.*, 2002; Caraccio *et al.*, 2002; Danese *et al.*, 2000), left ventricular dysfunction (Biondi *et al.*, 2002), and nonspecific symptoms such as fatigue, dry skin, and cold intolerance (Cooper *et al.*, 1984). Treatment with thyroxine prevents overt hypothyroidism, reduces total cholesterol and low density lipoprotein (LDL) cholesterol (Biondi *et al.*, 2002; Caraccio *et al.*, 2002; Danese *et al.*, 2000), with a possible secondary reduction in the risk of atherosclerosis, normalizes left ventricular dysfunction (Biondi *et al.*, 2002), and alleviates nonspecific symptoms (Cooper *et al.*, 1984).

Finally, given the age-related decline in thyroid hormone responsiveness, the question remains whether supplementing euthyroid elderly patients with thyroid hormone would minimize some of the age-related changes that resemble hypothyroidism. Support of such a hypothesis would require safety and efficacy data from double-blind randomized studies with thyroid hormone replacement in elderly subjects with normal and increased TSH levels.

Hyperthyroidism

The clinical diagnosis of hyperthyroidism is difficult because many signs and symptoms of hyperthyroidism are absent in elderly patients. Apathetic thyrotoxicosis is an extreme example, in which apathy, lethargy, pseudodementia, weight loss, and depressed mood are the major findings. In one study, a comparison of clinical signs and symptoms of hyperthyroidism in older versus younger patients revealed the findings of hyperactive reflexes, increased sweating, polydipsia, heat intolerance, tremor, nervousness, and increased appetite occurred significantly less frequently in older hyperthyroid patients. Only the findings of atrial fibrillation and anorexia were significantly more frequent in older hyperthyroid patients (Trivalle *et al.*, 1996) (Table 4). Note that the increased incidence of cardiac complications in hyperthyroid elderly persons is attributed to the increased prevalence of organic heart disease in this population, as there is no increase in myocardial response to thyroid hormone in the elderly (Mooradian and Wong, 1994).

Table 4 Comparison between old and young patients with symptoms and clinical signs of hyperthyroidism

Symptoms and signs	Older patients incidence (%)	Younger patients incidence (%)
Tremor	44	84
Anorexia	32	4
Nervousness	31	84
Hyperactive reflexes	28	96
Increased sweating	24	95
Polydipsia	21	67
Heat intolerance	15	92
Increased appetite	0	57
Atrial fibrillation	35	2

Source: Reproduced from Trivalle *et al.*, 1996, by permission of Blackwell Publishing Ltd.
Note: $P < 0.001$ for all comparisons.

An age-related desensitization of β-adrenergic receptors may be responsible for the absence of other adrenergic-system related hyperthyroid symptoms (i.e. tremor) in the elderly hyperthyroid patient (Case and Mooradian, 2000).

The treatment strategy for hyperthyroidism does not change in the elderly. β-Blockers are used for symptom control, and antithyroid drugs are used to attain a euthyroid state. Once the patient becomes euthyroid, radioactive iodine ablation of the gland may be performed. Repeated treatments with radioactive iodine may be necessary to achieve remission in patients with toxic nodular goiters, a more common cause of hyperthyroidism in the elderly. In the elderly patient, there is no concern about potential adverse effects of radioactive iodine on the reproductive system, and the potential risks are minimal as compared to surgical thyroidectomy. A potential risk of radioactive iodine therapy is thyroid "storm"; however, this becomes less likely with antecedent use of an antithyroid drug. Another potential toxicity in those with bladder outlet obstruction or atonic bladders is the increased incidence of cystitis secondary to stasis of radioactive iodine in the bladder. These people will present with increased lower urinary tract symptoms (LUTS). Note that the possibility of agranulocytosis, which occurs in 0.3–0.6% of all patients who take antithyroid drugs, increases with age especially in those over 40 years old (Cooper *et al.*, 1983). Treatment for subclinical hyperthyroidism (low TSH and normal FT4 and FT3) is recommended if the TSH is $<0.1\,\mathrm{mU\,l^{-1}}$, in the presence of Graves' disease or nodular thyroid disease (Surks *et al.*, 2004). Note that single low TSH measurements often normalize upon retesting weeks to months later, so the decision to treat should be based on persistently low TSH levels (Parle *et al.*, 1991). The basis for treatment of subclinical hyperthyroidism is to prevent detrimental cardiac and skeletal effects that can result in substantial morbidity in the elderly. Cardiac effects include a threefold increase in the risk of atrial fibrillation (Sawin *et al.*, 1994), and an increase in left ventricular mass (Biondi *et al.*, 2002). The association of thromboembolic disease and atrial fibrillation makes subclinical hyperthyroidism a risk factor for thromboembolism in the elderly (Biondi *et al.*, 2002). The skeletal effect of subclinical hyperthyroidism is a decrease in bone mineral density (Foldes *et al.*, 1993) as thyroid hormone directly stimulates bone turnover (Foldes *et al.*, 1993). In postmenopausal women, subclinical hyperthyroidism is a risk factor for osteoporosis (Foldes *et al.*, 1993; AACE, 2002).

Occasionally, a diagnostic dilemma emerges when the signs and symptoms are nonspecific and the thyroid function tests cannot conclusively distinguish between secondary hypothyroidism and subclinical hyperthyroidism. In such instances, it is best if the patient is referred to an endocrinologist for reevaluation and if need be, a short course trial with antithyroid medicine to evaluate TSH secretory reserve. To differentiate between hypothalamic and pituitary causes of low TSH, the TRH stimulation test can be helpful. Unfortunately, at the present time, TRH is not available in the United States for clinical use.

THYROID NODULES AND CANCER

Aging is commonly associated with increased propensity for developing neoplasms (Mooradian, 1994). As such, the thyroid gland is not an exception. It has been estimated that the prevalence of thyroid nodules increases with age, especially in women. Although the prevalence of thyroid nodules in the general population is approximately 1–5%, in the elderly, 6–10% of the population may have solitary nodules (Gupta, 1995). The vast majority of these nodules are benign cysts or adenomatous changes. In perhaps 10% or less of the cases, cancer can be found. More than 60% of carcinomas are of papillary type, yet most benign adenomas are of follicular type. The most common causes of thyroid nodules are listed in Table 5. Some adenomas produce excessive amounts of thyroid hormone, typically T3, and present with hyperthyroidisms. These adenomas can be ablated with radioactive iodine therapy. Most patients with thyroid adenomas or carcinomas are euthyroid. Occasionally, hyperthyroidism and thyroid cancer may coexist and this combination may carry worse prognosis especially if the hyperthyroidism is secondary to Graves' disease. The increased risk in such patients is attributed to the presence of circulating thyroid-stimulating immunoglobulins that will promote thyroid cancer growth and unlike endogenous TSH cannot be suppressed with thyroid hormone therapy.

The etiology of thyroid adenomas and carcinomas are not completely understood. Endemic goiters secondary to iodine deficiency are associated with the increasing formation of hyperplastic nodules probably because of overstimulation with TSH. Follicular and anaplastic carcinomas have been associated with endemic goiters, while the papillary cancer is not associated with endemic goiters. It has been estimated that 4–17% of patients with nodular goiter may develop carcinomas, mostly of the papillary type (Gupta, 1995). In addition to overstimulation with TSH, another important risk factor is exposure to irradiation. Nevertheless, exposure to irradiation to the neck increases the risk of thyroid cancers, notably the differentiated variety such as follicular or papillary type. The medullary cancers and anaplastic cancers have not been associated with irradiation exposure.

Medullary carcinomas constitute 2–5% of all thyroid cancers and are rare in the elderly. In 20% of the cases, they are familial arising as a component of multiple endocrine

Table 5 Differential diagnoses of thyroid nodules

Benign thyroid nodules	Multinodular goiter Hashimoto's thyroiditis Cysts Follicular adenomas Hurthle-cell adenomas
Malignant thyroid nodules	Papillary carcinoma Follicular carcinoma Medullary carcinoma Anaplastic carcinoma Primary thyroid lymphoma Metastatic carcinoma

neoplasia (MEN). These tumors secrete calcitonin and carcinoembryonic antigen (CEA), and these are good markers for follow-up. If familial disease is suspected, genetic testing for Ret oncogene is now available commercially.

In general, well-differentiated thyroid cancers in the elderly carry poorer prognosis compared to younger middle-aged subjects. Thus, it is essential that elderly patients with thyroid cancer are given the full benefit of total thyroidectomy coupled with radioactive iodine ablation of the remnant.

An unusually aggressive form of thyroid cancer, namely anaplastic cancer of the thyroid is primarily a disease of the elderly. This rare disease should be considered in all patients who present with rapidly enlarging solid mass in the neck or are found to have widespread metastasis (Mooradian *et al.*, 1983).

The workup of a patient presenting with thyroid nodule is summarized in Figure 1. In general, if TSH is not suppressed, the first step is fine-needle aspiration biopsy (FNAB). The differential diagnosis includes adenomas, carcinomas, thyroiditis, and thyroid cysts. Solitary nodules or a predominant nodule within a multinodular goiter are candidates for biopsy. The clinical risk factors favoring cancer include age (less than 20 or more than 60), male gender, history of irradiation, history of thyroid cancer, rapid growth, fixation of the nodule to the surrounding tissue, hardness, cervical lymph node enlargement, and dysphagia or hoarseness (Gupta, 1995). If the biopsy reveals cystic nature of the nodule, every attempt should be made to biopsy the wall of the cyst to acquire enough cells for evaluation. Cysts that continue to grow will require reaspiration with possible ablation with alcohol or referral to surgery. If the biopsy shows cancerous cells or is equivocal, then the patient is referred for surgery. Under certain circumstances a second look rebiopsy may be helpful. The suppressive therapy for benign nodules is not recommended in the elderly with increased risk of underlying cardiovascular disease and dubious efficacy of therapy.

SCREENING FOR THYROID DISEASE

As the clinical presentation of thyroid disease is not reliable in the elderly population, the physician should consider periodic screening for biochemical abnormalities. Clinically relevant biochemical tests do not change physiologically with aging, and therefore can be used to diagnose or exclude disease. However, the physician should be aware of alterations in serum TSH levels that can occur as a result of nonthyroidal disease or medications, which may occur more commonly in elderly patients with multiple comorbidities. Serum TSH levels may be slightly increased or decreased as a result of illness (Wiersinga, 2000), and decreased as a result of medications such as dopamine or glucocorticoids (Scanlon and Toft, 2000). Recommendations for screening guidelines vary. While the American Thyroid Association (Ladenson *et al.*, 2000) recommends screening men and women aged 35 and older every 5 years, and more frequently in those at high risk, the American College of Physicians (Helfand and Redfern, 1998) recommends periodic screening of only women aged 50 and older. The US Preventive Services Task Force (USPSTF, 2004) has concluded that evidence is insufficient to recommend for or against routine screening for thyroid disease in adults, however, it recommends having a

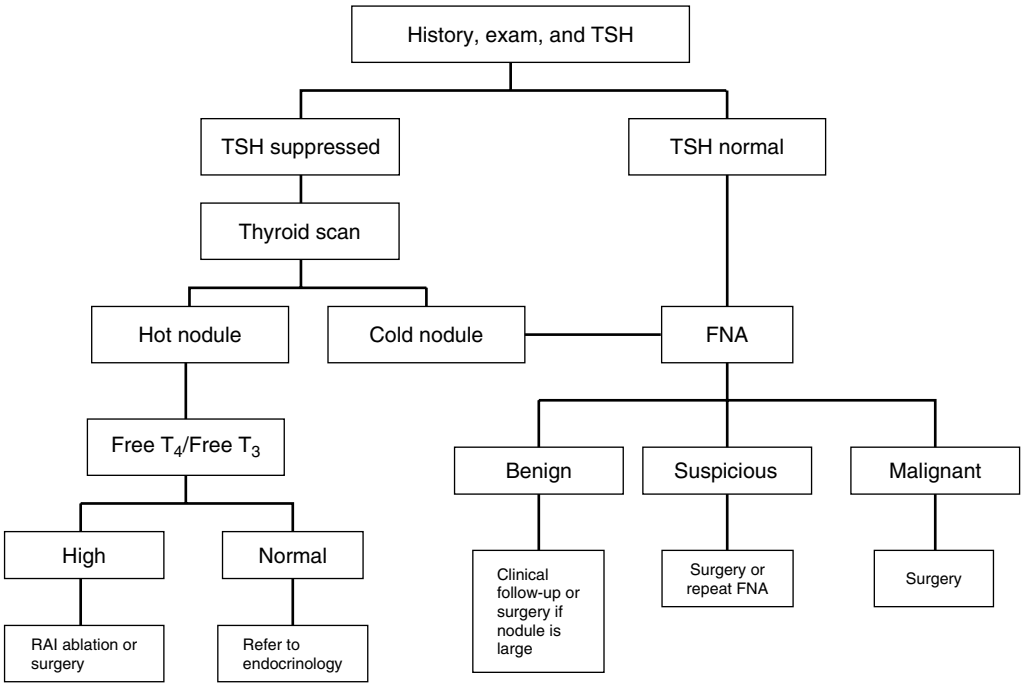

Figure 1 A suggested algorithm for workup of thyroid nodules. FNA: fine-needle aspiration biopsy

high index of suspicion in at-risk populations. Several studies including National Health & Nutrition Examination Survey (NHANES) III (Hollowell *et al.*, 2002) and The Colorado Thyroid Disease Prevalence Study (Canaris *et al.*, 2000) have shown an increased prevalence of elevated serum TSH in women and in the elderly. Thus, periodic screening with serum-sensitive TSH measurements in this at-risk population is recommended.

An understanding of the common etiologies of thyroid disease in the elderly would identify risk factors, the presence or absence of which would help determine screening frequency. The most common cause of hypothyroidism (Sawin, 2003) in the elderly is lymphocytic thyroiditis, which usually leads to an atrophic gland (as opposed to a goiter in younger persons). Elderly persons with other autoimmune diseases (i.e. type 1 diabetes mellitus, pernicious anemia) or a family history of thyroid disease are particularly at risk. Other causes of hypothyroidism in the elderly include head and neck radiation, a more common cause in elderly men with increased incidence of head and neck cancer, and medications (i.e. amiodarone, lithium). The most common cause of hyperthyroidism in the elderly is Graves' disease (Braverman, 1999), followed by an increased prevalence of toxic nodular goiter as compared to younger people. In addition, common iatrogenic causes of hyperthyroidism in the elderly include amiodarone therapy, use of iodinated contrast agents, iodine-containing expectorants, or supplements such as *kelp*.

The most effective way for screening for thyroid dysfunction is to order TSH with third-generation assays using one of the more recently developed immunoradiometric (IRMA) or immunochemilumenescence assays (IMCA). A suggested algorithm for evaluating thyroid dysfunction is shown in Figure 2. Generally, if serum TSH is normal, no further workup is needed. Increased TSH level over $10\,\mathrm{mU\,ml^{-1}}$ is usually diagnostic for primary thyroidal failure, unless there is a confounding variable such as interference with the assay, recovery from illness, or exposure to certain drugs, especially iodinated contrast agents. If free T4 is normal and TSH is less than $10\,\mathrm{mU\,ml^{-1}}$, subclinical hypothyroidism is suspected. For the latter, the presence of antithyroid peroxidase antibodies (anti-TPO) will help in the decision whether to initiate thyroid hormone replacement or to observe conservatively. If TSH is decreased and free T4 is low, evaluate the patient for pituitary hypothalamic dysfunction or surreptitious consumption of T3. If FT4 is elevated, then the diagnosis of hyperthyroidism is made, otherwise check for free T3 to exclude T3 toxicosis. If FT4 and FT3 are normal in the face of suppressed TSH, then the patient may either have subclinical hyperthyroidism or the set point of pituitary may be altered.

CONCLUSIONS

Thyroid gland anatomy and function change with age. Decreased thyroid hormone action, as evidenced by a decrease in gene products that are positively regulated by thyroid hormone, suggests that there may be an age-related resistance to thyroid hormone. Though an increase in serum thyroid hormone levels is expected in a resistance syndrome,

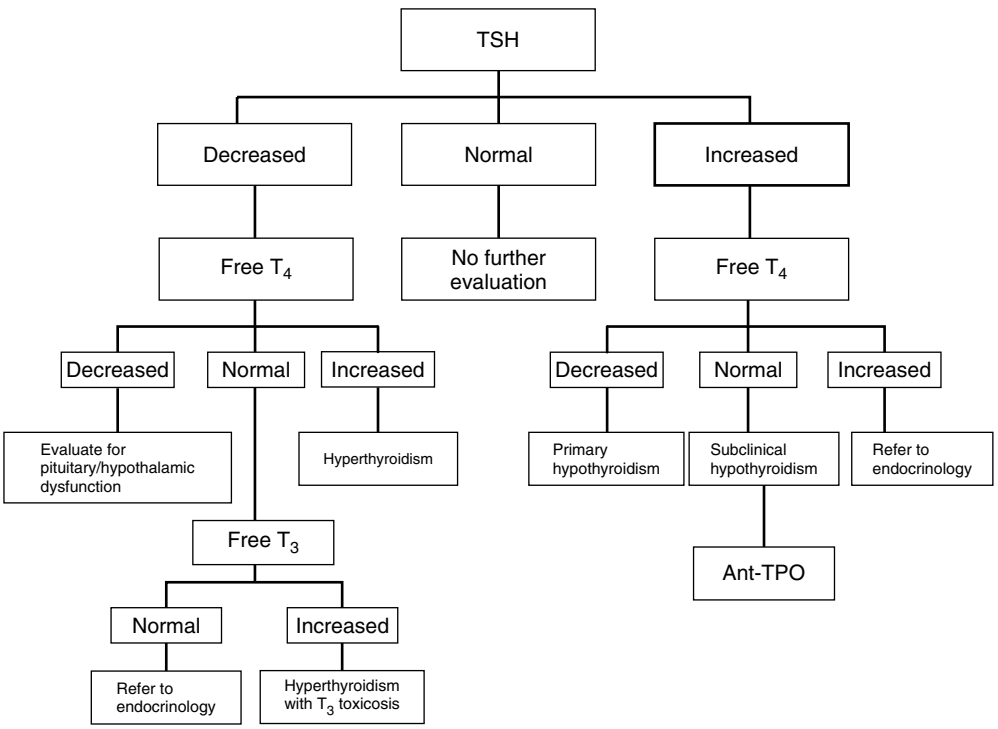

Figure 2 A suggested algorithm for diagnosing thyroid dysfunction

unchanged serum thyroid hormone levels in the euthyroid elderly person likely reflect additional changes in thyroid hormone economy that occur with aging. For example, increased suppressability of TSH, decreased conversion of T4 to T3, and decreased thyroidal sensitivity to TSH, may preclude expected increases in thyroid hormone concentrations (Case and Mooradian, 2000). While thyroid hormone resistance may account for clinical similarities among euthyroid elderly persons and hypothyroid subjects, and the lack of classical clinical findings in hyperthyroid elderly persons, it is unclear whether this actually reflects thyroid disease. Certainly, these clinical presentations are apparent in elderly persons with and without biochemical abnormalities. Therefore, the most important difference in the evaluation of thyroid disease in older versus younger persons lies in diagnosing the disease in the absence of clinical clues. In this case, the physician must rely on intermittent biochemical screening, as there are no age-related changes in the biochemical tests used in clinical practice to diagnosis thyroid disease. Once the disease is detected, there may be differences in treatment strategies as a result of age-related changes in thyroid hormone economy. Specifically, as thyroid hormone degradation decreases with age, the hypothyroid elderly patient will require a decreased dose of thyroid hormone replacement to avoid overreplacement. Finally, the physician must be aware of possible consequences of both untreated thyroid disease and overtreated thyroid disease, which may be exacerbated in the elderly patient based on the increased prevalence of underlying comorbidities in this population, for example, cognitive impairment, coronary artery syndrome, cardiac systolic dysfunction, atrial fibrillation, and metabolic bone disease.

KEY POINTS

- Changes in thyroid gland anatomy and function occur with aging.
- Thyroid hormone production and clearance are decreased equally such that the steady state plasma levels of thyroid hormones do not change significantly with age.
- Tissue effects of thyroid hormone action may be reduced with age.
- The presence of coexisting diseases, malnutrition, and a host of medications may complicate the interpretation of thyroid function tests in the elderly.
- Since thyroid disease is very common in this age-group, it is advisable to have a screening program that incorporates measuring serum TSH and antithyroid peroxidase antibody titers.
- For those presenting with a thyroid nodule and have normal serum TSH values, the most expedient workup is fine-needle aspiration biopsy for cytologic studies.

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Ovarian and Testicular Function

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MENOPAUSE

The word menopause originated from the Greek words "meno" meaning menses and "pause" meaning cessation. The diagnosis of menopause is made retrospectively and is clinically defined as *amenorrhea* for 12 months. Menopause can be "natural" or "induced". Induced menopause can result from bilateral oophorectomy. Premature ovarian failure is the onset of menopause before 40 years and is seen in some conditions like oophoritis. The average age at menopause is 51 years. Menopause is a normal event in a woman's life and is not considered as a disease. Menopause can be a positive and liberating experience for some women and negative for others.

In 2000, there were approximately 41.75 million women in the United States. The percentage of women over the age of 50 years has tripled in the last century. During this time, the mean life expectancy of women in the United States has increased from 50 years to 81.7 years, suggesting that menopause will occur at a time when women have yet to experience almost a third of their life span. In the next 20 years, about 40 million women will experience menopause. Early menopause occurs before the age of 46 and is seen in one-tenth of the women.

Menopause occurs in three stages: perimenopause, cessation of menses, and postmenopause. Perimenopause marks the beginning of the postmenopausal period; this transition is a slow process. During this time, the ovarian functions are changing and take between 2 and 8 years till the final menopausal period is reached. The majority of women experience menstrual irregularities during this time, followed by cessation of menses and then the postmenopausal stage. The Practice Committee of the American Society for Reproductive Medicine recommended using the term "menopausal transition" (MT) instead of using "perimenopause" or "climacteric" in scientific papers.

"The MT was defined by the Stages of Reproductive Aging Workshop (STRAW) held in 2001. It begins with variations in the length of menstrual cycle in a woman who has a rise in the monotropic follicle-stimulating hormone (FSH) and ends with the final menstrual period" (The Practice committee of the American Society for Reproductive Medicine, 2004).

RISK FACTORS OF EARLY MENOPAUSE

One-tenth of the women reach early menopause and the risk factors include:

1. smoking (appears to be dose and duration related) (Tauber, 1996; Olshansky *et al.*, 1990)
2. nulliparity
3. short menstrual cycles and
4. maternal history of early menopause.

Menopause offers the primary health-care provider an opportunity to assess a woman's health, her concerns, and her needs for health promotion and disease prevention measures.

HORMONAL CHANGE

During the perimenopause period, the ovarian follicles decrease in number through the process of apoptosis and the ovarian estrogen production also decreases (Driancourt and Thuel, 1998). Both luteinizing hormone (LH) and FSH rise, with the increase in FSH being more than the increase in LH (Santro *et al.*, 1997). FSH is responsible for the maturation of the follicles and ovulation, while LH provides the stimulus for ovulation and secretion of steroids from the corpus luteum. The rise in FSH is related to the loss of negative biofeedback by gonadal steroids and cessation of inhibin production by the ovarian follicles. Inhibin inhibits the secretion of FSH by acting on the pituitary gland, and increases cell proliferation and gonadotropin-dependent steroid production by its action on the gonads. Inhibin B levels fall before Inhibin A (Burger *et al.*, 1998). Androgen production by the ovaries continues under the

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influence of elevated LH concentration. Activin functions as an autocrine/paracrine regulator and plays a role in the induction of FSH receptors and folliculogenesis (Li *et al.*, 1995). Since menopause is more than a state of estrogen deficiency, its replacement may not return the level of FSH to the premenopausal level. FSH is predominately under the control of inhibin. Inhibin remains low in menopause. FSH, therefore, will remain elevated even in the face of estrogen administration, and thus FSH may not be completely reliable as a measure of sufficient or reliable estrogen administration. There might be a further decline in the levels of gonadotropins with age and other comorbid conditions (Quint and Kaiser, 1985). During the transition to menopause, both estradiol and estrone concentrations fall, though the concentration of estradiol is much lower than the estrone, which is exactly opposite to that in the case of younger women. Estradiol in postmenopausal women comes from the peripheral aromatization of androgen from the ovarian and adrenal glands.

During menopause there is decrease in the production of the androgens, dehydroepiandrostenedione (DHEA) and dehydroepiandrostenedione sulphate (DHEAS), by the ovaries and adrenals (Longscope, 1978). There is a reduction of the total and bioavailable testosterone levels in postmenopausal women undergoing total abdominal hysterectomy with bilateral salpingo-oophorectomy compared to women undergoing hysterectomy alone with conservation of the ovary or ovaries (Meldrum *et al.*, 1981). Longitudinal hormonal studies have shown a decline in both testosterone and androstenedione approximately 3 years before the occurrence of menopause (Laughlin *et al.*, 2000).

CLINICAL FEATURES OF MENOPAUSE

Table 1 shows the changes associated with menopause (Tariq Syed and Morley, 2003).

Table 1 Changes with menopause

Skin	Dryness, loss of hair, atrophy, and loss of elasticity
Skeleton	Loss of teeth and development of osteoporosis
Breast	Softer consistency and smaller breast size
Endocrine	Hot flashes
	Flushing and sweating
	Palpitation
	Anxiety
	Sleep disruption
	Mood changes
	Decrease in libido
Neurological	Cognitive, sleep, and mood changes
Urogenital	Vaginal dryness
	Vaginal bleeding
	Itching/burning/irritation in the labial/mons
	Urge incontinence
	Dysuria
	Nocturia
	Dyspareunia
	Urinary tract infections

Hot Flashes

Hot flashes are one of the most common characteristic symptoms of menopause. Typically, a woman experiences intense heat (hot flashes) and subsequent cooling by cutaneous vasodilatation, perspiration, and chills (Overlie *et al.*, 1999; Bachmann, 1999). These symptoms last from a few seconds to several minutes and vary in intensity from being mild to intolerable. Hot flashes are more severe in women who have undergone oophorectomy (Shanafelt *et al.*, 2002). McKinlay *et al.* (1992) reported that 58% of the women experience hot flashes within 2 years of menopause. Hot flashes last for 1–5 years in two-thirds of women undergoing menopause, but in about 10–15% of the women it will last for more than 5 years (McKinlay *et al.*, 1992). Hot flashes are reported more in the western hemisphere (up to 80%) compared to as low as 10% in East Asia (Flint and Samil, 1999; Thompson *et al.*, 1973). Hot flashes vary in different cultures, with reports of fewer hot flashes in Chinese and Indonesian women. It is not clear whether these differences are related to the perception of menopause, use of herbs, genetic factors, or differences in the reporting of symptoms, or because of other factors (Beyene, 1986).

Kronberg (1990) reported that 87% of the women had current symptoms of hot flashes daily, 15% had more than 10 hot flashes lasting for 1–5 minutes daily, and 6% had hot flashes lasting more than 6 minutes. Hot flashes are reported when the cutaneous temperature exceeds 0.3 °C.

Hot flashes are associated with the disruption of sleep, work, and social relationships. At times hot flashes could be brought about by body contact, which could make relationships worse. The pathophysiology of hot flashes has not been fully elucidated. Hot flashes respond very well in a dose-response fashion to hormone replacement, but may take up to 12 weeks to see the improvement in symptoms (Kronberg, 1990). Human studies have failed to show any quantitative difference in estrogen levels and the occurrence of hot flashes (Steingold, 1985; Walsh and Schiff, 1990; Thompson *et al.*, 1973; Freedman, 2001). The abrupt drop in estrogen is more related to the symptoms of hot flashes rather than hypoestrogenemia (Silva and Boulant, 1986). LH pulses are temporally related to the occurrence of a hot flash but do not appear to be the cause of the flash. Other hormones that increase with a hot flash include adrenocorticotropic hormone (ACTH), cortisol, and neurotensin (Hammond, 1996; Lightman *et al.*, 1981). The active area of interest lies in the central adrenergic system. Clonidine, an α-2 adrenergic receptor agonist, has been shown to reduce vascular responsiveness to norepinephrine, epinephrine, and angiotensin (Freedman *et al.*, 1990). Clonidine is also effective in tamoxifen-induced hot flashes in women with breast cancer (Ginsburg *et al.*, 1985).

Sexual Dysfunction

The prevalence of sexual activity varies, 70% among those aged 45–54 (Pandya *et al.*, 2000) and 60% among those aged 55–64 (Fantl *et al.*, 1994). This prevalence is similar to

that reported in community-based surveys from Europe and the United States (Greendale *et al.*, 1996; Dennerstein *et al.*, 2000; Diokno *et al.*, 1990). Hot flashes affect the quality of life markedly as well as adversely affect libido (Greendale *et al.*, 1996). It is not certain that reduced sexual activity is related to menopause *per se*, but may be related to some menopause-related symptoms that interfere with sexuality, for example, vaginal atrophy results in vaginal dryness and friability leading to dyspareunia and even reduced sexual arousal in some women (Fantl *et al.*, 1994; Lindgren *et al.*, 1993).

Estrogen is responsible for the development of primary and secondary sexual characteristics in women, although there is an increasing consensus regarding the role of androgens, as a major factor in enhancing libido. Lower testosterone levels in women have been found to be related to the reduction in the frequency of sexual intercourse, reduced sexual arousal, and a reduction in self-related sexual gratification scores (Osborn *et al.*, 1988; McCoy and Davidson, 1985). Free testosterone levels have a positive correlation with sexual desire (Osborn *et al.*, 1988). Testosterone replacement was shown to improve sexual desire in studies of women who have had oophorectomy and received higher doses of testosterone (Hutchinson, 1995; Sherwin and Gelfand, 1985). It is debatable if such a finding can be applied for similar testosterone replacement in women with natural occurring menopause. At the same time, the safety of the high dose of testosterone necessary for this effect is questioned (Sherwin *et al.*, 1985). It is unclear as to when and in whom androgen therapy should be utilized in women. The presence of depression and medications are major factors causing low libido. The risk and potential benefits of androgen remain to be elucidated. Doses for women can be individualized and the potential side effects monitored very closely, that is, hirsutism, lipid disorder, hepatic dysfunction, fluid retention, and potential polycythemia. A trial of low-dose oral methyltestosterone (1.25–5 mg daily) has been used for postmenopausal women who report low sexual desire. Myers *et al.* (1990) reported that a dose of 5 mg methyltestosterone showed an increase in self-stimulation, but not a self-reported arousal. In countries, where available, testosterone undecanoate can be used. Pharmacists have also compounded vaginal testosterone creams.

Urogenital Atrophy

Women with vaginal atrophy present with symptoms of dyspareunia, vaginal dryness, itching, and irritation frequently. At the onset of menopause, withdrawal of estrogen results in atrophic changes, that is, an increase in the friability of urogenital tissue and relevant pelvic organs. As a result, there is a decrease in the thickness and vascularity of the vulva and vaginal walls and a decrease in the size of the uterus. The secretion by the Bartholin's and cervical glands also decreases. In addition, the depleted lactobacillus from the vagina is replaced by normal flora. Normally, lactobacillus produces lactic acid to maintain a vaginal pH of 4.5, but with the loss of lactobacillus there is an increase in the vaginal pH (alkaline) resulting in an increase in urinary tract infections. Atrophic changes affecting the trigone, urethra, and bladder neck, acting in concert with postmenopausal reduction in α-adrenergic bladder neck receptors may result in urinary urgency and urge incontinence (Casson and Carson, 1996; Greendale *et al.*, 1999a; Rekers *et al.*, 1992). The prevalence of urogenital atrophy is estimated to be from 10 to 40% (Milsom *et al.*, 1993). Twenty-seven percent of the women reported vaginal dryness and dyspareunia and 36% complained of micturition symptoms, incontinence, or urinary tract infection at the time of menopause (Greendale and Judd, 1993). Symptoms of itching, burning, incontinence, and dyspareunia can be disabling (van Geelen *et al.*, 2000).

Depression

Several longitudinal population-based studies suggest no association between menopause transition and depression (Barlow *et al.*, 1997). Kaufert *et al.* (Pearlstein *et al.*, 1997) reported in a Canadian study that 51% of menopausal women had a positive depression screening (Center for Epidemiologic Studies Depression Scale) at least once during a 3 year period of observation, but these high scores were related to perceived poor health and not because of menopause. Two other studies have identified a higher incidence of depression in menopausal women with a preexisting history of depression (Kaufert *et al.*, 1992; Avis *et al.*, 1994). Although there is no scientific evidence associating menopause and the increase in the risk of depression, the failure of health professionals to differentiate without any doubt among transient periods of depressed mood, depressed mood due to adjustment disorder, and major depression has led to this myth in the mind of the layperson. Regardless of this, postmenopausal women complain of increased irritability, anxiety, and depressed mood.

Estrogen replacement appears to enhance mood and this could be the effect of β-endorphin, which increases with estrogen replacement. In postmenopausal women, the response of cortisol and prolactin to the antagonist (1-metchlorophenyl piperazine) was blunted as compared to younger women and those on estrogen replacement (Hunter, 1990). This diminished response to serotonin may explain some of the mood-altering effects of estrogen; however, it is not clear that these changes are persistent (Halbreich *et al.*, 1985). The combination of hormone replacement therapy (HRT) plus SSRIs (selective serotonin reuptake inhibitors) may confer benefit in treating depression (Oppenheim, 1984) compared to either one of the therapy alone. The impact of progesterone on mood is also unclear and studies exist showing conflicting results, as has been seen with estrogen (Schneider *et al.*, 1997; Sherwin, 1991).

Sleep

Sleep disruption is frequently perceived during the perimenopause period both by the subject and the health-care

professional. Insomnia is not the immediate presenting issue in perimenopause, but its incidence is higher in women during this time in their life span (Greendale *et al.*, 1999b; Shaver and Zenk, 2000). Insomnia could present as difficulty in falling asleep, disruption of sleep by hot flashes, fragmented sleep, and early morning awakenings. Sleep studies had shown that the hot flashes and the rapid eye movement (REM) sleep tends to occur at the same time, thereby compromising the quality of sleep (Baker *et al.*, 1997). In asymptomatic women (without hot flashes), the higher prevalence of insomnia could be a result of obstructive sleep apnea. The prevalence of obstructive sleep apnea rises in women after menopause but remains stable with aging in men (Shaver *et al.*, 1988; Polo-Kantola *et al.*, 2001). There is poor correlation between estrogen levels and the level of insomnia. The etiology of insomnia is poorly explored at this time.

Cognition

Clinical studies have suggested the presence of estrogen receptors in the cerebral cortex, pituitary gland, limbic system, and hypothalamus. Until recently, the commonly held view was that estrogen/hormone therapy (ET/HT) helped prevent postmenopausal women from developing dementia, particularly Alzheimer's dementia (AD) because of the neuroprotective effect of estrogen on the brain (Lamberg, 1997). The Women Health Initiative Memory Study (WHIMS), a randomized, double-blind, placebo-controlled clinical trial, examined 93% of the postmenopausal women from Women Health Initiative (WHI) (Birge, 1997). The estrogen plus progestin segment of the study enrolled only women aged 65 and older, with an average age of 71 years. These patients were diagnosed with possible dementia. The results of the WHIMS were quite perplexing. Sixty-one women were diagnosed with possible dementia (most likely AD), and among these women 40 were on estrogen/progestin therapy, which is twice the number of women on placebo. A risk-benefit analysis suggested the discontinuation of estrogen/progestin therapy, as there were no significant differences in women 65 years and over. There was a higher incidence of diagnosing AD in the second year, which is very difficult to explain as it is a very slow and progressive disease. The causes of these findings need to be explored further. These findings do not apply to women in the menopausal transitional period. It should be remembered that women in this study received premarin and these findings may not apply to other forms of estrogen.

Coronary Heart Disease

Cardiovascular disease is the leading cause of death (43%) among women aged 50 and older (Shumaker *et al.*, 2003). Women have approximately 10 times the risk of heart disease in their lifetime than of breast cancer, reproductive cancer, or osteoporotic fracture. The HERS (Heart and Estrogen/Progestin Replacement Study) trial examined 2763 postmenopausal women with heart disease, suggesting no significant difference between ET/HT and placebo groups (Mosca *et al.*, 1997). However, there was an increase in the risk of cardiovascular events in the first year of hormone replacement, which decreased over time. HT is also associated with a significant risk in venous thromboembolism (VTE) and gall bladder disease; however, a significant improvement in lipid profile was observed in ET/HT users despite the lack of effect on cardiovascular disease, with a 11% lowering of low-density lipoprotein levels and a 10% increase in high-density lipoprotein (HDL) levels than in the placebo group despite the increase in events in the first year. The WHI Study also observed an increase in heart disease death, nonfatal myocardial infarction, pulmonary thromboembolic disease, and deep vein thrombosis. The findings from both HERS and WHI studies suggest not initiating HRT for the primary and/or secondary prevention of heart disease.

Stroke

The WHI study analyzed the risk of stroke among the 16 608 women enrolled in the study. The overall hazard ratio (HR) for stroke (fatal and nonfatal stroke) was 1.41 after an average of 5.2 years of follow-up (Hulley *et al.*, 1998). Those who used estrogen/progestin had a higher incidence of nonfatal stroke but not fatal stroke. A recent update of WHI confirms that there were 7 additional strokes per 10 000 women across all age-groups per year, representing a 31% increase in risk (Rossouw *et al.*, 2002). This increase is reported to exist from the second through the fifth year of estrogen/progestin usage.

Osteoporosis

The prevalence of low bone mineral density (BMD) in women 50 years and older is about 50–68% (Wassertheil-Smoller *et al.*, 2003; Looker *et al.*, 1998). Osteoporotic fracture accounts for 1.5 million low-impact fractures each year. The lifetime risk of hip, spine, and radial fracture is 40% for postmenopausal women, and most of these fractures are accounted for by white women. In the first year after hip fracture, the mortality rate is about 20%. Hip fracture results in a significant loss of function with about one-third requiring institutionalized care (Siris *et al.*, 2001). Loss of BMD begins in the fourth decade in both men and women at a rate of approximately 1% per year. Age-related bone loss results in about 25% of trabecular and cortical bone loss in women. Some women are predisposed to accelerated bone loss on entering menopause. During this time, the trabecular bone loss progresses at a rate of about 5% each year, and the etiology of accelerated bone loss during menopause is unclear.

PERIMENOPAUSAL EVALUATION

During the perimenopausal period, questions should be directed about vasomotor symptoms, menstrual irregularities, sexual dysfunction, prevention of osteoporosis, increased risk of cardiovascular events after menopause, and the exclusion of pregnancy to confirm menopause. Measuring hormonal levels to help diagnose menopause is not clear, but an FSH level of 40 mIU L^{-1} or greater is considered diagnostic of menopause. Several studies have shown wide fluctuations in the perimenopausal values for FSH, making it an unfavorable tool to be used for the diagnosis of menopause (Riggs and Melton, 1995; Santoro *et al.*, 1996).

MANAGEMENT OF PERIMENOPAUSAL SYNDROME

Hormone Replacement Therapy

Currently, 20–45% of the women in the United States between the ages of 50 and 75 take some form of HRT. About 8 million American women use estrogen alone and about 6 million American women use estrogen-progestin therapy. Approximately 20% of the women do so for more than 5 years. Earlier studies suggesting that HRT exerted a protective role against osteoporosis, cardiovascular disease, and dementia suggested that it could be the "fountain of youth" for women (Santoro *et al.*, 1996; Keating *et al.*, 1999). The HERS study (Mendelsohn and Karas, 1999) reported that the use of conjugated estrogen 0.625 mg and medroxyprogesterone acetate (MPA) did not reduce the risk of cardiovascular events in women with documented coronary artery disease. In fact, there was an increase in cardiovascular events in the group treated with HRT. The treatment also increased the rate of thromboembolic events and gallbladder disease. There was a pattern of early increase in the risk of coronary heart disease (CHD) events and no overall cardiovascular benefits; starting HRT treatment for the purpose of secondary prevention of CHD is not recommended. A follow-up study to the HERS II looked to determine whether the risk reduction observed in the later years of HERS persisted and resulted in an overall reduced risk of CHD events with additional years of follow-up. After 6.8 years, HT did not reduce the risk of cardiovascular events in women with CHD. HERS II recommends that postmenopausal HT should not be used to reduce the risk for CHD events in women with CHD (Hulley *et al.*, 1998).

The estrogen plus progestin component in the study by the WHI was a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50–79 years with an intact uterus were treated with HRT. The trial was stopped prematurely after a mean of 5.2 years of follow-up. The estimated HRs by the major clinical outcomes were as follows: CHD, 1.29 with 286 cases; breast cancer, 1.26 with 290 cases; stroke, 1.41 with 212 cases; pulmonary embolism (PE), 2.13 with 101 cases; colorectal cancer, 0.63 with 112 cases; endometrial cancer, 0.83 with 47 cases; hip fracture, 0.66 with 106 cases; and death due to other causes, 0.92 with 331 cases. The absolute increased risks per 10 000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10 000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures (Grady *et al.*, 2002).

Postmenopausal HT is known to increase the risk of venous thrombosis (VT). Cushman and colleagues reported (Writing Group for the Women's Health Initiative Investigators, 2002) the analyses of the data from the WHI Estrogen Plus Progestin trial, which included assessment of the interaction of HT with other demographic and clinical risk factors for VT. The authors found that HT increased the risks of VT associated with age, overweight or obesity, and factor V Leiden. In a second article, Smith and colleagues (Cushman *et al.*, 2004) compared the risk of first VT among women taking esterified estrogen or conjugated equine estrogen (CEE) with or without progestin, versus nonusers of HT. They found that the current use of conjugated equine estrogen, but not esterified estrogen, was associated with an increased risk of VT compared with nonuse, and the risk was increased with concomitant progestin use. With all this evidence, the use of HRT is not recommended as the risks outweigh the benefits.

Hot Flashes

The main triggers are spicy or hot food, caffeine, or alcohol, all of which should be avoided. Removing layers of clothing, drinking cold beverages, moving to an open window or cool place, putting ice on the forehead, or using a handheld fan are some ways to reduce the subjective effects of a flash. Even talking about a flash can help reduce the psychological effects it can produce.

Herbal Therapies

Many women in the United States use herbal therapies for menopausal symptoms (Smith *et al.*, 2004). The common herbs used in the United States include black cohosh (*Cimicifuga racemosa*), chaste tree berry (*Vitex agnus-castus*), dong quai (*Angelica sinensis*), Gingseng (*Panax gingseng*), evening primrose oil (*Oenethera biennis*), motherwort (*Leonurus cardiaca*), red clover (*Trifolium pratense*), and licorice (*Glycyrrhiza glabra*).

Black cohosh is the most popular herb used traditionally by Native Americans for gynecological conditions. There are four randomized controlled trials on black cohosh with 2–6 months follow-up in a total of 285 women. One of the four trials was placebo controlled (Beal, 1998), one used both treatment and placebo control (Jacobson *et al.*, 2001), and two were treatment controlled (Warnecke, 1985;

Stoll, 1987). Three studies showed no difference between black cohosh and the control and in the fourth trial, there was no difference between the treatment groups. All clinical studies of black cohosh have used the standardized product remifemin, however, the formulation and dosages were different. There is a concern for long-term use of these herbal products since there is no data available on its long-term safety, especially regarding endometrial or breast stimulation. Black cohosh may be useful for hot flashes but long-term use may not be safe as there is no data available regarding its safety.

Many foods contain phytoestrogens, primarily phenolic (rather than steroidal) compounds that include isoflavones, ligans, and coumestans. Isoflavones are found in soy. Lignan precursors are found in vegetables, rye, whole grain, seeds, and legumes.

Soy products are used in Japan, China, and Korea with a reported lower prevalence of menopausal symptoms in these countries (Lehmann-Willenbrock and Riedel, 1988; Lock *et al.*, 1988). Soy is also used in the United States, and currently there are 11 randomized controlled trials (RCT) with soy and soy extract in a total of 1172 women (Adlercreutz *et al.*, 1992; Van Patten *et al.*, 2002; Kronenberg and Fugh-Berman, 2002; Baber *et al.*, 1999; Knight *et al.*, 1999). The duration of these studies is from 1 to 4 months. Of these RCTs, six showed some difference in hot flashes such as severity, frequency, or symptoms score (Van Patten *et al.*, 2002). Comparisons are difficult because of variation in the dosage, menopausal symptoms of hot flashes, and menopausal status of patients. The products used in these studies ranged from soy foods to pure isoflavone products. Soy products have been used for years in Asian cuisines and are safe, but it is not wise to assume that products with high doses of isoflavones that are currently available in health stores are also safe. Studies of longer duration need to be conducted in order to ensure safety of these products and differentiate among whole foods, soy protein, and isoflavone.

Red clover is a Native American herb that is not traditionally used long term for hot flashes, and its effect on breast or endometrium stimulation is unknown. Red clover contains the phytoestrogens formononetin, biochanin A, daizein, and genistein. Two Australian RCTs of 3-month duration with 88 patients showed no significant difference of red clover extract compared to placebo for hot flashes (Kronenberg and Fugh-Berman, 2002; Baber *et al.*, 1999).

Dong quai, a Chinese herb is sold in the United States in the form of nontraditional herb combinations. Dong quai has been reported to produce no clinical benefit for hot flashes (Knight *et al.*, 1999). Dong quai contains coumarins and furocoumarins, which, if used with warfarin, can lead to an increase in bleeding tendencies and photosensitization respectively (Hirata *et al.*, 1997; Amato *et al.*, 2002). Dong quai does not contain the typically reported phytoestrogen and as such has a controversial effect on breast tissue stimulation (Fugh-Berman, 2000; Foster and Tyler, 1999).

Ginseng in one trial was shown to have a positive effect on mood but no benefit on menopausal symptoms and quality of life (Zava *et al.*, 1998). There are case reports linking both topical and ingestion of ginseng with postmenopausal bleeding (Wiklund *et al.*, 1999; Greenspan, 1983; Punnonen and Lukola, 1980). Ginseng also reduces the INR (international normalization ratio) in patients receiving coumadin.

Oil of evening primrose is being evaluated for hot flashes. In one trial, there was no benefit between evening primrose oil and placebo on hot flashes (Hopkins *et al.*, 1988).

In a recent literature review, postmenopausal vasomotor treatments that are safe in the short term are (Chenoy *et al.*, 1994): black cohosh, exercise, gabapentin, medroxyprogesterone acetate, paroxetine hydrochloride, and soy protein.

Initial small studies suggest the use of megestrol acetate and venlafaxine. One needs to be aware of the side effects of megestrol acetate such as thromboembolic disease and the rare Cushing's syndrome. The HOPE study, a randomized, double-blind, placebo-controlled trial (the Women's Health, Osteoporosis, Progestin, Estrogen study) examined 2673 healthy, postmenopausal women with an intact uterus. The reduction in vasomotor symptoms was similar with conjugated equine estrogen of $0.625\,\mathrm{mg\,d^{-1}}$ and medroxyprogesterone acetate of $2.5\,\mathrm{mg\,d^{-1}}$ (the most commonly prescribed doses) and all lower combination doses. CEE of $0.625\,\mathrm{mg\,d^{-1}}$ alleviated hot flashes more effectively than the lower doses of CEE alone. Vaginal maturation index improved in all active treatment groups. It was concluded that lower doses of CEE plus MPA relieve vasomotor symptoms and vaginal atrophy as effectively as commonly prescribed doses (Fugate and Church, 2004).

Atrophic Vaginitis

Both systemic and topical estrogen preparations are effective in treating the symptoms of atrophic vaginitis by reducing vaginal pH (Utian *et al.*, 2001) and restoring the premenopausal index. Some of the commonly used vaginal preparations are estrogen cream 0.625 mg, estriol cream, estradiol tablets, and estradiol rings. Nonhormonal preparations are also used and are effective such as polycarbophil or asroglide.

Sexual Dysfunction

Women with androgen deficiency due to chemotherapy and/or bilateral salpingo-oophorectomy have decreased libido and sexual responses. Sherwin *et al.* found that surgical menopausal women on estradiol and testosterone reported greater sexual desire, arousal, and more frequent fantasias than women on estradiol alone or placebo. These changes in behavior covaried with testosterone but not with estradiol serum concentration, which supports the hypothesis that testosterone, not estrogen, has a major role in female sexual interest (Stone *et al.*, 1975; Yu *et al.*, 1997).

Minimal data is available on the use of testosterone in older women. Testosterone, in addition to improving libido also

decreases the hot flashes, improves the general well being, and decreases estrogen deficiency-related headaches and mastalgia. Testosterone has been demonstrated to increase BMD and lean body mass in postmenopausal women.

For women, oral testosterone (methyl testosterone) is available in combination with estrogen (Estratest), but may cause elevation of liver enzymes. Testosterone patches are also being developed for women. Testosterone gel can either be compounded by local pharmacist or obtained from androgel packets. Testosterone pellets can be implanted subcutaneously. Testosterone cream application can be utilized for treating atrophic vulvar dystrophy. It has been suggested that testosterone cream applied to the clitoris will increase orgasm in anorgasmic women. Tibolone is a unique agent that has mixed estrogenic-progestagenic-androgenic properties and as such appears to be an ideal replacement therapy. Effects of testosterone include hirsutism, deepening of voice, and an oily skin. DHEA has mixed androgenic-estrogenic properties in postmenopausal women. It has been shown to increase libido in women over 70 years of age. It is not recommended because of variable quality of DHEA and its potential carcinogenic effect on the postmenopausal breast.

Sildenafil was tried in postmenopausal women and it seems that it did not improve sexual function significantly, though it was well tolerated and improved lubrication and clitoral sensitivity (Cheng, 1999).

Finally, older women need to be educated about erectile dysfunction in the male partner along with female sexual aging. Women need to be educated that there is diminished erection and need for more genital stimulation, rather than assuming that the problem is her own inability to arouse her partner.

Postmenopausal Health Maintenance

Current evidence suggests that the use of HRT is no more justifiable, based on the increased adverse events related to its use. It is the responsibility of the physician and the women themselves to increase awareness of the important preventive component of women's health care. An increase in such awareness will result in a healthy lifestyle by bringing in a change in lifestyle.

Cardiovascular Disease

The results of HERS and HERS II study suggested that HRT is not beneficial in secondary prevention of cardiovascular disease but increases the risk of cardiovascular events in women with documented CHD. Lately, the WHI study also failed to demonstrate any benefit of HRT in the primary prevention of CHD or in the reduction of all-cause mortality. The WHI showed 29% increase in CHD event, 42% increase in stroke, a twofold increase in pulmonary embolism as well as an increase in deep vein thrombosis and a 26% increase in breast cancer. The WHI did show a 24% reduction in hip fracture and a 37% decrease in colorectal cancer, and there was no change in endometrial cancer, lung cancer, or the total incidence of cancer. It is important to recognize that the estrogen-only arm of the study in hysterectomized women was not stopped, suggesting progesterone was the main agent responsible for the adverse effects. Similarly, another study of hormone replacement in postmenopausal women reported a significant increase in the risk of ovarian cancer in women who received estrogen replacement for 10 or more years (Shaw *et al.*, 1997).

Postmenopausal Osteoporosis

The prevalence of low BMD in women over the age of 50 is 50–68% (Wassertheil-Smoller *et al.*, 2003; Looker *et al.*, 1998). The lifetime risk of hip, spine, and radial fracture is 40% for postmenopausal women. The mortality rate is 20% at 1 year after a fracture.

The National Osteoporosis Foundation supports the testing of BMD for all women over the age of 65, and women under the age of 65 with risk factors. Once osteoporosis is identified, the next step is to treat it appropriately.

SUMMARY

In summary, ovarian hypofunction results in menopause and at this stage using HRT is counterproductive. Cessation of menses, the hallmark of menopause is considered by many as the starting point for screening and treating chronic diseases. It is imperative to start educating women about the risks resulting from ovarian hypofunction and carry out discussions involving measures to modify risk factors of chronic diseases before the onset of menopause, and perform appropriate screening tests and implement preventive therapies (pharmacological or nonpharmacological) as indicated.

- Menopause is a normal rather than a disease process.
- Women in this age-group need education and understanding the process of menopause and while adapting to the new lifestyle.
- Emphasis needs to be placed on the preventive aspects of chronic diseases that occur during this time and to avoid HRT.

MALE HYPOGONADISM (ANDROPAUSE)

Hypogonadism is a clinical condition associated with testosterone deficiency with specific signs and symptoms, such as diminished libido and sense of energy, erectile dysfunction, decreased muscle mass and strength, decreased BMD, depression and anemia, increased fatigue, and impaired cognition (Matsumoto, 2002; Morley, 2001). When Hypogonadism occurs in the older men, the condition is called

andropause, androgen deficiency of aging man (ADAM), and partial androgen deficiency of the aging male, male climacteric, male menopause, or even viropause.

Andropause is seen in men over 50 years of age. It has been described in the Chinese text of Internal Medicine in the sixteenth century. Testicular extract was used by Brown-Sequard for treating his menopausal symptoms. Testosterone was first isolated from the bull testes in the laboratory in 1930s. Werner described the symptoms of testosterone deficiency in the 1940s (Werner, 1946).

Hypogonadism affects an estimated 2–4 million men in the United States, and its prevalence increases with aging (Harman *et al.*, 2001; Morley *et al.*, 1997a). Currently, only 5% of the affected men are receiving treatment (Food and Drug Administration, 1996). Recent media attention to testosterone-replacement therapy has been fueled not only by the increased medical awareness of hypogonadism but also by the marketing of new topical testosterone formulations, and the desire of "baby boomers" to maintain vitality and health into their more mature years.

DECLINE IN TESTOSTERONE WITH AGING

Both cross-sectional and longitudinal studies have clearly shown that testosterone levels in men decrease with age at a rate of 1–2% per year (Korenman *et al.*, 1990; Kaiser *et al.*, 1998; Harman *et al.*, 2001; Haren *et al.*, 2001; Zmuda *et al.*, 1997). Circulating testosterone is mainly (60%) bound to sex hormone binding globulin (SHBG). About 38% is bound to albumin and 1–2% circulates freely in the blood. The SHBG increases with increase in age, which leads to an increase in bound testosterone; reflecting a total testosterone level higher than expected for the level of tissue available testosterone. The free and albumin-bound testosterone can enter the cell under physiological conditions and are available to activate the testosterone receptors. It is also believed that there is an alteration in the binding capacity of SHBG with aging (Haren *et al.*, 2001). Whatever the cause, there is a low amount of testosterone available to tissues in older adults. Total testosterone is an inappropriate measure of hypogonadism in older adults.

Both bioavailable testosterone and free androgen index (which can be calculated using the program at www.Issam.ch) are acceptable methods to measure testosterone levels in older adults. Using these measures, 2–30% of men between the ages of 40 and 59 years and 34–70% of men between the ages of 60 and 80 years are hypogonadal (Morley *et al.*, 1997a; Zmuda *et al.*, 1997; Khosala and Melton, 2001).

Reports indicate that testosterone-replacement therapy produces a wide range of benefits for men with hypogonadism, which includes libido (Tenover, 1998; Kim, 1999; Snyder *et al.*, 2000), bone density (Kenny *et al.*, 2001; Snyder *et al.*, 1999), muscle mass (Snyder *et al.*, 2000; Kenny *et al.*, 2001; Sih *et al.*, 1997), body composition (Snyder *et al.*, 2000; Sih *et al.*, 1997; Snyder *et al.*, 2001), mood (Snyder *et al.*, 2000; Dobs *et al.*, 1999), erythropoiesis (Snyder *et al.*, 2000; Dobs *et al.*, 1999), and cognition (Dobs *et al.*, 1999; Cherrier *et al.*, 2001; Moffat *et al.*, 2002).

Perhaps the most common controversial topic concerning the ongoing discussion of testosterone-replacement therapy is its long-term safety and risks. Recent reports from the HRT studies have aroused concerns that men receiving hormones may also be vulnerable to an increase in health risks.

PATHOPHYSIOLOGY OF HYPOGONADISM

The causes of hypogonadism in older adults seem to be multifactorial.

- Hypogonadism could be either primary or secondary, but in older adults it is mostly secondary in nature, that is, lower testosterone levels fail to elevate the LH outside the normal range (Korenman *et al.*, 1990; Leifke *et al.*, 2000).
- Decrease in Leydig cell function in the testes of older men (Mulligan *et al.*, 2001).
- Partial desensitization of Leydig cells to LH with aging (Mulligan *et al.*, 2001).
- Decrease in testosterone response to human chorionic gonadotropin (Harman and Tsitouras, 1980).
- Decrease in pituitary responsiveness to gonadotropin releasing hormone with aging (Winters and Atkinson, 1997).
- Testosterone replacement in older men is a more potent inhibitor of LH than in younger men (Winters and Atkinson, 1997).
- In healthy older men, there is a decrease in LH pulse amplitude and frequency and irregularity of the secretion of LH (Mulligan *et al.*, 2001; Pincus *et al.*, 1996).
- Increased aromatization of testosterone to estradiol and in 5α reductase activity to dihydrotestosterone (DHT). DHT levels stay stable, while testosterone decreases with aging (Ukkola *et al.*, 2001).
- There is a decrease in fertility and spermatogenesis with aging (Baccarelli *et al.*, 2001).
- Decrease in Inhibin B levels with aging (Baccarelli *et al.*, 2001).
- FSH levels increase more than LH with aging (Morley *et al.*, 1997a).

EFFECTS OF TESTOSTERONE REPLACEMENT IN OLDER ADULTS

Coronary Artery Disease

Testosterone was used successfully to treat angina. Studies have shown that low testosterone levels are associated with both coronary artery disease and the degree of atherosclerosis (Jaffe, 1997; English *et al.*, 2000a). Testosterone dilates the brachial artery and thereby increases the blood flow (Rosano *et al.*, 1999; Webb *et al.*, 1999) reduction in the ST depression during exercise stress test (Jaffe, 1997; Wu and Weng,

1993; English *et al.*, 2000b) reducing myocardial infarction (Anderson *et al.*, 1995) or causing no effect on myocardial infarction (Hajjar *et al.*, 1997). Anderson *et al.* (1995) reported that testosterone replacement decreases the prothrombotic factors and prothrombinase activity, and protein C and S appeared to be counterbalanced by an increase in antithrombin III activity and fibrinolytic activity. There was no effect on platelet activity. Testosterone-replacement therapies have not demonstrated an increase in the incidence of cardiovascular disease or events such as myocardial infarction, stroke, or angina (Hajjar *et al.*, 1997).

Lipid Profiles

Testosterone decreases cholesterol, low-density lipoprotein cholesterol levels, and HDL cholesterol levels (Sih *et al.*, 1997; Zgliczynski *et al.*, 1996; Anderson *et al.*, 1995; Wittert *et al.*, 2003; Tenover, 1992; Ferrando *et al.*, 2002; Morley *et al.*, 1993; Kang *et al.*, 2002). Whitsel *et al.* (2001) in their meta-analysis on the effect of intramuscular testosterone injection on serum lipid in hypogonadal men reported that HDL levels were reduced in three studies and remained unchanged in 15. Five studies showed reduction in total cholesterol, increase in 2, and unchanged in 12. Low-density cholesterol was either unchanged or reduced in 14 of the 15 studies.

Although the data appear reassuring, definitive assessment of long-term effects of testosterone-replacement therapy on cardiovascular health require prospective, large scale, placebo-controlled studies.

Libido and Erectile Dysfunction

Epidemiologic studies have shown that decreased sexual activity and libido are associated with a decrease in free or bioavailable testosterone levels (Davidson *et al.*, 1983; Schiavi *et al.*, 1991). These studies suggested that aging was a more important contributor than androgen levels in sexual behavior in healthy older men.

Testosterone replacement improves libido and quality of erection in hypogonadal men (Billingtom *et al.*, 1983; Nankin and Lin, 1986). Sildenafil is reported to improve erection in older men (Wagner *et al.*, 2001). It is reported that certain men with low testosterone do not respond to sildenafil alone unless their testosterone is replaced (Tariq *et al.*, 2003). This seems to be because testosterone is essential for the synthesis of nitric oxide synthase. DHT is also shown to be associated with the ability to maintain erection (Endo *et al.*, 2002).

Body Composition and Frailty

Aging is associated with a decrease in muscle mass and strength. Conservation of muscle mass and strength has been shown to be reversed with resistance training (Klein *et al.*, 2002; Evans, 2002; Trappe *et al.*, 2001). Excessive loss of muscle in a person results in sarcopenia and an increase in the risk of becoming frail (Gillick, 2001; Fried *et al.*, 2001; Lipsitz, 2002). Free testosterone index and bioavailable testosterone index are better predictors of muscle mass and strength (Baumgartner *et al.*, 1999a; Perry *et al.*, 2000).

Studies with testosterone replacement have clearly shown that it produces an increase in muscle mass, which is reported even in older men who are not hypogonadal (Wittert *et al.*, 2003; Tenover, 1992; Ferrando *et al.*, 2002; Morley *et al.*, 1993). Most of the studies have shown increased strength in the upper extremities in the case of hypogonadal men (Tenover, 1992; Bakhshi *et al.*, 2000; Morley, 1997), but failed to increase strength in men who were not hypogonadal (Kenny *et al.*, 2001; Snyder *et al.*, 1999). DHT is shown to increase knee flexion strength (Ly *et al.*, 2001). Testosterone replacement is also beneficial in improving the functional independence measure (FIM) during rehabilitation following hospitalization (Bakhshi *et al.*, 2000).

Leptin level increases with age in males and this has been shown to be associated with a decrease in testosterone (Morley, 1997; Baumgartner *et al.*, 1999b; Baumgartner *et al.*, 1999c; Munzer *et al.*, 2001; Morley *et al.*, 1997b).

Testosterone replacement decreases fat mass (Kenny *et al.*, 2001; Snyder *et al.*, 1999; Ferrando *et al.*, 2002) with subcutaneous adiposity being reduced to a greater extent than abdominal visceral fat (Munzer *et al.*, 2001).

Behavioral Effects

Epidemiologists have shown a strong correlation between low testosterone and cognitive decline with aging (Morley *et al.*, 1997b; Barrett-Connor *et al.*, 1999). Low testosterone in middle age is predictive of developing AD (Henderson and Hogervorst, 2004). Testosterone replacement improves working spatial memory and trail-making B (Kenny *et al.*, 2001; Janowsky *et al.*, 1994; Janowsky *et al.*, 2000; Cherrier *et al.*, 2001); effects on verbal memory are controversial (Janowsky *et al.*, 2000; Cherrier *et al.*, 2001) and in other studies it has shown failure to alter cognition (Kenny *et al.*, 2001; Sih *et al.*, 1997).

Dysphoria has been related to low levels of testosterone (Barrett-Connor *et al.*, 2000; Seidman *et al.*, 2002). Testosterone replacement did improve depression in one study (Giorgi *et al.*, 1992), but other studies have failed to show the same results (Sih *et al.*, 1997; Janowsky *et al.*, 2000; Seidman *et al.*, 2001; Reddy *et al.*, 2000).

Bone

Testosterone is converted by the process of aromatization to estradiol that acts on the bone. Testosterone increases BMD by acting on the osteoblasts. Testosterone increases BMD at the hip and lumbar spine (Katznelson *et al.*, 1996; Anderson *et al.*, 1996). There are no studies examining the effect of testosterone on hip fracture.

Polycythemia

Replacement of testosterone appears to stimulate erythropoiesis. Hemoglobin levels increase by 15–20% in boys at puberty, in parallel with serum testosterone levels. Lower testosterone levels are associated with anemia in men (Basaria and Dobs, 1999). A rise in hematocrit is generally beneficial in anemia; elevation above the normal range may have grave consequences for coronary, cerebrovascular, or peripheral vascular circulation (Basaria and Dobs, 1999; The Endocrine Society, 2002). Increase in hemoglobin is associated with the route of testosterone replacement. Injection increased hematocrit by 44%, transdermal nonscrotal patch by 15% (Dobs *et al.*, 1999), and scrotal patch by 5% (Leifke *et al.*, 2000). Wang *et al.* (2000) reported a direct relation between testosterone dosage and the incidence of erythrocytosis. Erythrocytosis was reported in 2.8% of men on 5 mg of nonscrotal patches, 11% with 50 mg day^{-1} and 18% with 100 mg day^{-1} gel respectively.

Benign Prostatic Hypertrophy

It is a well-established fact that androgens are required for the causation of benign prostatic hypertrophy (BPH) and that a decrease in serum testosterone causes a reduction in the size of the prostate (Huggins *et al.*, 1941). However, a number of studies have failed to show that testosterone replacement exacerbated the voiding symptoms of BPH or caused increased urinary retention compared to placebo (Kenny *et al.*, 2001; Sih *et al.*, 1997; Dobs *et al.*, 1999; Comhaire, 2000; Krieg *et al.*, 1993; Pechersky *et al.*, 2002; Marcelli and Cunningham, 1999; Slater and Oliver, 2000).

Prostate Cancer

Case reports have suggested that testosterone-replacement therapy may convert occult cancer into a clinically apparent lesion (Curran and Bihrle, 1999; Loughlin and Richie, 1997). To date, prospective studies have demonstrated a low frequency of prostate cancer in association with testosterone-replacement therapy. A compilation of published prospective trials of testosterone-replacement therapy followed for 6 to 36 months showed prostate cancer in 5 of 461 men (1.1%) (Zmuda *et al.*, 1997; Snyder *et al.*, 2000; Kenny *et al.*, 2001; Sih *et al.*, 1997; Dobs *et al.*, 1999; Wang *et al.*, 2000), a prevalence rate very similar to that in the general population. There is some concern that the underlying prevalence of occult prostate cancer in men with low testosterone levels appear to be substantial (Morgentaler *et al.*, 1996).

Despite decades of research, there is no compelling evidence to show that testosterone has a causative role in prostate cancer (Pechersky *et al.*, 2002; Marcelli and Cunningham, 1999; Carter *et al.*, 1995; Heikkila *et al.*, 1999; Hsing, 2001).

Other side effects include gynecomastia, water retention, hypertension, and sleep apnea.

Screening for Hypogonadism

Three screening questionnaires have been developed for hypogonadism. These tests are useful but not diagnostic. The Saint Louis University ADAM Questionnaire and the Aging Male Survey both have good specificity, but the Massachusetts Male Survey utilizes risk factors and has poor specificity.

TESTOSTERONE THERAPIES

Testosterone replacement can be achieved in several ways:

- Oral and injectable therapies.
- Transscrotal and transdermal patches.
- Subcutaneous gels.
- Buccal preparations.
- Selective androgen receptor molecule (no effects on prostate). These are under development.
- Sublingual and inhalation forms are under development.

CONCLUSION

Hypogonadism is a very common condition in older males. Appropriate screening is suggested to clinicians, and it is important to exclude the diagnosis of depression and hypothyroidism before initiating the laboratory work-up (bioavailable testosterone, etc.). Testosterone replacement is available in different forms with minimal side effects if closely monitored. From the current literature, there is no increase in the risk of prostate cancer in subjects with replacement therapy. A long-term study is required to answer the questions regarding the risks and benefits of testosterone therapy.

KEY POINTS

- Hypogonadism is very common in older males.
- Screening tools are available to screen high-risk patients.
- Bioavailable testosterone levels should be checked rather than total testosterone.
- Monitor therapy and watch for any side effects.

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Type 2 Diabetes Mellitus in Senior Citizens

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INTRODUCTION

Diabetes care systems for older people require an integrated multidimensional approach involving general practitioners, hospital specialists, and other members of the health-care team. There should be an emphasis on diabetes prevention and its complications, early treatment for vascular disease, and functional assessment of disability due to limb problems, eye disease, and stroke.

Inequalities of care are common in many health-care systems due to variations in clinical practice, particularly in relation to older people. This may be manifest as lack of access to services, inadequate specialist provision, poorer clinical outcomes, and patient and family dissatisfaction. The recent development of clinical guidelines that are responsive to the needs of older people with diabetes may be an important step to minimize deficits in care from country to country, worldwide.

Type 2 diabetes mellitus is a common disabling chronic cardiovascular and medical disorder that has a tremendous health, social, and economic burden, and has a high prevalence of 10–30% in subjects above 65 years of age across Europe. About 60% of total health-care expenditure on diabetes in this special group can be accounted for by acute-care hospitalizations and compared with nondiabetic counterparts, the relative risk for admission to hospital is 5.0. At any one time, about 1 in 12 district hospital beds are occupied by older people who have diabetes and their length of stay is double compared to nondiabetic inpatients. The introduction of insulin to their regimen results in expenditure quadrupling, presumably because of the additional resources required in both hospital and community settings to monitor and support the use of insulin.

A direct approach to the metabolic management of type 2 diabetes in older subjects is to concentrate on strategies designed to limit and ameliorate both defective insulin secretion and insulin resistance. Type 2 diabetes represents a cluster of cardiovascular-risk factors that represent a significant vascular threat, and in aging subjects, the added effects of aging and renal impairment increase the impact of this syndrome, while some of the features may be present up to 10 years before the onset of overt hyperglycemia, thus increasing the cardiovascular risk before the onset of diabetes. Since up to 50% of the variability in insulin action in insulin-resistant states may be associated with lifestyle differences: obesity, physical activity levels, and cigarette smoking, it becomes obvious that environmental, preventative, and health promotional strategies are of vital importance in limiting the impact of this epidemic.

Management of diabetes in older people can be relatively straightforward, especially when patients have no other comorbidities and when vascular complications are absent. In many cases, however, special issues arise that increase the complexity of management and lead to difficult clinical decision making. It is thus not surprising that the present state of diabetes care for older patients varies throughout Europe and North America. Although *geriatric diabetes* is developing as a subspeciality interest in the United Kingdom, there is little evidence of its presence in other national diabetes care systems and virtually no specific provision for those who are housebound or in institutional care.

Diabetes care for the old is, however, generally improving as more and more health-care systems are being audited, standards of care highlighted and deficiencies in care addressed. This chapter can be considered to be a learning program that aims to provide a succinct but comprehensive review of diabetes care for older people focusing on special areas of concern.

We have identified two principal aims: (1) To develop and enhance the knowledge and application of the principles of diabetes and diabetes care in older persons and (2) to provide clinicians with the knowledge and skills, and to influence attitudes to maximize their effectiveness in applying this learning within their own clinical setting. In addition, we have suggested that clinicians who study this chapter in depth should be able to demonstrate: (1) an in-depth understanding of diabetes in older people and to analyze their own organization's provision and care, with a view to enhancing

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local care; (2) an understanding of the means by which the diabetes care team in their own organization and key players in their own community can be engaged in improving the quality of diabetes care for older people. Further goals might include the ability to (3) reflect on their personal learning and apply that learning to the approaches they take with team members, other care professionals, patients, and carers; and (4) analyze and evaluate outcomes in the delivery of care to older people who have diabetes, taking into account the roles of other care professionals and the beliefs of people from different ethnic and cultural backgrounds.

EPIDEMIOLOGY, PATHOGENESIS, AND MODES OF PRESENTATION

Within the next decade, it is projected that the number of diabetic individuals in the world will double to 221 million. Several important risk factors (Table 1) are likely to underpin this increase in prevalence such as advancing age of the population, greater numbers of people from ethnic minority backgrounds adopting a "transitional" lifestyle, greater levels of overweight and obesity, and more sedentary lifestyles. From an epidemiological perspective, aging is an important factor: in the United States, the number of people with diabetes aged 75 years and over doubled between 1980 and 1987. In most populations, peak rates are generally found in the sixth decade and, subsequently, although in Pima Indians, the peak rate is between the fourth and fifth decades.

Most developed countries have a prevalence rate of about 17% in white elderly subjects and 25% in nonwhite subjects. The prevalence of white British elderly is only around 9% although the prevalence in nonwhite British elderly is about 25% and the prevalence in British care homes is 25%.

There is an increasing view that diabetes in the elderly has a genetic basis (Meneilly, 2001). Older people with a family history are often more likely to develop this illness as they age. In genetically susceptible people, various factors may increase the likelihood of type 2 diabetes developing. Elderly patients with diabetes have normal hepatic production of glucose, which is in contrast to younger subjects (Meneilly and Ellitt, 1999). In lean elderly subjects, the principal defect appears to be impaired glucose-induced insulin release, while in the obese elderly, resistance to insulin-mediated glucose disposal is the major problem (Meneilly and Ellitt, 1999). Multiple drugs, reduced physical activity, and a diet with low intake of complex carbohydrates also contribute to this increasing prevalence. Further research into discovering the molecular abnormalities in older people with diabetes is warranted.

Table 1 Risk factors for diabetes mellitus in older subjects

- Aged 65 years and over
- People of Asian, Afro-Caribbean, or African origin
- BMI $>27\,kg\,m^{-2}$ and/or large waist circumference
- Those with manifest cardiovascular disease or hypertension with or without hyperlipidemia
- Presentation with a stroke
- Presentation with recurrent infections
- Use of diabetogenic drugs: for example, corticosteroids, estrogens
- A family history of diabetes mellitus
- Those with IGT/IFG

MODES OF PRESENTATION

Diabetes in older people has a varied presentation and may be insidious, which ultimately delays diagnosis (Sinclair, 2001) (Table 2). Detection of diabetes during hospital admissions for other comorbidities or acute illnesses is relatively common, although even when hyperglycemia has been recognized initially, about half the subjects receive no further evaluation for diabetes or treatment (Levetan *et al.*, 1998). Some patients do not have the classic features of either diabetic ketoacidosis or hyperosmolar nonketotic coma but present with a "mixed" disturbance of hyperglycemia (blood glucose levels 15–25 mM), arterial blood pH of 7.2 or 7.3 (not particularly acidotic), and without marked dehydration or change in level of consciousness.

IMPACT OF DIABETES MELLITUS

Older patients with diabetes appear to burden the hospital care system two to three times more than the general population (Damsgaard *et al.*, 1987a) and use primary care services two to three times more than nondiabetic controls (Damsgaard *et al.*, 1987b). This latter primary care study from Denmark indicated that insulin-treated patients accounted for more than half of the service provision, mainly due to chronic vascular disease, with a correspondingly high number of hospital clinic visits. Several UK-based studies

Table 2 Varying presentation of diabetes in older people

Asymptomatic (coincidental finding)	
Classical osmotic symptoms	
Metabolic disturbances	Diabetic ketoacidosis
	Hyperosmolar nonketotic coma
	"Mixed" metabolic disturbance
Spectrum of vague symptoms	Depressed mood
	Apathy
	Mental confusion
Development of "geriatric" syndromes	Falls or poor mobility: muscle weakness, poor vision, cognitive impairment
	Urinary incontinence
	Unexplained weight loss
	Memory disorder or cognitive impairment
Slow recovery from specific illnesses or increased vulnerability	Impaired recovery from stroke
	Repeated infections
	Poor wound healing

have defined the prevalence of elderly patients in hospital diabetic populations. This has ranged from 4.6% (Edinburgh (Harrower, 1980)) to 8.4% (Cardiff (Hudson *et al.*, 1995)).

Several important population-based and community studies have revealed that diabetes in older subjects is associated with considerable morbidity, mainly due to the long-term complications of diabetes. These include the Oxford Study (Cohen *et al.*, 1991), the Poole Study (Walters *et al.*, 1992), the Nottingham Community Study (Dornan *et al.*, 1992), and the Welsh Community Diabetes Study (Sinclair and Bayer, 1998). In the latter study, in subjects aged 65 years, one in three subjects with diabetes had been hospitalized in the previous 12 months (compared with one in six nondiabetic controls). One in four diabetic subjects required assistance with personal care and older people with diabetes had significantly lower levels of health status compared with nondiabetic counterparts. Visual acuity was impaired in 40% of diabetic subjects (compared with 31% controls) and diabetes was found to be associated with an increased risk of visual impairment (OR 1.50 (1.09–2.05)). Factors that were significantly associated with visual loss in diabetic subjects included advanced age, female sex, history of foot ulceration, duration of diabetes, and treatment with insulin.

Diabetic Foot Disease

A recent study from the Netherlands (Van Houtum *et al.*, 1995) identified increasing age and a higher level of amputation as important factors leading to increases in both the period of hospitalization and the associated costs. The 3-year survival following lower extremity amputation is about 50% (Palumbo and Melton, 1985), and in about 70% of cases, amputation is precipitated by foot ulceration (Larsson *et al.*, 1995). The principal antecedents include peripheral vascular disease, sensorimotor and autonomic neuropathy, limited joint mobility (which impairs the ability of older people to inspect their feet), and high foot pressures (Young and Boulton, 2001).

The majority of the elderly diabetic population is at increased risk of developing foot ulcers and various risk factors have been identified (Table 3). Peripheral sensorimotor neuropathy, which is the primary cause or contributory factor in the vast majority of cases, may cause common symptoms of numbness, lancinating and burning pain, "pins and needles", and hyperesthesia, which is typically worse at night, and evidence of high foot pressures leading to gait disturbances, falls, and other foot injuries. The presence of visual loss may exacerbate the consequences of this situation (Cavanagh *et al.*, 1993).

Table 3 Risk factors for foot ulceration in the elderly

Peripheral sensorimotor neuropathy
Automatic neuropathy
Peripheral vascular disease
Limited joint mobility
Foot pressure abnormalities, including deformity
Previous foot problems
Visual loss
History of alcohol abuse

Erectile Dysfunction

After the age of 60 years, erectile dysfunction (ED) may affect 55–95% of diabetic men, while the corresponding figure for nondiabetic counterparts is 50% (Vinik and Richardson, 2001). ED is defined as the inability to attain and maintain an erection satisfactory for sexual intercourse, and is a complex problem involving several mechanisms: vasculopathy, autonomic neuropathy, hormonal dysregulation, endothelia dysfunction, and psychogenic factors have all been implicated. Drug-related causes may be a particular problem in older patients, with thiazide diuretics, cimetidine, β-blockers and spironolactone especially being implicated. An alcohol history must be looked for. ED is evaluated initially with an interview with the patient and sexual partner where appropriate. A comprehensive history, full medical examination, blood testing for diabetes control, lipids, testosterone, and thyroid function tests are necessary. Other more sophisticated tests are available through diabetes ED clinics in most large centers and may involve testing for prolactin, other gonadotrophins, and for nocturnal penile tumescence. For many older patients, extensive testing is often avoided.

Metabolic Comas

Older subjects with diabetes may present with either diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar nonketotic (HONK) coma. HONK occurs predominantly in subjects aged over 50 years. Compared to the young, older subjects with hyperglycemic comas have a higher mortality, have a higher length of stay in hospital following admission, are less likely to have had diabetes diagnosed previously, are more likely to have renal impairment, and require a greater amount of insulin as treatment (Croxson, 2001).

The tendency to hyperosmolarity in HONK comas may be worsened in elderly people, who may not appreciate thirst well, may have difficulty drinking enough to compensate for their osmotic diuresis, and may also be on diuretics. It also appears that hyperosmolarity not only worsens insulin resistance but may also inhibit lipolysis.

Death may be due to the metabolic disturbance and to acute illnesses such as pneumonia and myocardial infarction. The cause of the hyperglycemia may be infection, infarction, inadequate hypoglycemic treatment or inappropriate drug treatment. Residents of care homes are also at increased risk of HONK coma associated with appreciable mortality (Wachtel *et al.*, 1991). Thiazide diuretics and steroids are known to increase blood glucose levels and may precipitate DKA; thiazide diuretics and frusemide may be particularly likely to precipitate HONK coma.

Diabetes-related Disability, Cognitive Dysfunction, and Depression

Diabetes is associated with both functional impairment and disability. The wide spectrum of vascular complications, acute metabolic decompensation, adverse effects of medication, and the effects of the condition on nutrition and lifestyle behavior may all create varying levels of impairment and/or disability. These changes may have adverse rebound effects on vulnerability to other comorbidities, independence, and quality of life.

In the *Health and Retirement Survey (1998)* (>6300 subjects aged 51–61 years at baseline), diabetes was identified as an important predictor of failing to recover from a mobility difficulty over a 2-year follow-up period (Clark *et al.*, 1998). In a systematic literature review of longitudinal studies examining the relationships between various risk factors and functional status outcomes (Stuck *et al.*, 1999), diabetes was one of five conditions (others were hypertension, stroke or TIA, arthritis), which reported 10 or more studies showing a significant association between the risk factor and subsequent functional decline.

In a study examining the relationship between various chronic disease states and disability, a survey from Madrid, Spain (Valderrama-Gama *et al.*, 2002), of 1001 subjects aged 65 years and over living at home showed that diabetes was one of four chronic diseases (the others were cerebrovascular disease, depression/anxiety disorders) that had a strong association with disability (OR, 2.18, 1.24–3.83).

The Welsh Community Diabetes Study (Sinclair and Bayer, 1998) revealed significant excesses in physical (Barthel ADL, $p < 0.0001$; Extended ADL, $p < 0.0001$), cognitive (Mini Mental State Examination (MMSE), $p < 0.001$; Clock Test, $p < 0.001$), mobility (use of walking aid, $p < 0.01$), and visual disabilities (Snellen VA chart, $p < 0.01$) in diabetic subjects assessed by objective measures.

In a cross-sectional survey of community-dwelling older Mexican Americans aged 65 years and over ($n = 2873$), the presence of diabetes predicted poorer performance on tests of lower limb function (Perkowski *et al.*, 1998).

The Third National Health and Nutrition Examination Survey (NHANES III) revealed that diabetes was a major cause of physical disability among subjects aged 60 years and over (Gregg *et al.*, 2000a). Disability in at least one of the physical tasks examined was reported in 63% of diabetic women (controls, 42%) and 39% of diabetic men (controls, 25%) with stronger associations between diabetes and more severe forms of disability. Diabetes was shown to have a two- to threefold increased likelihood of a mobility disorder, with coronary heart disease being a major contributor to this excess disability in both sexes, and stroke being an important contributor among men.

Other studies that have examined this relationship include the *Women's Health and Aging Study (2002)* (Volpato *et al.*, 2002) and the *Study of Osteoporotic Fractures (2002)* (Gregg *et al.*, 2002). In this latter study, in community-dwelling white women aged 65–99 (mean 71.7) years, diabetes was associated with a 42% increased risk of any incident disability and a 53–98% increased risk of disability for specific tasks, for example, walking two to three blocks on level ground, or doing housework.

Cognitive Dysfunction

A decline in cognitive function has been demonstrated in older subjects with type 2 diabetes (Strachan *et al.*, 1997). This can be demonstrated using relatively straightforward tests such as the Folstein MMSE (Folstein *et al.*, 1975) or the Clock Test (Shulman, 2000).

The Zutphen Study (1995) (Kalmijn *et al.*, 1995) and the Kuopio Study (1998) (Stolk *et al.*, 1997) showed that impaired glucose tolerance (IGT) is linked to cognitive dysfunction, and increased serum insulin may be associated with decreased cognitive function and dementia in women. The Rotterdam Study (1996) showed that type 2 diabetes may be associated with both Alzheimer's Disease and vascular dementia (Ott *et al.*, 1996), and the Rochester Study (1997) has demonstrated that the risk of dementia is significantly increased for both men and women with type 2 diabetes (Leibson *et al.*, 1997). In a 7-year follow-up study (The Hisayama Study, 1995), type 2 diabetes was associated with an increased risk of developing vascular dementia (Yoshitake *et al.*, 1995). Poor glucose control may be associated with cognitive impairment that recovers following improvement in glycemic control (Gradman *et al.*, 1993). A recent prospective cohort study involving 682 women with self-reported diabetes (mean age of population sample 72 years) followed up for 6 years indicated a twofold increased risk of cognitive impairment and a 74% increased risk of cognitive decline (Gregg *et al.*, 2000b). Women with diabetes for longer than 15 years had a threefold increase of having cognitive impairment at baseline and a doubling of the risk of decline.

In the Framingham Study (1997), type 2 diabetes and hypertension were found to be significant but independent risk factors for poor cognitive performance (on tests of visual organization and memory) in a large prospective cohort sample followed for over 20 years (Elias *et al.*, 1997). This relationship between cognitive decline and with the presence of either diabetes and hypertension was also observed in the Atherosclerosis Risk in Communities (ARIC) study (2001) in a 6-year follow-up of nearly 11 000 individuals aged 47–70 years at initial assessment (Knopman *et al.*, 2001). Hyperinsulinemia in hypertension has also been shown to be associated with poorer cognitive performance (Kuusisto *et al.*, 1993).

Various benefits may accrue from the early recognition of cognitive impairment in older people with diabetes (Table 4). Depending on its severity, cognitive dysfunction in older diabetic subjects may have considerable implications, which include increased hospitalization, less ability for self-care, less likelihood of specialist follow-up, and increased risk of institutionalization (Sinclair *et al.*, 2000).

Cognitive dysfunction may result in poorer adherence to treatment, worsen glycemic control due to erratic taking of

Table 4 Benefits of early recognition of cognitive impairment in diabetes

- Prompts the clinician to consider the presence of cerebrovascular disease and to review other vascular risk factors
- May be an early indicator of Alzheimer's Disease and provides early access to medication
- Allows patients and families to benefit early with social and financial planning and access to information about support groups and counseling
- Creates opportunities to consider interventions for diabetes-related cognitive impairment: optimizing glucose control; controlling blood pressure and lipids

diet and medication, and increase the risk of hypoglycemia if the patient forgets that he or she has taken the hypoglycemic medication and repeats the dose.

Type 2 Diabetes Mellitus and Depression

Diabetes was found to be significantly associated with depression, independent of age, gender, or presence of chronic disease in one study (Amato *et al.*, 1996), also, the presence of diabetes appears to double the odds of developing depression (Anderson *et al.*, 2001). The finding of depression was the single most important indicator of subsequent death in a group of diabetic patients admitted into hospital (Rosenthal *et al.*, 1998). Failure to recognize depression can be serious since it is a long-term, life-threatening, disabling illness, and has a significant impact on quality of life (Egede *et al.*, 2002). Depression may be associated with worsening diabetic control (Lustman *et al.*, 2000) and decreased treatment compliance. In the *Baltimore Epidemiological Project (1996),* a 13 year follow-up of more than 3400 household residents (about 1 in 7 was aged 65 years and over), major depressive disorder had an adjusted OR of 2.23 for predicting the onset of type 2 diabetes (Eaton *et al.*, 1996).

Importance of Functional Evaluation

Functional evaluation of older people with diabetes mellitus using well-validated assessment tools is an essential step in the initial assessment process. Evaluation of functional status should be a multidisciplinary approach and comprise at least three main areas for measurement: physical, mental, and social functioning. However, further evaluation with measures of self-care abilities and independent living skills (generally assessed by activities of daily living (ADL) tools) are also required. The benefits of functional assessment in the context of diabetes is indicated in Table 5.

Functional assessment is a primary component of Comprehensive Geriatric Assessment (CGA), which is an essential methodology for geriatric medical practice (Kane and Rubenstein, 1998). CGA is crucial at the initial assessment, and helpful in planning care and rehabilitation, and monitoring progress. CGA can be performed in many clinical and

Table 5 Benefits of functional assessment: diabetes-related

- Measures ability to comply with treatment goals and adherence to nutritional advice
- Assesses self-care ability and ability to apply sick-day rules
- Assesses the impact of vascular complications of diabetes, for example, peripheral vascular disease, or neuropathy
- Assesses likely ability to gain from educational interventions
- Assesses need for carer support
- Identifies any quality-of-life issues related to the disease or its treatment

Table 6 Criteria for targeting patients with type 2 diabetes for comprehensive geriatric assessment

- Presence of a "geriatric syndrome": confusional state, depression, falls, incontinence, immobility, pressure sores
- Those with several coexisting morbidities apart from diabetes with complex drug regimens
- Those with disabilities due to lower limb vascular disease or neuropathy requiring a rehabilitation program
- Absence of a terminal illness or dementing syndrome

health-care locations, and not only involves a basic assessment of functional status but also includes various limited screening techniques, evaluation of social and medical problems, instigating initial treatment, and ensuring follow-up. CGA and its variants (including in-home assessment packages) have been demonstrated to reduce mortality (by 14% at 12 months), increase the chance of remaining at home after referral (26% at 12 months), reduce hospital admissions (12% at 12 months), with gains in cognition and physical function having also been observed (Stuck *et al.*, 1993). Not all patients gain from this approach, and targeting is required. Criteria for older subjects with type 2 diabetes who may derive benefit from comprehensive assessment methods with a measure of functional status are shown in Table 6. A summary of the various assessment methods in common use is given elsewhere in this textbook. The authors do not advocate that all practitioners in Europe should adopt CGA as a routine part of their assessment processes, but suggest that functional assessment become a routine measure in older people with type 2 diabetes at diagnosis and at regular intervals thereafter.

Treatment and Care Issues: Learning from Recent Literature

The major aims in the management of older people with type 2 diabetes involve both medical and patient-orientated factors (Table 7). An initial plan for the early evaluation of patients is reflected in Table 8, which should form a framework for instigating the appropriate treatment pathway. An important aim of risk assessment in the general population is to identify subclinical cardiovascular risk, which may be the principal cause of undetected functional impairment or frailty in older people. Coronary risk charts are often based on Framingham data (Wilson *et al.*, 1998; Menotti *et al.*, 2000) and can be used to identify either 5- or 10-year event rates, but it is important to note that cardiovascular-risk data are based generally on populations of individuals

Table 7 Major aims in managing older people with diabetes

Medical	Patient-orientated
Freedom from hyperglycemic symptoms	Maintain general well-being and good quality of life
Prevent undesirable weight loss	Acquire skills and knowledge to adapt to lifestyle changes
Avoid hypoglycemia and other adverse drug reactions	Encourage diabetes self-care
Estimate cardiovascular risk as part of screening for and preventing vascular complications	
Detect cognitive impairment and depression at an early stage	
Achieve a normal life expectancy for patients where possible	

Table 8 Care plan for initial management of diabetes in an elderly person

1. Establish realistic glycemic and blood pressure targets
2. Ensure consensus with patient, spouse or family, general practitioner, informal carer, community nurse, or hospital specialist
3. Define the frequency and nature of diabetes follow-up
4. Organize glycemic monitoring by patient or carer
5. Refer to social or community services as necessary
6. Provide advice on stopping smoking, increasing exercise, and decreasing alcohol intake

up to a maximum age of 74 years only. In a large proportion of older people with type 2 diabetes, excess cardiovascular risk is evident and active intervention should be considered.

A summary of the therapeutic areas for intervention and the relevant evidence base is provided in Table 9, and a table indicating the main types of insulin regimes employed is given in Table 10. The treatment algorithm that should be used as a framework for glucose regulation in older people with type 2 diabetes is shown in Appendix 1. In the United Kingdom, the license for thiazolinediones (TZD) (pioglitazone and rosiglitazones) has recently been modified to allow "triple" therapy (a TZD and both a sulphonylurea and metformin to be coprescribed).

Appendix 1: Algorithm for Glucose regulation based on reference – European Diabetes Working Party for Older People, 2001–2004

On the basis of these studies and interpretation of the likelihood that older people with type 2 diabetes may benefit (derived from the European Diabetes Working Party for Older People, 2001–2004), a number of major recommendations on therapy can be made.

Glucose Regulation

The management of blood glucose must form part of a multifaceted approach to dealing with the metabolic disorder of type 2 diabetes in older people since most patients have evidence of other cardiovascular-risk factors and at least half are likely to satisfy the criteria for the metabolic syndrome proposed by a WHO Expert Committee in 1998 (Alberti and Zimmet, 1998) and more recently by the International Diabetes Federation (Alberti and Zimmet, 2005).

While there is now overwhelming evidence that the level and duration of glycemia influences the development of diabetes-related complications, specific studies in older subjects (>70 years) with type 2 diabetes are lacking.

The majority of the studies conducted in older populations have involved patients of Caucasian ancestry affected by type 2 diabetes. The applicability of these results to the elderly type 1 diabetic patient or to the non-Caucasian type 2 diabetic patient remains to be assessed. However, no randomized controlled trials assessing the impact of achieving optimal glucose control on primary prevention of cardiovascular outcomes are available in the elderly diabetic patient.

Recommendations

The following represent some of the more important recommendations on glucose regulation taken from the European Guidelines (European Diabetes Working Party for Older People, 2001–2004):

1. At initial assessment and annually thereafter, older patients with type 2 diabetes should have a cardiovascular-risk assessment and evaluation of both microvascular and macrovascular complications. Evidence level 2++; Grade of recommendation C. *Evidence in subjects older than 75 years is lacking and a lower Grade of recommendation (D) may be applicable.*
2. For older patients with type 2 diabetes, with single system involvement (free of other major comorbidities), a target HbA1c (DCCT aligned) range of 6.5–7.5% and a fasting glucose range of 5–7.0 mmol l^{-1} should be aimed for. *The precise target agreed will depend on existing cardiovascular risk, presence of microvascular complications, and ability of individual to self-manage.*
3. For frail (dependent; multisystem disease; care home residency including those with dementia) patients where the hypoglycemia risk is high and symptom control and avoidance of metabolic decompensation is paramount, the target HbA1c range should be >7.5 to ≤8.5%, and the fasting glucose range >7 to ≤9.0.
4. Glibenclamide should not be prescribed for newly diagnosed cases of type 2 diabetes in older adults (>70 years) because of the marked risk of hypoglycemia.
5. In older adults with diabetes, the use of premixed insulin and prefilled insulin pens may lead to a reduction in dosage errors and an improvement in glycemic control.
6. Where the risk of hypoglycemia is considered moderate (renal impairment, recent hospital admission) to high (previous history, frail patient with multiple comorbidities, resident of a care home) and a sulphonylurea is considered, use an agent with a lower hypoglycemic

Table 9 Treatment targets and intervention studies for elderly diabetic patients

Blood glucose levels	Blood pressure	Blood lipid levels	Aspirin use
No specific studies in older people with diabetes	UKPDS: $\leq$140/80 mmHg (not based on older subjects)	Few studies in older people with diabetes	Antiplatelet Trialists Collaboration: 75–325 mg/day reduced major cardiovascular events in high-risk patients by 25%; NNT 26 (17–66)
	A 10 mmHg (systolic) and 5 mmHg (diastolic) fall in blood pressure in the intensive group resulted in a 24% decrease in risk of any diabetes-related endpoint, 44% reduction in risk of stroke, and 37% risk reduction in macrovascular disease	PROSPER: pravastatin for 3.2 years resulted in a 1.0 mmol l^{-1} fall in LDL cholesterol and a modest RR of 15% for the primary composite outcome; no change in the decline of cognition was seen	
UKPDS: HbA1c <7%; fasting blood glucose <7 mmol l^{-1}	HOT Study: diastolic lowering to $\leq$83 mmHg	Heart Protection Study:	HOT Study: 75 mg/day reduced major cardiovascular events by 15% and myocardial infarction by 36%; stroke was unaffected
A reduction in HbA1c of 0.9% between the study groups resulted in a 12% reduction in risk of any diabetes-related endpoint, but no significant reduction in major cardiovascular events	A systolic BP less than 80 mmHg resulted in a 51% reduction in major cardiovascular events compared with the target group of equal to or less than 90 mmHg	Treatment with simvastatin for 5 years resulted in a fall of 1.0 mmol l^{-1} of HDL cholesterol and a 25% RR in incidence of first nonfatal or fatal stroke	
	SHEP Study: systolic <150 mmHg	LIPID, CARE, 4S, VA-HIT studies: Total cholesterol <5 mmol l^{-1}	
	A 34% reduction in risk of cardiovascular disease in the actively treated group was observed	HDL cholesterol >1.0 mmol l^{-1}	
		Triglycerides <2.0 mmol l^{-1}	
	Syst-Eur Study: systolic BP <160 mmHg	ALLHAT-LLT : 4.9 years of pravastatin showed modest reductions in cholesterol only and did not reduce mortality or coronary heart disease	
	A fall of 23/7 mmHg in the actively treated group was associated with a 55% decrease in mortality, and a 69% reduction in cardiovascular end-points		
	MICRO-HOPE was not target driven but showed highly significant reductions in cardiovascular risk with ramipril for 4.5 years (22% RR in myocardial infarction; 33% RR in stroke). LIFE study: 24% RRR in primary composite endpoint of cardiovascular mortality, stroke, and all myocardial infarction after minimum 4 years of losartan treatment compared with atenolol. ALLHAT showed that after a mean of 4.9 years of follow-up, there were no significant differences in outcome between chlorthalidone, lisinopril, or amlodipine.	ASCOT-LLA: study stopped after 3.3 years showing highly significant benefits of atorvastatin; a fall of 1.0 mmol l^{-1} of HDL cholesterol gave a 36% RR of primary end point but subgroup analysis of diabetic patients showed no benefit	

potential, for example, gliclazide, tolbutamide. *Risk of hypoglycemia: glibenclamide > glimepiride > gliclazide > tolbutamide* (Schernthaner *et al.*, 2004).

7. Optimal glucose regulation may help maintain cognitive performance, improve learning and memory, and may help to minimize symptoms of mood disorder in patients with depression.
8. Optimizing glucose control may help maintain functional status and may decrease the risk of falls.

Blood Pressure Regulation

Adverse cardiovascular outcomes (stroke and coronary heart disease) are clearly and directly related to increasing levels of blood pressure. In nondiabetic individuals, this is more pronounced in men than in women; antihypertensive treatment has been shown to produce worthwhile reductions in risk, especially in high-risk patients such as those with diabetes or the elderly, where the absolute benefit is greater.

Table 10 Practice orientated guidelines for insulin treatment in older people

	Indications	Advantages	Disadvantages
Once-daily insulin	Frail subjects Very old (>80 years) Symptomatic control	Single injection Can be given by carer or district nurse	Control usually poor Hypoglycemia common
Twice-daily insulin	Preferred if good glycemic control Suitable for type 1 diabetes	Low risk of hypoglycemia Easily managed by most older diabetic people	Normoglycaemia difficult to achieve Fixed meal times reduce flexibility Expensive
Basal/bolus insulin	Well-motivated individuals Can reduce microvascular complications	Enables tight control For acute illness in hospital Flexible meal times	Frequent monitoring required to avoid hypoglycemia
Insulin plus oral agents	If glycemic control is unsatisfactory with oral agents alone To limit weight gain in obese subjects	Limits weight gain by reducing total daily insulin Increased flexibility	May delay conversion to insulin in thin or type 1 patients

Increasing age is also an independent risk factor for cardiovascular disease even in low-risk individuals with normal blood pressure.

There is an age-related increase in systolic blood pressure but diastolic blood pressure tends to peak at 66–69 years of age and then falls. A large percentage of older patients will have isolated systolic hypertension where the diastolic blood pressure is not raised. Hypertension is also associated with the insulin resistance syndrome in older subjects, and in diabetic subjects who develop microalbuminuria, thus increasing the risk of nephropathy and end-stage renal failure.

Diagnosis of Hypertension in Diabetes

Established hypertension exists when blood pressure readings are persistently above 140/90 mmHg (Korotkov 1-V) over at least 1 month or when the diastolic blood pressure exceeds 110 mmHg, or when there is evidence of target organ damage. As the presence of diabetes imposes a greater cardiovascular risk, it is reasonable to have lower blood pressure thresholds for treatment in these subjects, but most guidelines indicate 140/90 mmHg as the treatment threshold with lower target values for those with diabetes. Four national/international sets of guidelines for hypertension have recently been published, and these can be downloaded from the relevant website or author address: for example, http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf

Each major guideline has a section on the management of hypertension in diabetes, but age-modification of targets and thresholds is not detailed. In addition, there have been no specific randomized controlled trials in older subjects with type 2 diabetes and hypertension that have directly investigated the benefits and outcomes of treating blood pressure to target.

On the basis of an analysis of these sets of guidelines and the relevant clinical evidence base, the European Diabetes Working Party for Older People, 2001–2004 have set targets described in the clinical recommendations below.

Recommendations

1. The threshold for treatment of high blood pressure in older subjects with type 2 diabetes should be 140/80 mmHg or higher present for more than 3 months and measured on at least three separate occasions during a period of lifestyle management advice (behavioral: exercise, weight reduction, smoking advice, nutrition/dietary advice).
   This decision is based on the likelihood of reducing cardiovascular risk in older subjects balanced with issues relating to tolerability, clinical factors, and disease severity, and targets likely to be achievable with monotherapy and/or combination therapy, and with agreement with primary care colleagues. As most subjects aged 70 years and over with type 2 diabetes and hypertension will already by definition have a high CV risk, no additional weighting for extent of CV risk has been applied. A lower value of blood pressure should be aimed for in those who are able to tolerate the therapy and self-manage, and/or those with concomitant renal disease.
2. For frail (dependent; multisystem disease; care home residency including those with dementia) patients, where avoidance of heart failure and stroke may be of greater relative importance than microvascular disease, an acceptable blood pressure is <150/<90 mmHg.
3. In patients with type 2 diabetes and a recent acute stroke (within 4 weeks), consideration should be given to an active treatment approach of raised blood pressure and lipids, vascular prophylaxis with antiplatelet therapy (aspirin), and optimizing blood glucose control to reduce the rate of recurrent stroke.
   The PROGRESS Study (2001) (PROGRESS Collaborative Group, 2001) *has shown large absolute risk reductions* ($NNT = 11$) with the ACE inhibitor, perindopril (in combination with the diuretic indapamide) in patients surviving from a stroke.
4. Optimal blood pressure regulation should be aimed for to help maintain cognitive performance and improve learning and memory.

Guidelines on Specific Treatment Strategy and Medication

5. In older patients with a sustained blood pressure (≥140/80 mmHg) and in whom diabetic renal disease is absent, first-line therapies can include: use of ACE inhibitors, angiotensin II receptor antagonists, long-acting calcium channel blockers, β-blockers, or thiazide diuretics. *In terms of comparable efficacy, safety, and cost-effectiveness, treatment with a thiazide diuretic may be preferred as the first-line therapy. Short-acting calcium channel blockers should not be used.*
   The choice of antihypertensive agent should take into account metabolic factors, the presence or not of renal impairment or cardiovascular disease, and the likelihood of causing postural hypotension, which may have particularly adverse consequences in older subjects. At the present time, α-adrenoreceptor blockers have no special indications in the treatment of hypertension in diabetes and may be harmful. The use of low-dose fixed combinations of two agents such as a thiazide diuretic plus an ACE inhibitor may also have additional advantages (*European Society of Cardiology, 2003*).
6. In older patients with a sustained blood pressure (≥140/80 mmHg) with microalbuminuria or proteinuria, treatment with an ACE inhibitor is recommended. *An angiotensin II receptor antagonist may be considered as an alternative to an ACE inhibitor where the latter class of drug is not tolerated or contraindicated.*

Lipid Regulation

Coronary heart disease (CHD) is the most common cause of mortality in type 2 diabetes and remains the principal challenge for older people with this metabolic disorder. Elevated levels of blood lipids is an independent risk factor for CHD, and there is published evidence of cardiovascular benefit using a lipid-lowering regimen, although this is limited in older subjects. As part of a multifaceted approach to the metabolic consequences of diabetes, effective management of blood lipids is essential to optimize vascular outcomes. Attention to risk factors such as smoking and other metabolic derangements such as blood pressure is also of paramount importance.

Cardiovascular Risk Assessment

Categories of risk based on lipoprotein levels in adults with diabetes mellitus according to most international recommendations are given without modification concerning age and duration of diabetes. Since general cardiovascular risk is increasing with both variables, especially age, cardiovascular risk in older diabetic patients is generally underestimated according to non-age-specific risk assessment. One approach is calculating global risk in individuals without overt cardiovascular disease (primary prevention) using the Framingham Heart Study equation or the WHO-ISH risk table (Kannel and McGee, 1979; Winocour and Fisher, 2003). Another method relies on a calculation of individual risk on the basis of epidemiological data. For the purposes of this chapter, "high" and "low" cardiovascular risks are described in Table 11.

Table 11 High and low 10-year cardiovascular risk definition

High risk
Has manifest cardiovascular disease (history of symptoms of coronary heart disease, stroke, or peripheral vascular disease) or a coronary (Risk Assessment Chart)[a] event risk of >15%;
Low risk
Does not manifest cardiovascular disease and whose coronary event risk[a] is ≤15%

Adapted from NICE (UK).
[a]On the basis of Joint British recommendations: (BMJ 2000; 320:705–708).

Several large-scale clinical trials have shown benefit with statin therapy of high-risk (cardiovascular-risk) individuals, and these included a proportion of older subjects. They have also demonstrated that these agents are well tolerated and safe, with no consistent additional risk of cancer or nonvascular morbidity or mortality. Previous statin trials indicate that the absolute reduction in LDL cholesterol produces similar proportional risk reductions in older and younger people.

Target Values for Total Cholesterol and LDL Cholesterol

Target values for treatment decisions based on total/LDL cholesterol level in adults with diabetes should be adopted without age limitation, especially in otherwise healthy and independent individuals ("single disease model"). Categories of risk are available depending on lipid levels (*American Diabetes Association criteria*), although treatment decisions based on an estimation of a 10-year cardiovascular (CV) risk may also be used (*National Institute for Clinical Excellence* (*NICE*) guidelines). Additional measurement of HDL cholesterol provides a more accurate assessment of CV risk because of the inverse relationship between CV risk and HDL cholesterol. These recommendations may not be directly applicable for old (>75 years) and very old (>85) patients because of the presence of multiple comorbidities, high dependency levels, care home residency and/or end-stage dementia ("frailty model") (Sinclair, 2000). In these situations, limited life expectancy or competing noncardiovascular causes for mortality (for example, cancer or infections), may mask or remove any benefit from lipid lowering and increase the likelihood of adverse drug reactions. Lipid regulation on an individual basis is required.

Initial Assessment of the Older Patient

Initial assessment should include enquiry about alcohol consumption, presence or not of renal, thyroid, or liver

disease. An estimate of the level of physical activity is important, and overweight (and obese) subjects should be encouraged to lose weight and given exercise advice relative to their capability and overall functional status. Dietary modification may be of benefit as part of a revised lifestyle plan.

Assessments of total cholesterol, HDL-C, LDL-C, and triglycerides are usually required as part of the annual review process (Grade of recommendation C) and should preferably be fasting samples at the start of treatment for those with abnormal profiles.

For these *Guidelines*, an abnormal lipid profile in older subjects can be regarded as a total cholesterol of 5.0 mmol l^{-1} or higher, a LDL cholesterol of 3.0 mmol l^{-1} or higher, or triglycerides of 2.3 mmol l^{-1} or higher.

In general, pharmacological therapy of abnormal lipid levels should not be delayed or ignored because of the age of the individual and should be regarded as part of the routine interventions in managing older people with diabetes. In patients prescribed a statin, the clinician must always be alert to the potential side effects of treatment including reversible myositis and myopathy.

RECOMMENDATIONS

Some of the principal recommendations related to the use of statins and fibrates in older people with diabetes can be summarized as follows:

1. Statin therapy is well tolerated and can be safely used in older subjects with diabetes.
2. Primary Prevention: in subjects with no history of cardiovascular disease, a statin should be offered to patients with an abnormal lipid profile if their 10-year cardiovascular risk is >15%. *There is little evidence at the present time for primary preventative strategies for subjects aged greater than 80 years.*
3. Secondary Prevention: a statin should be offered to patients with an abnormal lipid profile who have proven cardiovascular disease.
4. A fibrate should be considered in patients with an abnormal lipid profile who have been treated with a statin for at least 6 months but in whom the triglyceride level remains elevated (≥2.3 mmol l^{-1}).
5. A fibrate should be considered in patients with proven cardiovascular disease who have isolated high triglyceride levels (≥2.3 mmol l^{-1}).
6. For patients with cardiovascular disease who have persistent raised fasting triglycerides above 10 mmol l^{-1}, referral to a specialist lipid or diabetes clinic is recommended.

CARE HOME DIABETES

Within the European Union, the structure and provision of diabetes care within residential care homes is highly variable. High-quality diabetes care is unlikely to be present in the majority of care homes with many underlying reasons accounting for this rather dismal situation. These include organizational difficulties within the institutions, lack of clarity relating to medical and nursing roles and responsibilities, funding issues, and a lack of a coherent professional framework for delivering diabetes care.

Table 12 Concerns and deficiencies in diabetes care – institutional facilities

- Increasing number of institutionalized diabetic elderly
- Lack of specialist medical follow-up
- Inadequate dietary care and lack of structured health professional input
- Lack of individualized diabetes care plans
- Lack of educational and training programs for care home staff
- No major intervention studies assessing the benefits of metabolic control and/or educational strategies
- Few national standards of diabetes care

Several deficiencies of diabetes care within institutional settings have been identified (see Table 12). They represent a series of concerns that highlight the need for standards of diabetes care to be established.

A recent UK study highlighted problems in diabetes care delivery (Sinclair *et al.*, 1997). This study involved a medical examination of and semistructured interview with residents with diabetes of long-term care facilities in South Wales, which revealed a prevalence of known diabetes of 7.2%. A third of residents with diabetes tested had a HbA1c >11.0%, 40% of those on oral hypoglycemic agents were taking the long-acting sulphonylureas, chlorpropamide or glibenclamide, and none of the homes had a policy in place for recording hypoglycemic events. Only 8 out of 109 diabetic residents had a specialist follow-up arranged. Other health professional input was minimal.

More recently, a retrospective, cross-sectional study using the *SAGE* (Systematic Assessment of Geriatric Drug Use via Epidemiology) database reported that 47% of residents with diabetes were receiving no antidiabetic medication and that the presence of advanced age, being black, having a low ADL score, cognitive impairment, and a low body mass index (BMI) (<21) increased the likelihood of not receiving antidiabetic medication (Spooner *et al.*, 2001).

These and other studies indicate that diabetic residents of care homes appear to be a highly vulnerable and neglected group, characterized by a high prevalence of macrovascular complications, marked susceptibility to infections (especially skin and urinary tract), increased hospitalization rates, and high levels of physical and cognitive disability. Communication difficulties (because of dementia and/or stroke) lead to unmet care needs and lack of self-care abilities, and water and electrolyte disturbances increase the risk of metabolic decompensation.

PREVALENCE OF DIABETES MELLITUS IN CARE HOMES

A number of prevalence surveys of diabetes within care homes provide estimates of between 7.2 and 26.7%, depending on the method used for identifying those with diabetes.

Additional information from the population-based SAGE database in the United States (Spooner *et al.*, 2001), which involves five states and evaluation of all residents using the 350-item minimum data set (MDS), revealed a prevalence of diabetes of 18.1%, which decreased as age increased (e.g. 27% in those aged 65–74 years compared with 13% in those aged 85 years and over). The highest prevalence was recorded in Hispanics (28%) and black non-Hispanics (26%).

In a recent study of screening care home residents for diabetes using two-point (fasting and 2-hour postglucose challenge values) oral glucose tolerance tests, the overall prevalence rate (newly diagnosed + known diabetes) was calculated as 26.7%, with a rate of 30.2% for impaired glucose tolerance (Sinclair *et al.*, 2001). The majority of diagnoses were made according to the 2-hour values rather than the fasting glucose levels, but it may be argued that these residents are at greater cardiovascular risk and may benefit from an intervention.

Intervention Studies in Care Homes

Few intervention studies of diabetic residents of care homes have been reported. In Denver, Colorado, USA, an educationally based intervention study in 29 nursing homes consisted of providing workshops and follow-up consultations to administrative staff designed to assist in developing and implementing diabetes care policies and procedures (Hamman *et al.*, 1984). By 1 year, a significant increase in the adherence to previously published diabetes care plans was observed, and although hospital admission rates had not changed, total bed days were smaller. Affiliation to a university-based academic faculty may also lead to an improvement in outcomes for nursing home residents with diabetes. In a study from California, USA, significantly better glycemic control was observed in a small group ($n = 47$) of nursing home diabetic residents (mean age 81 years; HbA1 8.9% on oral agents) compared with a group of ambulatory diabetic residents (mean age 66 years; 11.8% on oral agents) with only a small number of associated hypoglycemic events (Mooradian *et al.*, 1988).

A small study (18 subjects) in Stanford, USA (Coulston *et al.*, 1990), demonstrated that residents of care homes who are in good health, and in good glycemic control (mean fasting glucose of 7 mmol l^{-1}), that the introduction of a "regular diet" compared with the standard "diabetes" diet had minimal effects on glucose control, lipid levels, and body weight over a 16-week period. In a small study of Italian nursing home residents with diabetes ($n = 30$; mean age 77 years), the substitution with insulin *lispro* treatment for 4 months as part of a series of treatment periods using regular insulin led to a significant decrease in mean daily blood glucose, HbA1c (7.6 vs 8.5% (regular), $p < 0.01$), and hypoglycemic episodes (Velussi, 2002).

More recently, in an academic nursing home facility, a 5-month educational program on dyslipidemia treatment aimed at physicians and nurse practitioners led to an improvement in the frequency of prescribing lipid-lowering therapy (Ghosh and Aronow, 2003). This New York–based study demonstrated an increase from 26 to 67% for diabetic residents.

Table 13 Importance of early detection of diabetes mellitus in care homes

- Improved metabolic control may improve cognition, decrease the risk of hyperosmolar coma, and lessen osmotic symptoms
- Earlier treatment may delay vascular complications and reduce disability
- Knowledge of diagnosis of diabetes prompts physician to be alert to diabetes-related complications, for example, hyperosmolar coma
- Earlier dietary intervention may delay treatment (and therefore limit adverse drug reactions) with oral agents
- Treatment can reduce symptoms and may increase quality of life and functional well-being

Rationale for Early Detection of Diabetes Mellitus in Care Homes

In view of the absence of clinical trial data, the rationale for early detection of diabetes mellitus has not been justified. However, each resident has a right to active investigation and intervention (where appropriate) and it is feasible that several benefits may accrue from such a policy (Table 13):

Aims of Care for Diabetic Residents

Residents with diabetes in care homes should receive a level of comprehensive diabetes care commensurate with their health and social needs. The two most important *aims of care according to the European Guidelines* (European Diabetes Working Party for Older People, 2001–2004) are as follows:

(1) To maintain the highest degree of quality of life and well-being without subjecting residents to unnecessary and inappropriate medical and therapeutic interventions.
(2) To provide support and opportunity to enable residents to manage their own diabetes condition where this is a feasible and worthwhile option.

Other crucial objectives of care include: (3) achieving a satisfactory (but optimal) level of metabolic control that reduces both hyperglycemic lethargy and hypoglycemia, and allows the greatest level of physical and cognitive function; (4) optimizing foot care and visual health that promotes an increased level of mobility, reduced risk of falls, and prevents unnecessary hospital admissions; (5) to provide a well-balanced nutritional and dietetic plan that prevents weight loss and maintains nutritional well-being; and (6) to effectively screen for diabetic complications regularly especially eye disease, peripheral neuropathy, and peripheral vascular disease that predispose to foot infection and ulceration.

Diabetes Care Home Provision – Modern Approaches

Several important strategies to improve the quality and outcomes of diabetes care within these settings have been

proposed (BDA, 1999). A series of recommendations have been proposed by the European Diabetes Working Party on Older People:

Recommendations

1. At the time of admission to a care home, each resident requires to be screened for the presence of diabetes.
2. Each resident with diabetes should have an individualized diabetes care plan with the following minimum details: dietary plan, medication list, glycemic targets, weight, and nursing plan.
3. Each resident with diabetes should have an annual review where the medical component is undertaken either by a general practitioner, geriatrician, or hospital diabetes specialist.
4. If required, each resident with diabetes should have reasonable access to the following specialist services: podiatry, optometric services, hospital diabetes foot clinic, dietetic services, and diabetes specialist nurse.
5. Each care home with diabetes residents should have an agreed Diabetes Care Policy or Protocol that is regularly audited.

CONCLUSIONS

Diabetes mellitus in older subjects represents an often complex interplay between aging, functional loss, vascular disease, and the metabolic syndrome. Type 2 diabetes may be a potent cause of both premature and unsuccessful aging. Functional assessment and estimation of disability levels form part of the important screening process in older adults with diabetes. There is increasing evidence that improving metabolic control will have important benefits even in older subjects. The recently published European Guidelines on managing older people with type 2 diabetes represents an important step forward in the provision of clinical guidance of this often neglected but highly prevalent group. We should encourage more research by randomized controlled design studies that examine the benefits of metabolic intervention and explore the value and cost-effectiveness of different diabetes care models for managing the frail elderly diabetic subject.

KEY POINTS

- Diabetes mellitus has a high prevalence in aging populations and is associated with specific metabolic alterations.
- Cardiovascular disease is a major cause of morbidity and premature disability in older subjects with type 2 diabetes.
- Functional impairment remains a major challenge for clinicians managing older people with diabetes, and a working knowledge of assessment methodology is helpful in planning therapies.
- Cognitive dysfunction, depressive illness, and falls are important complications and strategies to prevent them require being included in the overall management plan.
- Further research (both basic science and clinical) into the pathogenesis and treatment of type 2 diabetes in senior citizens is urgently required.

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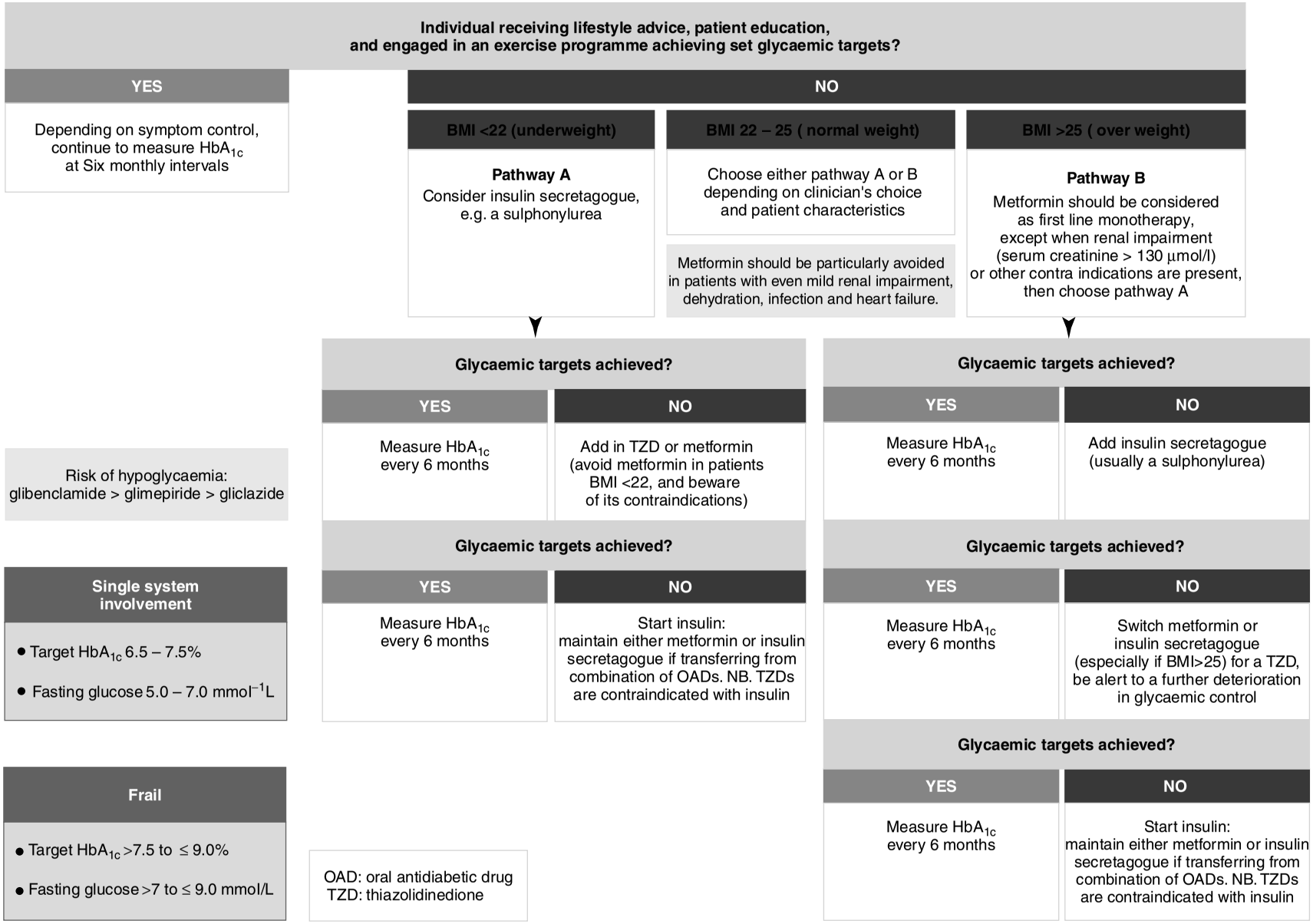
APPENDIX


Individual receiving lifestyle advice, patient education, and engaged in an exercise programme achieving set glycaemic targets?
YES
Depending on symptom control, continue to measure HbA1c at Six monthly intervals
NO
BMI <22 (underweight)
Pathway A
Consider insulin secretagogue, e.g. a sulphonylurea
BMI 22 – 25 (normal weight)
Choose either pathway A or B depending on clinician's choice and patient characteristics
Metformin should be particularly avoided in patients with even mild renal impairment, dehydration, infection and heart failure.
BMI >25 (over weight)
Pathway B
Metformin should be considered as first line monotherapy, except when renal impairment (serum creatinine > 130 µmol/l) or other contra indications are present, then choose pathway A
Glycaemic targets achieved?
YES
Measure HbA1c every 6 months
NO
Add in TZD or metformin (avoid metformin in patients BMI <22, and beware of its contraindications)
Glycaemic targets achieved?
YES
Measure HbA1c every 6 months
NO
Start insulin: maintain either metformin or insulin secretagogue if transferring from combination of OADs. NB. TZDs are contraindicated with insulin
Glycaemic targets achieved?
YES
Measure HbA1c every 6 months
NO
Add insulin secretagogue (usually a sulphonylurea)
Glycaemic targets achieved?
YES
Measure HbA1c every 6 months
NO
Switch metformin or insulin secretagogue (especially if BMI>25) for a TZD, be alert to a further deterioration in glycaemic control
Glycaemic targets achieved?
YES
Measure HbA1c every 6 months
NO
Start insulin: maintain either metformin or insulin secretagogue if transferring from combination of OADs. NB. TZDs are contraindicated with insulin
Risk of hypoglycaemia: glibenclamide > glimepiride > gliclazide
Single system involvement
• Target HbA1c 6.5 – 7.5%
• Fasting glucose 5.0 – 7.0 mmol−1L
Frail
• Target HbA1c >7.5 to ≤ 9.0%
• Fasting glucose >7 to ≤ 9.0 mmol/L
OAD: oral antidiabetic drug
TZD: thiazolidinedione

PART III

Medicine in Old Age

Section 11

Urogenital Disorders

Gynecology and the Older Patient

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Based in part on the chapter 'Gynaecology' by Jarmila Wiener and Joan Andrews, which appeared in *Principles and Practice of Geriatric Medicine*, 3rd Edition.

INTRODUCTION

The aging population presents a major challenge for the society and the health services worldwide. It is a reflection of longer life expectancy because of improvements in living standards and health care and falling mortality. In the United Kingdom, people aged 60 and above had outnumbered children under 16 (21 compared to 20%). By 2026, nearly 28% of the UK population will be over the age of 60 (Dening and Barapatre, 2004). Women constitute a majority of the elderly population as they outlive males by 5–7 years. Sixty-five years is the accepted starting point of old age, that is, the official retirement age in the western world. Female aging is unique in that it represents a combination of the aging processes and hormone deficiency. This chapter reviews the problems of the old-age gynecology patient with reference to the common symptomatology, the menopause, hormone replacement therapy, sexuality, and malignancies.

EFFECT OF AGING ON THE GENITAL TRACT

Vulva and Vagina

The lower genital tract undergoes atrophic changes with loss of connective tissue elasticity and thinning of the mucosa. There is a decline in intracellular glycogen production in the vagina, leading to a decrease in lactobacillae and lactic acid and an increase in the vaginal pH from acid to alkali. These changes lead to an increase in colonization by pathogenic bacteria and infective vaginitis. Senile or atrophic vaginitis is also common due to loss of vaginal tissue elasticity and shrinkage of the vagina. This can lead to postmenopausal bleeding and dyspareunia.

Cervix and Uterus

The cervix becomes atrophic and the ectocervix becomes flush with the vaginal vault. The squamocolumnar junction of the cervix recedes into the endocervical canal and it becomes difficult to obtain an accurate representative cervical smear. The uterus undergoes atrophy of myometrium and the uterine body becomes smaller. The endometrium becomes thinner and the glands become inactive.

Ovary and Fallopian Tube

In the perimenopausal years, the few remaining primordial follicles become unresponsive to the pituitary gonadotrophins and therefore the estrogen secretion falls. The ovaries become smaller and more wrinkled. The fallopian tubes become shorter with muscle replaced by fibrous tissue.

Pelvic Floor

Pelvic floor muscle weakness is due to the combined effects of estrogen withdrawal and age. This is compounded by the mechanical effects of previous childbirth. The endopelvic fascia surrounding both the genital tract and urinary tract atrophies. The fascial condensations of cardinal and uterosacral ligaments also atrophy, leading to an increased incidence of genital prolapse as age increases. In the elderly, chronic cough, constipation, and increased intra-abdominal pressure are other factors contributing to this.

Urethra and Bladder

Both the urethra and trigone of the bladder are sensitive to estrogen as they have estrogen receptors and there is deterioration in structure and function as a woman ages. The urethral

Principles and Practice of Geriatric Medicine, 4th Edition. Edited by M.S. John Pathy, Alan J. Sinclair and John E. Morley.
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lumen becomes more slit shaped and the folds become coarser. The mucosal lining changes from transitional in the proximal two-thirds to nonkeratinizing squamous epithelium (Stanton, 1997). Urethral closure becomes less competent. There is a reduction in detrusor contraction power during voiding and the contractions fade shortly after initiation of voiding. The bladder capacity is also reduced in the elderly. All these features account for a greater prevalence of urinary incontinence in the elderly. Withdrawal of estrogen may lead to a high prevalence of urinary tract infection in the elderly, which is aggravated by voiding difficulty and may lead to stress incontinence, urge incontinence, frequency, urgency, and nocturia (Dantas *et al.*, 1981).

HORMONAL CHANGES

In premenopausal women, ovarian function is controlled by the two pituitary gonadotrophins, follicle stimulating hormone (FSH) and luteinising hormone (LH). These are controlled by the pulsastile secretion of gonadotrophin releasing hormone (GnRH) from the hypothalamus. The ovary has the maximum number of oocytes at 20–28 weeks of intrauterine life. There is a reduction in these cells from midgestation onwards and the oocyte stock becomes exhausted in the perimenopausal age-group. The ovary gradually becomes less responsive to gonadotrophins and this results in a gradual increase in FSH and LH levels, and a fall in estradiol concentration. As ovarian unresponsiveness becomes more marked, cycles tend to become anovulatory and complete failure of follicular development occurs. Estradiol production from the granulosa and theca cells of the ovary ceases and there is insufficient estradiol to stimulate the endometrium; amenorrhea ensues. FSH and LH levels are persistently elevated. FSH level >30 IU/l is generally considered to be the postmenopausal range.

THE MENOPAUSE AND THE HRT (HORMONE REPLACEMENT THERAPY)

Menopause is defined as the permanent cessation of menstruation. The word menopause is derived from the greek words *menos* (the month) and *pausos* (ending). It is a retrospective diagnosis since a woman is menopausal only after 12 months of amenorrhea. The average age of menopause is 51 years and the female life expectancy is now over 80 years. Postmenopausal women spend more than 30 years in a profound estrogen-deficient state. The early symptoms of menopause are vasomotor symptoms, mainly hot flushes, night sweats, insomnia, and so on. The long-term consequences are osteoporosis, urogenital atrophy, and connective tissue atrophy.

Vasomotor symptoms

There is good evidence from randomized placebo-controlled studies that estrogen is effective in treating hot flushes and improvement is noted within four weeks (MacLennan *et al.*, 2001). Relief of vasomotor symptoms is the commonest indication for HRT and is used for less than 5 years. It must be remembered that as old age approaches, the symptoms of the menopause appear to resolve spontaneously, though of course, the risk of osteoporosis increases.

Osteoporosis

Osteoporosis has been defined by WHO as a "disease characterized by low bone mass and micro-architectural deterioration of bone tissues, leading to enhanced bone fragility and a consequent increase in fracture risk". In postmenopausal women, there is an accelerated bone loss, so that by the age of 70 years, 50% of bone mass is lost. The risk factors for osteoporosis are family history, low body mass index (BMI), cigarette smoking, alcohol abuse, early menopause, sedentary lifestyle, corticosteroids, and so on. Fractures are the clinical consequences of osteoporosis. The most common sites of osteoporotic fractures are the distal forearm (wrist or Colles fracture), proximal femur and vertebrae. Vertebral fractures lead to loss of height and curvature of the spine with typical dorsal kyphosis ("Dowager's hump"). This can affect their quality of life and ultimately impair the respiratory function. There is evidence from randomized controlled trials that HRT reduces the risk of osteoporotic fractures (Cauley *et al.*, 2003; The Women's Health Initiative Steering Committee, 2004). But recent advice from regulatory authorities has been that HRT should not be used for osteoporosis prevention as the risks of such treatment outweigh the benefits (Managing the Menopause – British Menopause Society Council, 2004). After the publication of the Million Women study in 2003, the Committee on Safety of medicines (CSM) pronounced that HRT was no longer to be considered as first line therapy for the prevention of osteoporosis. Bisphosphonates are probably the best choice for the over 60s, though there is actually less data on long-term safety.

Urogenital symptoms

Symptoms such as vaginal dryness, soreness, superficial dyspareunia and urinary frequency and urgency respond well to local estrogen, in the form of pessaries, gel, and so on.

Risks of HRT

Breast Cancer

HRT appears to confer a similar degree of risk as that associated with late natural menopause. In absolute terms, the excess risk in the Womens Health Initiative (WHI) study with continuous combined HRT at 50–59 years was 5; 60–69 years, 8; and 70–79 years, 13 cases of breast cancer

per 10 000 women per year (Chlebowski *et al.*, 2003). The unopposed estrogen only arm of this study did not show any evidence of an excess increase in breast cancer risk. The Million Women study found an increased risk with all HRT regimens, the greatest degree of risk was with combined HRT (Million Women Study Collaborators, 2003). So the addition of progestogen increases breast cancer risk compared with estrogen alone but this has to be balanced against the reduction in risk of endometrial cancer provided by combined therapy (Chlebowski *et al.*, 2003; Li *et al.*, 2003). Irrespective of the type of HRT prescribed, breast cancer risk falls after cessation of use, risk being no greater than that in women who have never been exposed to HRT by 5 years.

Endometrial Cancer

Unopposed estrogen replacement therapy increases endometrial cancer risk. Most studies have shown that this excess risk is not completely eliminated with monthly sequential progestogen addition especially when continued for more than 5 years. No increase has been found with continuous combined regimens (Anderson *et al.*, 2003).

Venous Thromboembolism

HRT increases risk of venous thromboembolism (VTE) twofold with the highest risk occurring in the first year of use. Advancing age and obesity significantly increase this risk. The absolute rate increase is 1.5 VTE events per 10 000 women in 1 year.

Cardiovascular Disease (Coronary Heart Disease and Stroke)

The role of HRT either in primary or secondary prevention remains uncertain and currently should not be used primarily for this indication. WHI study showed an early transient increase in coronary events. The excess absolute risk at 50–59 years was 4; 60–69 years, 9; and 70–79 years, 13 cases of stroke per 10 000 women per year. However, the timing, dose, and possibly, type of HRT may be crucial in determining cardiovascular effects. Therefore, HRT should currently not be prescribed solely for possible prevention of cardiovascular disease. The merits of long-term use of HRT need to be assessed for each woman at regular intervals. It should be targeted to the individual woman's needs.

Alzheimer's Disease

While estrogen may delay or reduce the risk of Alzheimer's disease, it does not seem to improve established disease. WHI study found a twofold increased risk of dementia in women receiving the particular combined estrogen and progestogen regimen. However, this risk was only significant in the group of women over the age of 75. More evidence is required before definitive advice can be given in relation to Alzheimer's disease.

Table 1 Common symptoms in the elderly

Postmenopausal bleeding
Discharge per vagina
Pelvic mass
Prolapse
Urinary incontinence
Vulval soreness or itching
Vulval pain

COMMON SYMPTOMS IN THE ELDERLY

Older women are usually reluctant to approach their practitioners due to embarassment when they suffer from the symptoms as in Table 1.

POSTMENOPAUSAL BLEEDING (PMB)

Postmenopausal bleeding is defined as bleeding from the genital tract after 1 year of amenorrhea. A woman not taking hormone replacement therapy who bleeds after the menopause has a 10% risk of having a genital cancer' (Gredmark *et al.*, 1995). In the vast majority of cases, the cause is benign, mainly atrophic vaginitis. The causes are as in Table 2.

Diagnosis

History should include the symptoms, drug history, and smear history. Examination may be difficult in an elderly patient and is further complicated by dementia, immobility, obesity, and arthritis. General examination including BMI, abdominal examination for masses, pelvic examination, both speculum and bimanual examination should be carried out.

Investigation

The principal aim of investigation is to exclude the possibility of cancer. Transvaginal ultrasound measurement

Table 2 Causes of postmenopausal bleeding

Atrophic	– Senile vaginitis
	Decubitus ulcer from a prolapse
Neoplasia	– Endometrial cancer
	Cervical cancer, vaginal cancer
	Vulval cancer, estrogen-secreting tumors, ovarian tumors
	Fallopian tube cancer, secondary deposits
	Endometrial polyps
Iatrogenic	– Bleeding on HRT
	Bleeding on tamoxifen
	Ring, shelf pessary
Infection	– Vaginal, endometrial
Others	– Hematuria, rectal bleeding, trauma, foreign body

of endometrial thickness will help in directing the need for an endometrial biopsy. An endometrial thickness of less than 5 mm is reassuring that the cavity is empty. The myometrium and ovaries can also be visualized for evidence of tumors. Investigation should also include a smear. Hysteroscopy is now the "gold standard" investigation for postmenopausal bleeding. The procedure can be carried out under general anesthetic or as an outpatient, although cervical stenosis associated with atrophic change may cause failures. It is mandatory for recurrent bleeding, and cystoscopy and sigmoidoscopy may be necessary if there is any doubt about the source of the bleeding.

Treatment

Treatment depends on the cause. If atrophic vaginitis, treatment is by local estrogen therapy. If any carcinoma, management is usually centralized in cancer units staffed by experienced gynecological oncologists.

DISCHARGE PER VAGINA

Vaginal discharge is a common gynecological complaint seen in the elderly. The causes are as in Table 3. Owing to the loss of vaginal tissue elasticity and shrinkage of the vagina, atrophic vaginitis is very common. Infective vaginitis is also common due to colonization by pathogenic bacteria when the vaginal pH shifts from acid to alkali.

UTEROVAGINAL PROLAPSE

Uterovaginal prolapse is a herniation of the female genital tract. It is extremely common with an estimated 11% of women undergoing at least one operation for this condition. The factors responsible for the development of prolapse are weakening of fascia and muscle support following the menopause and damage occurring during childbirth. Raised intra-abdominal pressure from an abdominal mass or cough is a contributory factor in some women as is congenital or postoperative weakness. Uterovaginal prolapse is commonly associated with urinary incontinence.

Table 3 Causes of discharge per vagina

Atrophic	–	Postmenopausal vaginitis
Infective	–	Bacterial vaginosis, candida, trichomoniasis.
Tumors	–	Cervical polyp, intrauterine polyp Cervical cancer, endometrial cancer, Fallopian tube cancer – rare
Fistulae	–	Vesicovaginal fistula, rectovaginal fistula
Pyometra	–	associated with carcinoma of the endometrium
Others	–	Foreign body, pessary

Classification

Anterior vaginal wall prolapse	
Urethrocele	– Urethral descent
Cystocele	– Bladder descent
Cystourethrocele	– Descent of bladder and urethra
Posterior vaginal wall prolapse	
Rectocele	– Rectal descent
Enterocele	– Small bowel
Apical vaginal prolapse	
Uterovaginal	– Uterine descent with inversion of vaginal apex
Vault	– Posthysterectomy inversion of vaginal apex

Diagnosis

Most commonly, the presenting symptom is a feeling of a lump coming down the vagina. They also present with a dragging or bearing down sensation of gradual onset which is worse with activity and settles with rest. A minor prolapse may become symptomatic in the presence of marked atrophic vaginitis. Trophic ulceration may occur with discharge and bleeding. Urinary symptoms such as frequency, urgency, incontinence, incomplete, or slow emptying result from distortion of the prolapsed bladder and urethra. Digital replacement of the anterior or posterior vaginal wall is sometimes necessary before micturition or defecation respectively.

A detailed obstetric history and sexual history to ascertain whether they are sexually active is important to decide the treatment. Also, a medical history like constipation, cough, and any major medical illness should be ruled out. A detailed social history is also important.

General examination: To assess if surgery is safe, to check BMI, and cardiorespiratory system examination.

Abdominal examination: Looking for pelvic masses.

Pelvic examination: Prolapse may be obvious when examining the patient in the dorsal position if it protrudes beyond the introitus, ulceration, and/or atrophy may be apparent. The anterior and posterior vaginal walls and cervical descent should be assessed with the patient in the left lateral position, using a firm Sims speculum. Combined rectal and vaginal digital examination can be an aid to differentiate rectocele from enterocele. Vaginal examination should be performed and pelvic mass excluded. Urine culture and sensitivity, cystometry, and cystoscopy to be considered when symptoms include both stress and urge incontinence and especially prior to consideration of surgery.

Management

The management of prolapse depends on the severity of symptoms, the degree of incapacity and the patient's

operative fitness. Operative treatment by repair of prolapse with or without vaginal hysterectomy is most effective. Obesity, heavy smoking, and constipation require improvement before surgery. Most patients tolerate surgery very well because of improved anesthetics and minimal postoperative morbidity. When such surgery is undertaken in an older woman, it is important to ascertain the level of sexual activity as this will influence the degree of narrowing achieved by surgery. Age *per se* is not a contraindication to surgery. Medical disorders develop with advanced age and these dictate any reasons for avoiding anesthesia.

When surgery is contraindicated or declined, conservative methods may be used. A polyvinyl ring pessary will be successful, providing there is adequate perineum to retain the pessary. Some patients, particularly those with large prolapses and very little perineum, may do better with a shelf pessary. Either type needs changing at 4–6 months interval and the vagina should be inspected to ensure no ulceration has occurred. If ulceration occurs, the pessary should be removed for a few weeks and local estrogen used daily to allow epithelial healing.

Physiotherapy: Pelvic floor exercises are useful for the prevention and improvement of incontinence. But they require good patient motivation. Physiotherapy may improve symptoms from a small prolapse but it is unlikely to help with more degree of herniation.

URINARY INCONTINENCE

Urinary Incontinence is defined as the involuntary loss of urine that is objectively demonstrable and is a social or hygiene problem. The causes are as in Table 4. The prevalence increases with age, with approximately 10% of those aged between 45 and 64 years of age being affected, rising to 20% of those greater than 65 years. It is even higher in women who are institutionalized and may affect up to 40% of those in residential nursing homes. This places huge financial demands on health resources, with 2% of the total budget being spent on incontinence services alone. Many women will not seek advice because of embarrassment.

Uninhibited detrusor muscle contractions are usually the cause in geriatric patients owing to age-related changes in the central nervous system. Genuine stress incontinence (GSI) occurs when the bladder pressure exceeds the maximum urethral pressure in the absence of any detrusor contraction and this is common in the early postmenopausal years. In many women, the two conditions exist together.

Table 4 Causes of urinary incontinence

1. Genuine/urodynamic stress incontinence – Bladder neck hypermobility, urethral sphincter weakness
2. Detrusor instability – Idiopathic, secondary to neurological disease – hyperreflexia
3. Retention with overflow – motor neurone lesions, drugs, pelvic mass, severe prolapse
4. Fistulae – Ureteric, vesical, urethral
5. Miscellaneous – Urinary infection

Assessment

A good history will help to differentiate GSI from detrusor instability to some extent. Examination to rule out any associated prolapse or pelvic mass should be carried out in these patients. Urodynamic studies are necessary to confirm the diagnosis, especially prior to any surgical treatment.

Management

Simple measures like exclusion of urinary tract infection, restriction of fluid intake, modifying medication like diuretics when possible play an important role in the management of urinary incontinence.

Genuine Stress Incontinence (GSI)

Conservative management: The treatment of GSI should be nonoperative initially, and the best results for mild/ moderate leakage are with pelvic floor exercises. The rationale behind pelvic floor education is the reinforcement of cortical awareness of the levator ani muscle group, hypertrophy of existing fibers and a general increase in muscle tone and strength. Motivation and good compliance are the key factors associated with success. Local estrogen therapy may have a small effect by improving the urethral mucosa in women with estrogen deficiency.
Surgical Management – the Aims of Surgery:

- Restoration of the proximal urethra and bladder neck to the zone of intra-abdominal pressure transmission
- To increase urethral resistance.

The procedures are Burch's colposuspension, transvaginal tape (TVT), periurethral bulking using collagen, macroplastique.

Detrusor Instability (DI)

DI can be treated by bladder retraining and biofeedback, all of which tend to increase the interval between voids and inhibit the symptoms of urgency. Drug treatment is mainly by Anticholinergics like Oxybutynin, Tolteridine, Regurin combined with local estrogen.

SEXUALITY AND OLD AGE

In the past, it was mistakenly assumed that a woman well past the menopause will not be sexually active. In

1953, Kinsey *et al.* described reduced sexual activity in elderly women. In this group of women, orgasm was more likely to be achieved by masturbation than by coitus (Kinsey *et al.*, 1953). In fact, sexual drive is not exhausted with aging, and as life expectancy increases, it is necessary to recognize that continued sexual activity is an important requirement to promote satisfactory relationships, personal well-being and quality of life (Brown and Cooper, 2003). Many older people were grown up in sexually restricted times so that ignorance is widespread. The organization of institutions for elderly people does not recognize their sexuality, so their needs are ignored (White, 1982). It has been proved that sexual activity remains relatively constant within a stable relationship and declines only following death or illness of the partner (George and Weiler, 1981).

Sexual Response and Aging

In the elderly, the changes of vasocongestion, pudendal swelling, and vaginal lubrication are reduced and delayed, and resolution occurs more rapidly. Also, vaginal lubrication diminishes and there is less vaginal elasticity leading to shrinkage of the vagina. Coital trauma to the vagina and urethra causes dyspareunia, dysuria, and postmenopausal bleeding. Lesions of the vulva like lichen sclerosus (LS) and surgical scarring may make intercourse impossible for some older women.

Health Factors that Inhibit Sexual Activity in Elderly People

Physical factors

- Stress incontinence
- Diminishing mobility
- Decreasing muscle tone
- Uterine prolapse
- Skin tone and sensitivity
- Diseases like diabetes and cardiovascular problems
- Chronic conditions like arthritis.

Psychological factors

- Sense of unattractiveness
- Facing mortality; depression, bereavement, and grief reactions
- Loss of partner or friends
- Lack of contact with others and loneliness.

Effect of Chronic Illness and Surgery on Sexuality

Chronic urological and gynecological conditions causing pain on intercourse, chronic anxiety and stress, neurological disorders, depression and fatigue can result in loss of sexual desire. Disfiguring and mutilating operations, especially of the breasts, genitals and reproductive organs, often have a deleterious effect on a woman's self image and sexuality. Dyspareunia can be a major problem, not only because of lack of arousal or secondary vaginismus after surgery but also because of the amount of scar tissue within the pelvis. Women who have a stoma-like colostomy or ileostomy also experience psychological problems. Patients' greatest fears are loss of control, bad odor, noise, leaking bags, and their partner's feelings toward them. Healthy adaptation to a stoma depends on preoperative and postoperative counseling and understanding by stoma nurses.

Management

A detailed sexual history including the problem, the duration, the couple's past life together and emotional relationship should be taken. Early experiences, difficulties with previous partner and any episode of sexual assault is also important. Examination should aim to look for a physical cause of the sexual problem. Behavioral techniques play an important part in the management of sexual dysfunction. Ignorance about sexuality is common. Changing negative attitudes resulting from past experiences, parental or religious influences will help. Talking to each other about sexual anxieties or needs, and discussion with a therapist increases their mutual understanding and ability to communicate.

Psychological Therapy

The psychological approaches include giving accurate information, general counseling, psychosexual therapy, behavioral therapy, sexual and relationship therapy. Before any operation, it is essential to discuss with the woman, preferably with her partner, the full implications of the operation on their sexual life. This helps to minimize sexual dysfunction after the operation.

Pharmacological Therapy

There is now evidence from randomized controlled studies that testosterone therapy improves sexual satisfaction and mood in surgically menopausal women treated with concurrent estrogen (Burger *et al.*, 1987; Davis *et al.*, 2003). However, long-term safety data for combined estrogen-testosterone therapy are lacking, and the effects of testosterone-only therapy on such factors as plasma lipids in postmenopausal women are unknown.

The use of appropriate creams to help with vaginal soreness – such as estrogen cream, KY Jelly, or aromatic oils may enable a woman and her partner to enjoy sexual activity much more fully.

VULVAL DISORDERS

As the lower genital tract undergoes atrophic changes, the labia majora lose their fat and elastic tissue content and become smaller. The vulval epithelium becomes thin, leading to vulval irritation. Other symptoms are itching and soreness. The conditions affecting the vulva can be a part of a more widespread problem, such as psoriasis or conditions specific to the vulva. Vulval disorders are important because of the chronicity and severity of symptoms and the association with carcinoma. The common vulval disorders are as follows:

1. Lichen sclerosus
2. Squamous cell hyperplasia
3. Other dematoses
4. Vulvodynia or chronic vulval pain.

Lichen Sclerosus (LS)

LS is a chronic skin condition characterized by the thinning of the epithelium with loss of keratin which frequently extends around the anus. The etiology is uncertain, but there is an association with genetic and hormonal factors and autoimmune disease (Meyrick *et al.*, 1988). The clinical signs include pale ivory white plaques often with a crinkly atrophic surface, purpura, and scarring with gradual destruction of the normal vulval architecture. Complications include narrowing of the introitus and rarely squamous cell carcinoma. Punch biopsies should be taken of any suspicious areas. Squamous cell carcinoma is more likely when there is ulceration, raised lesions or lymph node involvement. The most effective treatment is to use topical steroid ointment clobetasol propionate 0.05% plus a soap substitute.

Squamous Cell Hyperplasia

The skin is usually reddened with exaggerated folds. In certain areas, after rubbing, lichenification can be seen. The term squamous cell hyperplasia is applied for those women who have histological evidence for the cause.

Other Dermatoses

The most common general diseases causing vulval itching or discomfort are diabetes, uraemia, and liver failure. Other causes are allergic dermatitis caused by irritants like perfumed soap, washing powder, and so on. General skin diseases like psoriasis, lichen planus, and scabies may also affect the vulva.

Vulvodynia (Vulval Pain)

Vulvodynia is defined as chronic pain, discomfort or burning in the absence of a relevant skin condition. This condition is common in elderly women. The etiology is uncertain but psychological and physical factors play a role. Depression is also a compounding factor. Treatment initially is empirical using topical steroids, anesthetic and estrogen cream. The use of antidepressants should be considered. A multidisciplinary approach involving specialists in dermatology, pain relief, psychiatry, and gynecology is essential for intractable cases.

GYNECOLOGICAL CANCER

The most common types of gynecological malignancies are cervical cancer, ovarian cancer, endometrial cancer, and vulval cancer. Occasionally, skin cancers or sarcomas can also be found in the female genitalia.

Cervical Cancer

Worldwide, cervical cancer is the most common gynecological malignancy. The etiological factors include multiple sexual partners, early age of coitus, human papilloma virus (HPV) 16 and 18 infection. In developed countries, there is an overall decline in incidence and mortality from cervical cancer as a result of the cervical screening program. There is a defined premalignant stage, namely, cervical intraepithelial neoplasia – CIN1, CIN2 and CIN3. Screening for cervical cancer is by cervical smear. Liquid-based cytology and HPV testing are new developments taking place in this field. Abnormal cytological findings are an indication for further investigation by colposcopy and if necessary, directed biopsies or excision biopsy.

Approximately 500 000 new cases of cervical cancer are diagnosed each year in the world with 80% of these occurring in the less developed world (Cancer Statistics, 2003). More than 80% of cervical cancers are squamous cell carcinomas. The presenting symptoms are postcoital bleeding, vaginal discharge, or postmenopausal bleeding. Pain is experienced late and is due to pelvic infiltration or bony metastases. The first sign of this cancer may be obstructive renal failure from hydronephrosis due to advanced disease. On inspection, cancer of the cervix presents as an ulcer, growth, or a friable warty looking mass which bleeds on touch. As the carcinoma progresses, the mobility of the cervix is affected and the cervix eventually becomes fixed. Diagnosis is by biopsy of suspicious areas, preferably under general anesthesia so that clinical staging can be done. Treatment for clinical invasive carcinoma of the cervix is by surgery, chemoradiotherapy or a combination of all three. The management of gynecological cancer patients is now mostly centralized in units staffed by gynecological oncologists, so that all the treatment modalities can be offered to patients. If the disease is in an early stage confined to the cervix, then either surgery or radiotherapy may be offered since the prognosis is equally good for both. Surgery is by radical hysterectomy and pelvic node dissection, that is, Wertheim's hysterectomy. In the elderly, radiotherapy is usually offered because of the fear of

surgical complications. However, a fit patient will tolerate the procedure well and age by itself should be no bar to surgery. If the disease is in a late stage, then chemo-radiotherapy is the treatment of choice. In an unfit patient with advanced disease, palliative care may be the only option.

Endometrial Cancer

Carcinoma of the endometrium is considered as the gynecological cancer with a relatively favorable prognosis because of its early presentation with postmenopausal bleeding. The median age of patients with endometrial cancer is 61 years, with 80% of women being postmenopausal. The risk factors are obesity, diabetes mellitus, hypertension, nulliparity, late menopause, unopposed estrogen therapy and prior history of polycystic ovary syndrome. The presenting symptom in the elderly is almost always postmenopausal bleeding. Late diagnosis include pain and discharge from a pyometra. The diagnosis is by transvaginal ultrasound determination of endometrial thickness and outpatient endometrial biopsy. Outpatient hysteroscopy also may be undertaken, but if there is cervical stenosis, then hysteroscopy should be done under general anesthesia. Early disease is treated by total abdominal hysterectomy and bilateral salpingo-oophorectomy. In a poorly differentiated tumor or if the myometrium is involved beyond the inner third, postoperative radiotherapy is given. Advanced cancers are treated with radiotherapy. Progestational agents are used for recurrent disease to control vaginal bleeding and to reduce the pain from bony metastases.

Ovarian Cancer

Carcinoma of the ovary is common in developed countries. The peak incidence is in the 50–70 year age-group. Ovarian cancer remains the most lethal gynecological malignancy despite trials of many different treatment regimens to try to improve the poor prognosis. Most women present with advanced disease. There is no satisfactory screening method for ovarian neoplasia, but women with a family history of breast or ovarian cancer should be offered regular ultrasonic assessment and measurement of the tumor marker, Ca 125. This test is not sensitive or specific enough to be applied to the general population.

90% of ovarian carcinomas in older women are epithelial adenocarcinomas, but sex cord and germ cell tumors may also be seen in this age-group. Also, metastases may be seen from elsewhere, particularly colon and breast. Granulosa cell tumor is the most common sex cord tumor. This produces estrogen which can cause postmenopausal bleeding due to the resulting endometrial hyperplasia.

The presenting symptoms are often vague including abdominal discomfort, swelling, malaise, and weight loss. Later symptoms include abdominal pain and distension, ascites, and pleural effusion. Investigations include hematological, biochemical, imaging techniques like ultrasound and CT scan. Solid areas within an ovarian cyst and ascites are strongly suggestive of malignancy. The final diagnosis is by laparotomy.

Management

The mainstay of treatment is by debulking of the tumor with bilateral salpingo-oophorectomy, total hysterectomy, and omentectomy. Postoperative chemotherapy is used in all but early stages and indeed many patients will have residual disease after surgery. Taxol and Carboplatin are the chemotherapeutic agents of choice. Radiotherapy is limited to patients with symptomatic recurrence and is used only for palliation.

Vulval Cancer

Vulval cancer is a less common cancer and is most frequently seen in the 60–70 year age-group. The presenting symptoms are soreness, pruritus, irritation, ulceration, lump, or bleeding. Many women present very late because of embarrassment. Ninety-five percent of vulval carcinomas are squamous cell carcinomas, but basal cell carcinoma, malignant melanoma and adenocarcinoma of the Bartholin's gland may occur rarely. Diagnosis can be confirmed only by vulval biopsy.

Management

Radical vulvectomy with bilateral groin node dissection is the treatment of choice. The common complications are wound breakdown and infection. The primary tumor is resected and separate groin node dissections are performed to improve wound healing and reduce infection. The other complications are deep vein thrombosis, osteitis pubis, secondary hemorrhage, and so on. For patients unfit for surgery, wide excision of the lesion may be used as palliation. Pelvic irradiation is available for extensive nodal involvement.

HIV AND OLD AGE

The majority of those infected and affected by HIV are younger adults. The ability of highly active antiretroviral therapies (HAART) to extend survival means that those infected when younger may reach older age and so an increase in numbers of older individuals living with HIV is expected. There is evidence that older individuals engage in risky sexual behaviors and are drug users, suggesting potential for HIV transmission (Dougan *et al.*, 2004). For older women after menopause, condom use becomes unimportant, and normal aging changes such as a decrease in vaginal lubrication and thinning vaginal walls

can put them at higher risk during unprotected sexual intercourse.

Doctors may not discuss with their older patients about HIV/AIDS because they do not think they are at risk or they presume symptoms to be age related. As a result, many older people are diagnosed at a later stage in their infection, and many have an AIDS diagnosis the first time they become aware of their HIV infection. Older people are more likely to be diagnosed with HIV at a generally higher viral load and lower CD4+ cell count, making them more susceptible to opportunistic infections. More aggressive therapy may be required to successfully suppress the virus.

Data from the Center for Disease Control (CDC) HIV/AIDS surveillance report showed that 11% of all AIDS cases reported in 1999 were among people aged 50 and above (Centre for Disease Control, 1998). This percentage has remained stable since 1991. However, the CDC notes an alarming trend in that older AIDS patients had a greater increase in opportunistic infections than did younger AIDS patients. The report also says a higher proportion of people aged 50 and above died within 1 month of AIDS diagnosis. These deaths can be attributed to original misdiagnosis and immune systems that naturally weaken with age. These statistics seem to confirm the idea that older adults are naive about their risk of contracting HIV and their providers aren't discussing that risk with them. A 1997 study of Texas doctors found that most physicians rarely or never discussed HIV and risk factors with their older patients (Skiest and Keiser, 1997). Compounding the problem, AIDS symptoms often are more difficult to diagnose in older people because they mimic some common diseases associated with old age. Because of the stigma, it can be difficult for women to disclose their HIV status to family, friends, and their community.

For these reasons, physicians should keep HIV in mind as a possibility, even with their older patients. HIV experts recommend that physicians routinely ask all patients about their sexual behaviors during the annual physical or gynecological examination. Providers should educate the population over 50 years about possible exposures to HIV and safer sex practices.

CONCLUSION

Gynecology for the elderly patient includes the whole spectrum of gynecological disorders of which cancer, prolapse, urinary incontinence, and the problems of late menopause are the most important ones. The advice given for such women changes with each decade. Of particular note is our increasing reluctance to give long-term HRT and our increasing likelihood of undertaking surgery in women who are healthy despite their age. Many women, through fear and embarrassment avoid telling their problems to general practitioners, geriatricians, or gynecologists and so present with long standing disease.

KEY POINTS

- The female aging process is unique in that it represents a combination of the aging processes and hormone deficiency.
- Managing the menopause should be targeted to individual women's needs. Hormone replacement still offers the potential for benefit to outweigh the harm, provided the appropriate regimen has been instigated in terms of dose, route, and combination.
- Age *per se* should not be a contraindication to surgical management for any gynecological problem.
- There is no age limit for the expression of sexuality. The management of sexual problems should be guided by the same principles irrespective of age and condition of the patient.
- Older women, out of fear and embarrassment neglect early symptoms of gynecological diseases, some of which are potentially lethal.

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The Aging Bladder

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INTRODUCTION

The increase in human life expectancy unmasked a variety of genitourinary complaints. Most physicians are familiar with lower urinary tract symptoms (LUTS) suffered by the aging male related to prostatic enlargement. Equally debilitating though are bladder symptoms found in both sexes totally unrelated to obstruction of any kind. Symptoms of frequency, urgency and urge incontinence, commonly lumped together under the term "overactive bladder" are very prevalent in the aging patient and confront the physicians who care for them on a daily basis.

A multitude of other influences on the bladder also exist that affect its performance over a lifetime. Certainly, injury from infection or surgery can affect vesical function over both long and short-term horizons. Changes in the bladder outlet via prostatic obstruction in males or overzealous surgery in women can have effects ranging from mild to devastating, on detrusor function. Alterations in the neurological milieu of the lower urinary tract can profoundly alter bladder function. These variations, when severe enough, can not only create difficult symptomatology for the patient but can also occasionally be detrimental to renal function.

In this chapter, we hope to examine the aging bladder from a number of angles. The alterations in vesical anatomy, both gross and microscopic, are important in dysfunctional voiding and incontinence associated with aging. Neuronal and hormonal changes influence the aging bladder. Pharmaceutical agents are under intense scrutiny as to their effect in the urinary tract as well as their side effects in the elderly patient. Finally, special disease states found mostly in the older population have specific effects on the urinary tract that must be considered in the overall therapy for those diseases.

ANATOMY OF THE AGING BLADDER

The normal bladder is characterized grossly by its pelvic position in the adult. In the older male, the macroscopic anatomy of the bladder is most commonly affected by the growth of the prostate gland. Although most commonly, benign prostate growth occurs in the transition zone surrounding the urethra, occasionally this growth becomes unrestrained in a cephalad manner and pushes the trigone superiorly to give the bladder an elevated appearance radiographically. Gross inspection of the bladder interior often demonstrates a trabeculated appearance (Cockett *et al.*, 1992). Trabeculations are often thought to be a sign of chronic obstruction in males, but have been observed in the female bladder as well (Groutz *et al.*, 2001).

In women, the anatomical position of the bladder is most often altered by defects in the pelvic floor musculature. This leads to the presentation of cystoceles, effectively a herniation of the bladder through the anterior vaginal muscle layers. This defect, as well as rectoceles and enteroceles are commonly noted in parous individuals, although the impact of aging, obesity, and possibly, neurological dysfunction can be substantial (Pinho *et al.*, 1990; Constantinou *et al.*, 2002; Cummings and Rodning, 2000; Bakas *et al.*, 2001). Perucchini has demonstrated localized striated urethral muscle loss with aging at the bladder neck and dorsal wall of the urethra (Perucchini *et al.*, 2002). Others have shown an increase in paraurethral connective tissue in elderly females with a reduction of blood vessels (Verelst *et al.*, 2002). Falconer has demonstrated altered collagen production in women with stress incontinence with poor quality collagen seen in postmenopausal women possibly contributing to disorders related to prolapse in the elderly (Falconer *et al.*, 1994, 1996).

The histologic appearance of the aging bladder can give clues about its ultimate ability to function as a storage facility for urine. Ultrastructural changes in the aging bladder include collagen deposition, muscle degeneration, and axonal degeneration (Elbadawi *et al.*, 1993). The degree of these changes may correlate with specific abnormalities in voiding and incontinence such as detrusor overactivity and impaired contractility (Elbadawi, 1995). Chronic ischemia of the bladder may play a large causative role in these changes (Azadzoi *et al.*, 1999a,b).

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Table 1 Anatomical changes of the aging bladder

Gross anatomical changes
Trabeculations
Cystocele (females)
Muscle loss at bladder neck (females)
Histologic changes
Collagen deposition
Muscle degeneration
Axonal degeneration

Surgical procedures in both sexes can alter vesical anatomy. In females with pelvic prolapse and/or stress incontinence, certainly operations can successfully reposition the bladder and other pelvic organs toward normalcy. They also can cause difficulties if, for example, bladder neck prolapse is overcorrected and obstruction occurs. Certain women will suffer urgency and frequency symptoms even if no obstruction is present (Dunn *et al.*, 2004). In males, relief of obstruction at the level of the prostate may improve symptoms but changes in bladder configuration may not occur at the same rapid rate seen in symptom reduction. Furthermore, radical prostatectomy in the man with prostate cancer may alter bladder dynamics as well as cause sphincteric incontinence (Sebesta *et al.*, 2002). The anatomical changes of the aging bladder are summarized in Table 1.

BLADDER PHYSIOLOGY AND CORRELATION TO ANATOMY OF THE AGING BLADDER

Bladder function involves both the storage of urine and the expulsion of urine at a socially appropriate time. To maintain continence, the storage of urine must occur under low pressures and the bladder must empty adequately. Unfortunately, aging results in changes that occur intrinsically and extrinsically to the bladder that affect continence and emptying. Pathologic changes are seen in the bladder because of aging. In addition, nerve transmission can be altered because of age, disease states, surgical procedures, or drugs. Anatomic obstruction or lack of adequate support of the bladder neck also changes the ability of the bladder to empty and store urine.

The bladder consists of two parts: the body and the base or bladder neck. The smooth muscle fibers of the body are arranged randomly and those of the bladder neck are arranged in an inner longitudinal and outer circular layer. In the male urethra, the sphincter consists of both smooth muscles and striated muscles. The external sphincter consists of the periurethral striated muscle and the intramural striated muscle or rhabdosphincter. In the female, these muscles are attenuated. DeLancey proposes that female continence is created by a combination of muscular coaptation and passive compression of the urethra by the pubourethral hammock (DeLancey, 1989).

During urine storage, low level afferent bladder stimulation signals sympathetic contraction of the bladder neck and relaxation of the detrusor muscle or body of the bladder. This results in storage of urine under low pressure. The voiding reflex is initiated when afferent activity becomes intense. The pontine micturition center stimulates the parasympathetic pathway and inhibits the sympathetic pathway resulting in relaxation of the bladder outlet and contraction of the detrusor muscle and thus bladder emptying. The striated external sphincter, which has separate innervation from the bladder neck, is also influenced by the pontine micturition and storage centers. The voiding reflex results in inhibition of the external sphincter and the storage reflex results in activation of the pudendal nerve.

The bladder must be able to distend and contract adequately, for proper functioning. Structural changes in the tissues and abnormalities in bladder shape can alter urine storage and emptying. Bladder compliance is a measurable value defined as the change in volume divided by the change in intravesical pressure. A normally functioning bladder fills under a low pressure; therefore the bladder is compliant. Compliance is greatly affected by tissue composition, innervation, and vascular supply.

Histologic studies have shown that as collagen levels increase, compliance is lost (Macarak and Howard, 1999). Landau demonstrated that in bladders with poor compliance, the ratio of Type III to Type I collagen was significantly higher than that of normal bladders (Landau *et al.*, 1994). The aged bladder has a higher deposition of collagen; in addition, innervation of the detrusor smooth muscle changes with age. Neurochemical studies of human detrusor strips have shown an increase in purinergic neurotransmission and a decrease in cholinergic neurotransmission with age. It is felt that the shift in neurochemical transmission may change the resting tone of the bladder and contribute to the overactive bladder symptoms in aged bladders (Yoshida *et al.*, 2004).

Bladder wall blood flow is affected by intramural tension. A bladder with poor compliance has increased intravesical pressure and intramural tension, and therefore, a greater decrease in bladder blood flow (Ohnishi *et al.*, 1994). Ischemia can result in diminished contractility and patchy denervation (Van Arsdalen *et al.*, 1983). The end result is a bladder that empties inadequately and may have detrusor instability (Brading, 1997). Injured areas of the bladder can become weak and form diverticulum, resulting in ineffective bladder emptying.

The complexity of voiding dysfunction in the aged bladder makes it difficult to distinguish between the changes in the bladder that are secondary to the normal aging process and changes as a result of bladder outlet obstruction, or changes caused by diseases affecting the nervous system and/or vascular supply. Certainly, the LUTS of obstruction, instability, and impaired detrusor function often overlap. The changes seen in bladder function with aging must certainly overlap as well. A study by Homma found the symptoms of urgency, frequency, and nocturia increased with age in both men and women. The cystometric capacity declined with age in both sexes (Homma *et al.*, 1994).

Histologic changes in the aged bladder have been documented, including increased collagen deposition, widened

spaces between muscle fibers, and ultrastructural changes of the smooth muscle cell membrane (Levy and Wight, 1990; Elbadawi *et al.*, 1993). Elbadawi *et al.* showed that aged bladders without urodynamic evidence of obstruction had muscle cell membranes with dominant dense bands and depleted caveolae (Elbadawi *et al.*, 1993). These findings were reproducible and different from the ultrastructural changes seen with obstructed, overactive or hypocontractile bladders (Hailemariam *et al.*, 1997). These findings are thought to represent dedifferentiation of the smooth muscle fibers.

Changes in bladder compliance, nerve transmission, and vascularity, occur as the bladder ages. Certainly, multiple disease processes may worsen these changes. With advanced age, the expected bladder symptoms might include increasing frequency and urgency with a decreased bladder capacity.

SPECIAL DISEASE STATES

Several disease states especially affect the bladder in the geriatric population. Irrespective of whether it is caused by neurological disease, endocrine problems, iatrogenic intervention, or the aging process itself, these problems exact a particular morbidity on the lower genitourinary tract. The following conditions are particularly important.

Parkinson's Disease

Parkinson's disease affects 1% of all patients over the age of 60 and is rarely seen in those under 40. In addition to the characteristic tremors and motion deficits, the loss of dopaminergic neurons in the substantia nigra of the basal ganglia affects voiding by reducing the inhibitory effect of the basal ganglia on the micturition reflex as demonstrated in several animal studies (Albanese *et al.*, 1988; Yoshimura *et al.*, 1992).

The voiding symptoms of Parkinson's disease are frequency, urgency, and urge incontinence. These irritative symptoms are present in well over half of all patients with the disorder (Pavlakis *et al.*, 1983). A significant problem from a diagnostic viewpoint is the presence of these symptoms in elderly males. These irritative voiding symptoms mimic the LUTS associated with bladder outlet obstruction related to Benign Prostatic Hyperplasia (BPH). Without urodynamic evaluation, the neurogenic component to the symptoms may be overlooked, or not quantified well, and inappropriate therapy instituted. Furthermore, men with multiple systems atrophy rather than true Parkinson's disease may actually have mild detrusor-sphincter dyssynergia, which again could mimic the obstructive symptoms of BPH (Stocchi *et al.*, 1997).

The typical urodynamic findings of Parkinson's are detrusor hyperreflexia on filling cystometry. As much as 79% of bladder dysfunction in these patients can be related to hyperreflexia (Araki *et al.*, 2000). Other findings are not uncommon though. Hyporeflexia is present in 16% of patients in Araki's study (Araki *et al.*, 2000). Obstruction can also be present particularly in the male with prostatic enlargement or stricture disease from previous interventions. Multichannel urodynamics is essential to the evaluation of voiding dysfunction in patients with Parkinson's Disease.

Cerebrovascular Accident (CVA)

Stroke can be considered a major health problem among elderly patients. Roughly three-fourths of the 400 000 stroke patients per year in the United States are over the age of 65. The impact of this disorder on voiding and continence can range from mild to profound. When occurring in the aged patient, its effects can magnify preexisting bladder conditions and cause great confusion as to what the proper therapy should be. Depending on the location of the ischemic event, the bladder may range from hyperreflexic to areflexic. One can therefore present with an entire range of symptoms anywhere from nocturia and urgency/urge incontinence to voiding difficulties and urinary retention (Sakakibara *et al.*, 1996). The presence of urinary incontinence in the acute phase of a Cerebrovascular Accident (CVA) is a powerful predictor of a negative outcome (Wade and Hewer, 1985).

The patient presenting with LUTS following a CVA can be a diagnostic dilemma. In one study, detrusor hyperreflexia was seen in 68% of patients, detrusor-sphincter dyssynergia in 14%, and uninhibited sphincter relaxation in 36% (Sakakibara *et al.*, 1996). In that same study, there were patients with retention who were noted to have detrusor areflexia with an unrelaxing sphincter. No correlation was seen between site of lesion and urodynamic findings. In the elderly post-CVA male, neurogenic bladder problems may coexist with obstruction from the prostate gland. Nitti found in a group of men with a mean age of 70 with voiding complaints following a stroke that detrusor hyperreflexia was present in 82% of the group, but pressure-flow characteristics of definite obstruction were present in 63% (Nitti *et al.*, 1996). Multichannel urodynamics can be an important adjunct in the urologic management of these patients.

Nocturia

Nocturia is commonly listed as a symptom by the older patients. In males, it is often perceived as related to prostate enlargement. But this symptom is also commonly noted among aging women (Lose *et al.*, 2001). Menopausal status may contribute to the presence of nocturia (Chen *et al.*, 2003). In all likelihood, nocturia is a manifestation of normal aging.

Other factors impacting the presence of nocturia in the aging individual include sleep difficulties and nocturnal polyuria. Sleep disturbances are common in the elderly population and nocturia may be more related to those problems, rather than to a urinary tract dysfunction. Furthermore, the patient with nocturia, whatever be its cause, will have poorer sleep (Middelkoop *et al.*, 1996). The problem of nocturnal

polyuria in many of the elderly, which is reported as nocturia, can be difficult to manage. With lower renal concentrating ability, poorer conservation of sodium, loss of the circadian rhythm of antidiuretic hormone secretion, decreased production of renin-angiotensin-aldosterone, and increased release of atrial natriuretic hormone, there is an age-related alteration in the circadian rhythm of water excretion, leading to increased nighttime urine production in the older population. Exacerbated by age-related diminution in functional bladder volume and detrusor instability, nocturnal polyuria often leads to a dramatic version of nocturia (Miller, 2000).

Dementias

The elderly patient with dementia faces the dual difficulties of having to face the consequences of an aging bladder and in addition, the difficulties caused by an altered perception of his or her internal and external environments. This can lead to urinary incontinence or retention depending on what is influencing it, bladder factors or a central neurologic inability to properly perceive the urinary activity. The difficulties in the management of these patients' other significant conditions often pushes concerns about incontinence aside, but the fact remains that incontinence issues are the primary reason for institutionalization of the elderly patient.

Evidence of combined cerebral and urinary tract dysfunction comes from perfusion studies in elderly patients. From positron emission tomography (PET) scan studies, it has been demonstrated that the pontine micturition center in the dorsomedial pontine tegmentum, the periaqueductal gray matter and the pre-optic area of the hypothalamus are all active during various phases of micturition (Blok and Holstege, 1998). Furthermore, urge incontinence has been associated with underperfusion of the frontal areas of the brain (Griffiths, 1998). Clearly, cerebral atrophy, irrespective of the cause, can lead to disinhibition of the bladder and resulting incontinence. Treatment routines combining anticholinergic medications with prompted or timed voiding have been utilized to circumvent the loss of cerebral control over the micturition process in elderly patients afflicted with bladder dysfunction (Burgio *et al.*, 1998; Schnelle and Leung, 2004).

PHARMACOLOGY AS IT RELATES TO THE AGING BLADDER

With so many elderly at risk for bladder dysfunction, the use of medications among the elderly for urinary tract problems is rising almost exponentially. The number of prescriptions for one particular overactive bladder drug alone surpasses 50 000 per month, many presumably to older sufferers of the condition (Alza, 1999). Clearly, an understanding of how the common drugs for these urinary conditions work is essential for proper prescription and monitoring. Proper use of pharmaceuticals for urinary conditions can give maximum benefit to the patient's symptoms and pathology without engendering any undue risk in the aging population.

Receptors

The pharmacology of the bladder is primarily related to either the bladder itself or to the nervous innervation of the organ. At the level of the bladder itself, a number of receptor sites exist to varying degrees. These receptors govern to a great degree the function of the lower urinary tract and become more prominent in the elderly patient as various bladder conditions become more prevalent.

Among the adrenergic receptors, α- and β-receptors are found in the bladder although it has been thought that β-receptors predominate in the bladder body and α-receptors in the bladder base and bladder neck region. Urine storage is facilitated by relaxation caused by β-stimulation and tonic contraction in the area enriched by α-receptors (Khanna *et al.*, 1981). More recent work has elucidated (at least in the rabbit) that the division by receptors into bladder base and body may be overly simplistic and that further regionalization of the bladder based on differing mixes of α- and β-receptors might be more appropriate (Chou *et al.*, 2003). α-receptors are also well characterized in the prostatic urethra and stroma. Stimulation of these receptors causes contraction and thus possibly obstruction of the bladder neck (Caine, 1988).

Muscarinic receptors are the other major group of receptors influencing bladder behavior. These receptors, particularly the M2 and M3 subtypes are responsible for bladder contraction (Ehlert, 2003). The pharmacology of these receptors is influenced by their ubiquity. They are also found in gastrointestinal, airway, and salivary gland smooth muscle. Table 2 gives a summary of receptors located within the bladder and the effects of aging on these receptors.

Adrenergic Stimulation/blockade

α-stimulation in the elderly patient is most often a deleterious side effect from a pharmaceutical designed for action elsewhere. With the rich supply of α-receptors in the prostate, stimulation can cause contraction, and thus obstruction and

Table 2 Bladder receptors and aging

Receptor	Location	Action	Effect of aging
α-adrenergic	Prostate	Contraction smooth muscle	Stimulation-causes urinary retention Blockade-improves urine flow
α-adrenergic	Bladder base	Contraction smooth muscle	Shift in subtype may ameliorate bladder symptoms
β-adrenergic	Bladder body	Relaxation smooth muscle	Unknown at present
Muscarinic	Detrusor muscle (primarily M3)	Relaxation smooth muscle	Urinary retention Worsening of side effects at other locations

urinary retention (Beck *et al.*, 1992). α-blockade, although originally designed with hypertension in mind, has become a mainstay in the therapy of LUTS related to prostatic enlargement (Dunn *et al.*, 2002).

One effect of aging is the possible change in the type, sensitivity, and number of these receptors. With increasing age, α-adrenoceptor responsiveness either decreases or remains unchanged (Docherty and O'Malley, 1985). Furthermore, α-receptors in the aging bladder itself show a shift from the α-1a subtype to an α-1d predominance (Hampel *et al.*, 2004). If α-blockers have an effect in the bladder that aids in relief of LUTS as well as its effect on obstruction itself, then this change with aging could have implications for both short-term as well as long-term use in elderly men with prostate disease.

Antimuscarinics

Antimuscarinics are drugs that are utilized primarily in the therapy of symptoms of overactive bladder. Although the M2 subtype is the predominant population, it appears that the smaller population M3 subtype is the functionally important group (Fetscher *et al.*, 2002). Although several antimuscarinic agents exist in oral, intravesical, and transdermal forms, the lack of bladder M3 selectivity remains a problem.

In the elderly, antimuscarinic can be very effective for symptoms of frequency, urgency, and urge incontinence (Wein, 2003). Changes in the aging patient may, however, alter the pharmacology of these drugs in an adverse manner. Side effects such as dry mouth and constipation may be of more concern and less well tolerated in the elderly individual. Decreases in force of detrusor contraction in the aging male with an enlarged obstructing prostate gland may well push the patient into urinary retention. At least one of these agents crosses the blood-brain barrier and thus, particularly in the aging patient, could effect a higher incidence of confusion as a side effect (Todorova *et al.*, 2001). These effects could play a role in limiting the usefulness of the antimuscarinics in treating bladder dysfunction.

5-α Reductase Inhibitors

This group of drugs, although having therapeutic activity in the prostate gland, is known for their beneficial effect on bladder complaints caused by obstruction from the prostate gland. These agents inhibit the conversion of testosterone to dihydrotestosterone in the prostate gland and thus cause reduction in the size of the periurethral prostatic tissue (Tempany *et al.*, 1993). This leads to improvement in urinary flow and BPH related symptomatology. In the proscar long-term efficacy and safety study (PLESS), the main side effects in all age-groups are sexual side effects, particularly ejaculatory disturbances (Wessells *et al.*, 2003). This may be more profound in the elderly male with borderline sexual dysfunction although this was not borne out in the PLESS study.

SURGICAL DISEASE OF THE AGING BLADDER

Lower urinary tract surgery in the aged patient is common for two conditions having a large impact on the bladder – stress urinary incontinence in women and bladder outlet obstruction from prostatic enlargement in men. The elderly suffer disproportionately from these disorders but have benefited from advances in therapy for these conditions. With proper selection of treatment, this group of patients can enjoy great improvement in their quality of life related to their lower urinary tract.

Female Stress Urinary Incontinence

Stress incontinence occurs when abdominal pressure generated by such actions as coughing, sneezing, or other Valsalva maneuvers causes bladder pressure to exceed urethral pressure without a detrusor contraction and urine is expelled. Stress incontinence is associated with parturition, previous pelvic surgery and aging. Previously, major abdominal surgery was the only method considered for treatment and older age could be considered a relative contraindication. But with newer therapies, elderly women can be considered excellent candidates for realizing improvement in their condition.

Pelvic Floor Conditioning

Pelvic floor exercises have become a mainstay of conservative therapy for stress incontinence. They are absolutely safe and can be performed either alone or with biofeedback. Effectiveness as measured both subjectively by patient report as well as objectively with pad weights has been demonstrated in several studies (Bo *et al.*, 1999; Aksac *et al.*, 2003).

Some concern over the effectiveness in the elderly of pelvic floor rehabilitation can be raised. The reduction in estrogen effect on the vaginal tissues may reduce the benefit of these exercises in the elderly woman. Furthermore, the overall reduction of muscle tone with aging may also make these exercises less efficacious (Dimpfl *et al.*, 1998; Aukee *et al.*, 2003). Patients with significant intrinsic sphincter deficiency may not respond as well to pelvic floor conditioning. These exercises, however, are essentially risk-free, which makes them especially appealing as a first line effort for the elderly woman.

Pharmacologic Management

Stress urinary incontinence has been remarkably resistant to drug therapy in the past. Pharmacologic agents with α-adrenergic properties such as pseudoephedrine were occasionally utilized with moderate success in women with mild incontinence (Cummings, 1996). These medications were effective due to the presence of α-receptors in the bladder neck. These agents though, have recently been pulled

out of use owing to adverse events and so are not readily available. Estrogen therapy may also play a role in the medical management of stress incontinence in the older, postmenopausal woman (Ishiko *et al.*, 2001) but its true benefit has been disputed in some studies (Jackson *et al.*, 1999).

Anticholinergic agents, although truly indicated for urgency and urge incontinence, are often prescribed for stress incontinence. These drugs may be helpful in women with mixed incontinence (urge and stress incontinence) by reduction of the urge component and thus improving overall continence. Patients with pure stress incontinence may perceive a worsening of the problem in that the bladder capacity will increase, and they will leak larger volumes of urine with stress maneuvers (Chutka and Takahashi, 1998).

Although it is appealing to consider these pharmaceuticals as first line therapy for stress incontinence in the aging woman, one must consider certain factors. α-adrenergic agents have been associated with CVAs and increases in blood pressure (Cantu *et al.*, 2003; Beck *et al.*, 1992). Certain anticholinergic medications cross the blood-brain barrier and can cause confusion and drowsiness in the older patient (Yarker *et al.*, 1995). These adverse effects may outweigh the usually small benefits these drugs provide for stress incontinence.

The serotonin-norepinephrine reuptake inhibitors (SNRI) are being shown to have a therapeutic effect in female stress incontinence. These drugs have been shown to facilitate urine storage and facilitate rhabdosphincter activity. Thus, a positive effect on stress incontinence could be expected and trials are under way to study this possibility (Thor and Donatucci, 2004). Safety in the geriatric population would also need evaluation.

Injection Therapy

The concept of injecting substances at the bladder neck to aid in coaptation and thus improve continence dates back to the use of sodium morrhuate by Murless in the 1930s (Murless, 1938). This led later to the use of Teflon popularized by Politano with good results (Lopez *et al.*, 1993). Concerns over the safety of Teflon injection led to the use of glutaraldehyde cross-linked bovine collagen and later development of other injectables such as carbon beads. Injection treatments have been shown to have an improvement rate of about 40% (Groutz *et al.*, 2000) with best results occurring in women without low leak point pressures or maximum urethral closure pressures (Gorton *et al.*, 1999).

This therapy may be a good alternative for the older female. It is minimally invasive with a low rate of complications. The anesthetic requirements are not significant, with some reporting use of local anesthetic only. The major downside, especially for the geriatric patient is the frequent need for multiple injections to achieve success. Still, this is an excellent option for the older woman desiring aggressive treatment, but reluctant to undergo major surgical procedures (Khullar *et al.*, 1997).

Operative Therapy

With multiple procedures described for female stress urinary incontinence, it is difficult to discern what the role of surgery might be for the aging female. Several factors are clear though. Older women are, as a rule, healthier now and thus better able to tolerate surgery. Surgery offers the best chance for successful resolution of stress incontinence. Finally, modifications of many procedures have allowed good results with less morbidity than was seen with earlier operations.

Sling procedures have evolved from being a procedure designed only for those with severe incontinence to a rational alternative for all women desiring operative therapy (Morgan *et al.*, 2000). The procedure is commonly done today with alternative materials for the sling such as cadaveric fascia or dermis as opposed to the classic descriptions of harvesting the patient's own fascia. Bone anchors are now commonly available for fixation of the sling, allowing for a lower degree of invasiveness via an exclusively transvaginal approach.

The taping procedures for stress incontinence have also shown good results with minimal morbidity and may be ideal alternatives for the elderly female. The tension-free vaginal tape procedure as popularized by Ulmsten (Ulmsten *et al.*, 1998) and its modifications (suprapubic tapes and transobturator tapes) place a sling-like material at the midurethra and are often done under local anesthetic with light sedation only (Tash and Staskin, 2003). These procedures have been shown to be safe enough and have quite good results to be a reasonable alternative for the more active older female who requires aggressive treatment, but desires minimal morbidity (Walsh *et al.*, 2004).

Benign Prostatic Hyperplasia (BPH) in the Older Male

Benign enlargement of the prostate gland in the human male is a condition inexorably linked with aging. When the vesicourethral junction becomes obstructed by the growing tissue, symptoms such as slowing of the urinary stream, hesitancy, straining to void and a sensation of incomplete emptying result. Furthermore, irritative symptoms such as urinary frequency, urgency, and nocturia may also become common. It is estimated that the prevalence of symptoms related to BPH may be as high as 50% in a multinational survey (Rosen *et al.*, 2003).

Medical Therapy

Two broad classes of drugs are utilized for therapy for BPH, α-receptor blockers and 5-α reductase inhibitors. The bladder neck region in males is rich in α-receptors and blockade of these causes relaxation of the smooth muscle in the prostatic urethra. This results in a decrease in the tonic luminal pressure in the prostatic fossa and allows for more efficient urine outflow from the bladder (Debruyne, 2000).

Early α-antagonists were designed primarily for use as antihypertensives and thus a major side effect when used

for relief of voiding dysfunction from BPH was orthostasis. Normotensive men complained also of asthenia and fatigue (Lepor *et al.*, 2000). In older men with hypertension, attempted medical management of BPH along with hypertension became complex. Over the last several years, the introduction of α-adrenergic antagonists selective to the prostatic α-receptors has broadened the population that can be managed with these agents and includes many elderly men, ensuring also safe usage. (Dunn *et al.*, 2002).

The 5-α reductase inhibitors block the conversion of testosterone to dihydrotestosterone in the prostate gland, which is the active form stimulating prostate growth. With blockade, the prostate gland involutes and a reduction in prostate volume of up to 30% may be seen. This can result in an improvement in urinary flow and a decrease in symptomatology. The safety profile of these drugs is very good, making them a good choice in the older male, particularly those with very large prostate glands (Roehrborn *et al.*, 2004).

Combination therapy may also be of benefit in the elderly male. The recently completed Medical Therapy of Prostate Symptoms (MTOPS) study demonstrated a 66% decrease in acute urinary retention compared to placebo. α-blockade alone and 5-α reductase therapy alone showed 39% and 34% reductions respectively (McConnell *et al.*, 2003). Acute urinary retention in the elderly is a morbid event with an impact on quality of life similar to that of myocardial infarction; so prevention by means of a combined therapy may be worthwhile for the older population with LUTS related to BPH.

Minimally Invasive Therapy

A plethora of minimally invasive treatments for BPH now exist. Many are safe enough to be office-based and thus particularly applicable to the older male population. These therapies involve the delivery of energy to the prostate gland in order to heat the tissues to greater than 60 °C, which leads to protein denaturation and ultimately destruction of prostatic tissue and relief of obstruction. The differences in the methods lie in the type of heat delivery system; whether by externally generated microwaves (Osman *et al.*, 2003) or internally placed systems generating radiofrequency energy (Hill *et al.*, 2004) or laser energy (Costello *et al.*, 1999).

Safety makes these procedures particularly appealing for the older male (Berger *et al.*, 2003). Most of the complications center around irritative voiding symptoms. Bleeding essentially does not occur but postprocedure retention can be a problem. Furthermore, it takes several weeks before improvement in symptoms and flow occurs.

Transurethral Resection of the Prostate Gland (TURP)

The TURP procedure is still considered the "gold standard" of treatment for bladder outlet obstruction from BPH (Minardi *et al.*, 2004). It works quickly, since the obstructing tissue is removed immediately at the time of surgery. Symptom scores drop rapidly and flow rates are instantly improved. Although not without morbidity, improvements in instrumentation and optics have made this procedure much safer for the elderly patient, and in those with severe symptoms or retention, it is still the best choice for therapy, no matter what the age of the patient is, if he can reasonably tolerate anesthesia.

CONCLUSION

The effects of aging on lower urinary tract function can be profound. Anatomic variations, both at the macroscopic and ultrastructural levels occur frequently and induce functional changes. Disease states commonly seen in the older patient have significant impact on the bladder, which should be recognized as a major portion of the syndromes. Bladder changes from aging significantly impact on pharmaceutical effectiveness and alter the ability to manage many conditions. A multimodal approach including surgery to treat common geriatric disorders of the lower urinary tract can be both safe and very effective.

KEY POINTS

- Bladder anatomy changes with aging both macroscopically because of prostate enlargement in men and pelvic prolapse in women, as well as microscopically because of collagen deposition.
- Changes in anatomy lead to physiologic changes such as loss of compliance and variation in response to neurotransmitters and pharmaceuticals.
- Certain extravesical disease processes common in the older patient have a profound effect on the bladder.
- The common lower urinary tract symptom complexities of stress incontinence in women and obstructive voiding in women can be safely treated by a variety of means including surgery.

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Prostate Diseases

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INTRODUCTION

The prostate is perhaps the most diseased organ in the male body. The lifetime risk of being diagnosed with prostate cancer is approximately 16% while a 65-year-old male has about a 40% likelihood of having a focus of prostate cancer. Benign prostatic hyperplasia as an histological entity will affect almost all men if they live long enough and 25% will receive treatment during their lifetime. Prostatitis has a clinical prevalence of 16% in men over 65 while its histological prevalence is close to 100%.

The above perhaps underscores the importance of prostatic pathology upon the well being of older men. This chapter will review these basic diagnostic entities and the approach to treatment of the aging male.

BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) has generally been used as a synonym for lower urinary tract symptoms (LUTS) (Abrams, 1994). While BPH is one cause of LUTS, age-related detrusor dysfunction, neurogenic disease, and diabetes are other major causes (Kelly and Zimmern, 2003). This chapter will address LUTS rather than BPH *per se*.

Anatomy

The prostate is a golf ball–sized organ, which lies between the bladder and the pelvic floor anterior to the rectum (Figure 1). The transition zone is situated around the urethra and is responsible for hyperplastic growth (benign prostatic hyperplasia). This may take the form of lateral lobes encroaching on the urethral lumen, or less frequently, a middle lobe of prostate, which may enlarge and develop like a tongue within the bladder (Figure 2). This may then act like a ball valve during urination.

The two major requirements for prostatic growth are androgens and aging. For a more detailed review of the molecular biology of prostatic growth this is reviewed in detail elsewhere (Roehrborn and McConnell, 2002).

Histologically prostatic growth is both epithelial and stromal (Roehrborn and McConnell, 2002). Most patients have varying degrees of stromal and glandular hyperplasia but with both elements usually being present.

Prevalence

BPH usually starts during the early 40s and increases thereafter. Several autopsy studies have been published demonstrating almost no existence before age 40, 50% prevalence by age 60, and with a peak of 90% by age 90 (Berry *et al.*, 1984). Clinically, the Baltimore longitudinal study of aging demonstrated a prevalence of 30% by the fifth decade, 50% in the sixth, and reaching 80% in the eighth decade of life (Arrighi *et al.*, 1991). The prevalence of moderate to severe symptoms for patients in various studies performed globally is enormous ranging from 10 to 60% for men in their sixth decade (Roehrborn and McConnell, 2002). A US study from Olmstead County demonstrated moderate to severe BPH symptoms in 31% of men in their sixth decade rising to 44% in their eighth decade (Chute *et al.*, 1993). Overall, from the patient perspective, the main criterion for initiating treatment is "bother"; how much do these symptoms intrude upon the patient's lifestyle? As patients react differently to the same set of symptoms, how the symptoms affect the patient is more important than an absolute count of the symptoms.

Natural History

The question, which most patients and physicians pose, is what will happen to my symptoms with time? Will I go into acute retention? One study evaluated LUTS in

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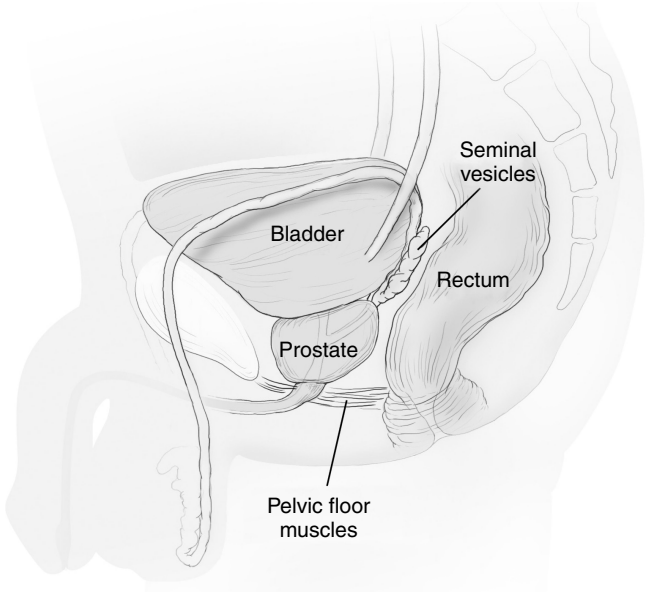

Figure 1 Sagitaal section of male pelvis

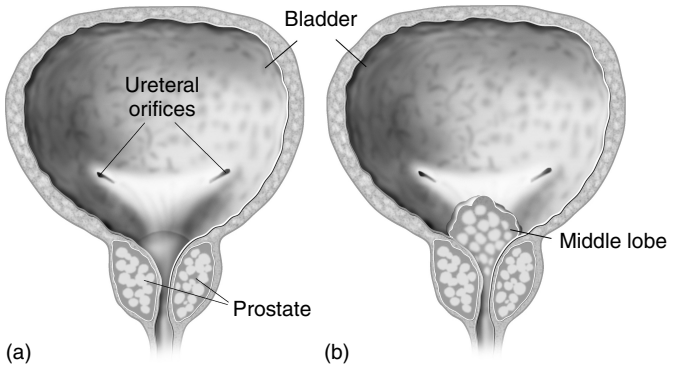

Figure 2 Coronal section of prostate and bladder (a) normal (b) with prostatic and middle lobe enlargement

community-dwelling men over age 60 years (Lee *et al.*, 1996). Of interest, 23% of men with severe symptoms at baseline were asymptomatic 1 year later. Most natural history data, however, comes from the placebo arms of randomized controlled trials for the treatment of LUTS (Flanigan *et al.*, 1998; McConnell *et al.*, 1998; McConnell *et al.*, 2003). The most significant of these is the recently published medical therapy of prostate symptoms (MTOPS) trial (McConnell *et al.*, 2003). Of the 737 men involved in the placebo arm only 18 men went into acute urinary retention during this study (5 years). This rate was 0.6 per hundred person years. The comparison rate in the best treatment arm (finasteride plus doxazosin) was 0.1 per hundred person years. These data demonstrate not only the natural history but also that while medical treatment decreased the acute urinary retention rate by a significant percentage (80%), the absolute risk is relatively small to begin with. Additionally, prostate size as measured by PSA, also correlates with acute urinary retention risk (McConnell *et al.*, 2003). Patients with a PSA less than $1.4\,\mathrm{mg\,ml^{-1}}$ had a very low risk of acute urinary retention.

Patient Evaluation

The key elements to patient evaluation are shown in Table 1. Urinary symptomatology may be evaluated using the international prostate symptoms score (Table 2). For an assessment of symptoms along with an impact score the BPH impact score can be used (Table 3) as an assessment of bother. For most patients, treatment is based upon the negative quality of life impact that they have (bother) rather than any absolute symptomatic criteria. Additionally, it is important to evaluate the rest of the patient's medical history to determine if other medical conditions may lead to bladder dysfunction, polyuria, and so on (Table 4).

A symptom score of 0–7 is considered mild while 8–19 is considered moderate, and 20–35, severe. The impact (Table 3) score should be used in conjunction with the International Prostate Symptom Score. For example, a patient with moderate symptoms but without any bother probably does not warrant treatment, while a patient who is bothered by his symptoms should at least have a discussion of treatment options along with their attendant risks and side effects.

Physical examination should include a rectal examination as well as a focused neurologic examination and evaluation of the patient's mental status. Clearly, dementia amongst many neurologic conditions will affect urinary symptomatology. Many demented patients are referred for incontinence while their bladder function is essentially normal for their age. Treatment of these patients will often be behavioral such as timed voiding (initiated by the caregiver), rather than interventional.

Laboratory Evaluation

Urinalysis is a specifically recommended test to rule out a urinary tract infection or bladder cancer (presence of hematuria). Additionally, the presence of glycosuria in diabetic patients may identify problems for management, not only of diabetes but secondarily, with associated lower urinary tract symptomatology. Patients with primarily irritative urinary symptoms (frequency, urgency, nocturia) should be considered for urinary cytology as well as all men with hematuria. Microscopic hematuria alone should lead to a formal urologic

Table 1 Patient evaluation (AUA Practice Guidelines Committee, 2003)

- Medical history of voiding dysfunction
  - Identify other etiologies and comorbidities for voiding dysfunction
  - Obtain international prostate symptom score
- Physical Examination
  - Include DRE, focused neurologic examination
- Urinalysis
- PSA for select patients
  - Life expectancy greater than 10 years or those for whom PSA measurement would change treatment options

Table 2 AUA BPH symptom score (AUA Practice Guidelines Committee, 2003)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None	1 time	2 times	3 times	4 times	5 or more times

Total Symptom Score _____

Table 3 BPH impact index (AUA Practice Guidelines Committee, 2003)

1. Over the past month how much physical discomfort did any urinary problems cause you?	None ☐	Only a little ☐	Some ☐	A lot ☐
2. Over the past month, how much did you worry about your health because of any urinary problems?	None ☐	Only a little ☐	Some ☐	A lot ☐
3. Overall, how bothersome has any trouble with urination been during the past month?	Not at all bothersome ☐ Bothers me a little ☐	Bothers me some ☐ Bothers me a lot ☐		
4. Over the past month, how much of the time has any urinary problem kept you from doing the kind of things you would usually do?	None of the time ☐ A little of the time ☐ Some of the time ☐	Most of the time ☐ All of the time ☐		

Table 4 Medical diseases affecting urinary symptoms

Cardiac Disease	Especially CHF. Peripheral edema will revascularize at night adding to nocturia
Diabetes	Poorly controlled diabetes will act as osmotic diuretic
Neurologic disease	MS, SCI, PID with nerve compression
Mental disease	Dementia, Alzheimer's
Other urologic conditions	OAB, bladder cancer

CHF, Congestive Heart Failure; MS, Multiple Sclerosis; SCI, Cord Injury; PID, prolapsed intervertebral disc; OAB, overactive bladder.

workup generally consisting of a CT urogram, cystoscopy, and urinary cytology. These studies will evaluate the kidneys, ureters, bladder, and complete lower urinary tract for pathology.

Previously a serum creatinine was recommended, but studies have shown that in the absence of other medical issues this is not a helpful test (AUA Practice Guidelines Committee, 2003). European urologists (European Association of Urology, 2004), however, continue to recommend its collection as did the 4th International Consultation of Benign Prostatic Hyperplasia in 1997 (Koyanogi *et al.*, 1998).

The measurement of PSA remains controversial. In the BPH guidelines (AUA Practice Guidelines Committee, 2003), the general recommendations is for patients with a life expectancy of greater than 10 years or where measurement would make a difference to treatment. For example, in octogenarians, the diagnosis of prostate cancer is not usually a basis for treatment. However, if the patient had severe urinary tract symptomatology then it may be that treatment of the prostate cancer would be appropriate treatment for the LUTS. Patients whose symptoms are complex or who fail medical therapy may require further urodynamic evaluation. Either way this would require referral to an urologist. Measurement of urinary flow rates, post void residuals, ultrasounds, and other urodynamic studies are not generally considered routine.

Treatment

The treatment for LUTS may be separated into four groups: watchful waiting, medical therapy, minimally invasive treatment, and invasive surgical therapy (Table 5).

Watchful Waiting

For patients with mild symptoms and no complications (e.g. renal insufficiency, urinary tract infection) and who are not

Table 5 Treatment options for BPH

Watchful waiting	Symptoms minimal (IPSS < 8) and there is little bother. These are not mandatory indications for treatment
Medical therapy	Symptoms and/or bother are moderate but the patients wants treatment
α blockers	
5α reductase inhibitors	
Phytotherapy	
Minimally invasive surgery	Moderate to severe symptoms/bother
Microwave	Comorbid indications for surgery:
Radiofrequency	Bleeding
	Renal failure
	Recurrent UTI
	Urinary retention
Invasive surgery	Moderate to severe symptoms
TUIP	Indications for surgery
TURP	Failure of other therapies
Open prostatectomy	

IPSS, International prostate symptom score; UTI, Urinary Tract infection; TURP, Transurethral Resection of Prostate; TUIP, transurethral incision of prostate.

bothered by their symptoms, monitoring of the symptoms without active intervention is appropriate. Generally, this would include all patients with symptom scores less than 8 and many with symptom scores between 8 and 19.

Medical Therapy (Lepor and Lowe, 2002)

Medical therapy consists of α-blockers, 5-α-reductase inhibitors, and phytotherapy.

α-blockers

The basis for this treatment utilizes the fact that the prostate and bladder neck are richly innervated by $\alpha 1_a$ receptors. The bladder body is primarily innervated with $\alpha 1_d$ receptors while $\alpha 1_b$ receptors are present on blood vessels throughout. By blocking the $\alpha 1_a$ and $\alpha 1_d$ receptors, the prostate and detrusor smooth muscle will relax, allowing for a better flow and reduced irritative urinary symptomatology. The effect on $\alpha 1_b$ receptors tends to cause vascular relaxation and potentially hypotension. Indeed, the earliest drugs (terazosin and doxazosin) were first approved by the FDA as hypotensive agents. Most of the α-blockers are non-subtype selective (alfuzosin, doxazosin, terazosin). Because of their effect upon blood vessels, the dose needs to be increased over several weeks. Even so, many patients, especially the elderly, may have problems with dizziness and postural hypotension. Alfuzosin (long acting) and tamsulosin, because of less effect upon blood pressure, do not require dose titration. Tamsulosin is a different class of drug and is primarily α-$1_{a/d}$ specific. As such, it has less potential interaction with hypotensive agents than the other drugs. Overall, the efficacy of the drugs are similar, although the side effect profiles differ somewhat with perhaps tamsulosin having the best side effect profile.

Of special note is the interaction between α-blockers and the phospho-diesterase-5 inhibitors (Sildenofil, Tadalafil, and Vardenofil). Sildenofil (Viagara), tadalafil (cialis) and vardenafil (levitra) are contraindicated within 6 hours of taking α-blockers. Levitra is contraindicated with all α-blockers though work is underway to try and remove this FDA proscription. Tamsulosin is the only α-blocker approved by the FDA for use in combination with Cialis.

5-α-reductase Inhibitors

These drugs block the conversion of testosterone to dihydrotestosterone (the active metabolite). Two enzymes exist: type I in the skin and liver and type II in the reproductive organs. Dutasteride blocks both enzymes, while Finasteride blocks only the type II enzyme. Despite this difference, the overall suppression of testosterone is similar. Because of the mechanism of action, it takes 3–6 months for full clinical effect. Further, these drugs are most efficacious on large prostates (>50 g).

Combination Therapy

The recent MTOPS trial demonstrated maximal effect in reducing prostate size and improving symptoms by combining both an α-blocker (doxazosin) with a 5-α-reductase inhibitor (finasteride) (McConnell *et al.*, 2003). While the differences in risk for symptom progression and urinary retention were large (approximately 25% greater than single treatment alone (McConnell *et al.*, 2003)) the absolute reductions were relatively small: nine episodes to five episodes per 100 patient years for urinary retention and 25 per 100 patient years for symptom progression (>4 points on the symptom score). Two features of practical utility did stand out. Patients with small prostates had little risk of going into retention irrespective of treatment option. PSA has also been demonstrated to be a surrogate for prostate size. Patients with low PSA's (less than 1.4 ng ml^{-1}) also have small prostates and minimal risk of retention. Conversely, patients with large prostates had a much greater risk of retention and therefore are likely to benefit more from this aspect of 5-α-reductase therapy.

Phytotherapy

A variety of plant extracts have been utilized for the treatment of LUTS. Unfortunately, because they are designated as food additives and not regulated by the Food and Drug Administration no good randomized prospective clinical trials have been performed. Despite this, several compounds do appear to have real activity. These are currently being studied in the Complimentary and Alternative Medicine (CAMUS) trial funded by the National Institutes of Health (NIH). This study will randomize patients to placebo, Saw Palmetto, Africanum Pygeum, or an α-blocker/5-α-reductase inhibitor combination. The results of this study will unfortunately not be available for several years.

Perhaps the most widely used plant is Seranoa Repens (Saw Palmetto). The extracts of this plant contain a mixture of fatty acids, sterols, flavenoids, and other compounds (Lowe and Fogelman, 2004). Its mechanism of action suggests 5-α-reductase inhibition, anti-inflammatory action and effects upon apoptosis.

One of the largest problems with these unregulated drugs is batch-to-batch variation and also manufacturer-to-manufacturer variation. Studies have been performed analyzing the active ingredients from multiple manufacturers demonstrating that the content varies between excess of that stated on the package to none at all.

Minimally Invasive Therapy

Surgical therapies are generally out with the scope of practice for gerontologists. For that reason, the following discussion will center on information, which will help the physician guide, the patient toward the best therapy for them. More detailed reviews of the subject have been published (Fitzpatrick and Mebust, 2002). The most commonly utilized methods for minimally invasive treatment are transurethral needle ablation (TUNA) and microwave thermotherapy. Both act by heating the prostatic tissue. The TUNA device is a rigid cystoscope like instrument passed transurethrally under vision. Two needles (which look a bit like snake fangs) can be extended from the instrument into the prostatic tissue. Utilizing a radiofrequency signal the tissue is heated between 46 and 100 °C. The microwave devices look like a urinary catheter with a normal balloon area (to seat it at the bladder neck) but with the microwave area distal to that. Using microwave energy the prostatic tissue is heated to 69 °C. Overall, tissue heated to greater than 45 °C will lead to hemorrhagic necrosis. These procedures are generally performed in the office or a surgicenter under local anesthetic or conscious sedation.

Overall, most studies show a marked reduction in Symptom Score (50% or more) and with improvement in peak flow from 30 to 100%. Comparative studies have not yet been performed, however, the NIH is sponsoring the trial of minimally invasive surgical therapy (MIST), which will compare TUNA with microwave thermotherapy with combined medical therapy (α-blocker plus 5-α-reductase inhibitor). The results of this trial however will again not be available for several years.

Given that most patients are treated for "bother" rather than absolute need the complication rates are extremely important. The complications of TUNA include postoperative urinary retention with rates of 13–42%. Forty percent will have retention for the first 24 hours. Likewise, 40% of patients will have irritative urinary symptoms early on after treatment. Up to 14% of patients will undergo another form of therapy within 2 years. To the extent that some patients without benefit will not undergo additional therapies this perhaps underscores the lack of efficacy rate.

The complications of microwave thermotherapy include 36% catheterization rate for 1 week postoperatively. Satisfaction rates have dropped off to 34% at 2 years. One recently reported study of microwave thermotherapy demonstrated that over a 5-year period, 29% underwent additional treatment while only 59 of 150 patients remained in the study (Miller *et al.*, 2003). While these dropout rates are similar to dropout rates for medical (drug) therapy the economic impact is greater. If drug therapy is stopped the cost (of the drug) also stops. Once a relatively expensive treatment is performed the total cost has already been incurred.

Despite all the cautionary notes mentioned earlier, Medicare has approved both TUNA and microwave thermotherapy for reimbursement. Because they are generally performed in the office/surgicenter setting, utilization has increased dramatically over the last few years.

Invasive Surgical Therapy

In today's society most patients with lower urinary tract symptomatology will first be tried on medical therapy. Depending upon the experience of the urologist, equipment availability, or the patient circumstances some patients may next be treated with minimally invasive therapy. If that fails or is not appropriate patients may proceed to invasive therapy namely transurethral incision of the prostate or transurethral resection of the prostate (TURP). Both of these procedures are performed in the hospital operating room under spinal or general anesthesia. The patients are generally admitted for at least one night postoperatively. If the prostate is small and especially if there is a high bladder neck (between the prostate prostatic urethra and bladder) then a transurethral incision of the prostate may be preferable. Not only is this a single cut from the bladder trigone to the verumontanum of the prostate simple, but there is much less blood loss than with a TURP. Additionally, because the whole bladder neck has not been resected the risk for bladder neck scarring and stricture formation is much less. In general, bladder neck contractures are seen more frequently after resections of small prostates rather than with large prostates. Additionally, men will usually have antegrade ejaculation afterwards, which is a major issue for many men of all ages (including octogenarians).

A transurethral resection of prostate entails resecting the tissue from the bladder neck to the prostatic apex. The "surgical capsule" represents the boundary between the transition and peripheral zones of the prostate. Most men have a catheter in for 1–2 days and take about 6 weeks to fully recover. Significant postoperative bleeding occurs in about 10% and may occur 10–14 days postoperatively. Because the lower urinary tract symptomatology is often associated with prostatic problems and bladder neck dysfunction the symptomatic improvement may not be as marked as urologists would like to think. Indeed, for the occasional patients with primarily irritative symptoms these may even become worse postoperatively. In general, however, the dysuria, frequency, and urgency routinely experienced postoperatively will resolve within 2 months.

More recently lasers have been used to resect the prostate. The technique entails resecting "the benign adenoma" and

delivering it into the bladder where it is then morcellated and extracted. Overall, the surgical process is slower than traditional electrocautery but there is much less bleeding. For a detailed review of technical issues associated with these invasive surgical procedures this may be found elsewhere (Lepor and Lowe, 2002).

Open Prostatectomy

For patients with very large glands (>100 g), it is difficult to treat the adenoma within a reasonable time frame. For these patients an open suprapubic approach is best. A lower midline incision is made. Next a midline incision is made in the bladder, which may be extended into the prostatic capsule. The benign adenoma is then shelled out using finger disection. Major bleeders are oversewn and the bladder neck often reconstructed as part of oversewing of the bleeding vessels. A three-way irrigating catheter is inserted. There is often significant bleeding at the time of enucleation (≤500 ml). Otherwise the risks/complications are broadly the same as for a TURP.

PROSTATE CANCER

Prostate cancer is the most common cause of malignancy in men in the United States (Jenal *et al.*, 2003). The incidence of prostate cancer increases with age making this a pertinent topic in the geriatric population. Advances in diagnosis and treatment allow for earlier detection and improved treatment of the disease. The unique challenge in the geriatric population is patient selection for continued screening and choice of treatment modalities.

Epidemiology

Prostate cancer incidence in the United States has risen dramatically in the past three decades. The incidence of prostate cancer increased 2.7% annually from 1973 to 1988 (Jenal *et al.*, 2003). From 1988 to 1992 it increased 16.2% annually and then fell to 11.7% from 1992 to 1995. Since then data suggests that incidence rates may have leveled off and perhaps are following the curve established before the spike in 1992, which was almost certainly driven by the introduction of widespread use of PSA. African-American males have the highest rate of prostate cancer incidence in the United States (Jenal *et al.*, 2003).

Prostate cancer incidence is also age dependent. In men under 65 years the annual incidence is 58.8 cases per 100 000 men. In men over age 65, the incidence increases to 982.2 cases per 100 000 males per year (Jenal *et al.*, 2003). While screening and treatment advances have recently focused on the younger male, prostate cancer remains predominately a disease of the older male.

Screening and Detection

Early prostate cancer rarely causes symptoms as cancers generally arise in the peripheral portion of the gland. Symptoms from prostate cancer tend to arise with advanced or metatstatic disease. Often these take the form of urinary symptoms. Symptoms may include obstructive urinary symptoms, irritative urinary symptoms, hematuria, hematospermia, bone pain, weight loss, spinal cord compression, and fecal or urinary incontinence. Thus, screening for prostate cancer has become widespread and widely accepted. However, the method of screening and the population to be screened remain controversial. The challenge for the geriatric population is to define the population who will benefit from screening.

Prior to the widespread use of prostate-specific antigen (PSA) only individuals with palpable nodules, or symptoms resulting from prostate cancer underwent transrectal ultrasound guided biopsy (TRUS). Today, screening measurement of PSA often prompts the performance of prostate biopsies.

PSA, although widely utilized as a screening tool, is still controversial. The American Urological Association (AUA), American Cancer Society, and American College of Physicians all support the use of PSA as a screening modality as long as the patient has been given counseling regarding the use of PSA for early detection and treatment (Thompson *et al.*, 2000; Smith *et al.*, 2000; Coley *et al.*, 1997).

The AUA recommends screening only for men with a 10-year life expectancy. Using life assurance tables this approximates to age 74 years. The reason for 10 years is based upon the fact that for periods of less than 10 years it is difficult to show outcome differences for treated versus untreated patients. Thus, for the young geriatric population (65–75 years) recommendations are similar to those for younger men. For the true elderly (>75 years), the approach to screening needs to be individualized. Certainly, as population longevity increases it may be appropriate to screen, diagnose, and treat much older patients.

Prostate-specific Antigen

Prostate-specific-antigen (PSA) is a serine protease produced by both normal and malignant prostate cells. It functions in the liquefaction of the seminal coagulum (Han *et al.*, 2004). Approximately 90% of PSA exists bound to α-1-antichymotrypsin and α-2-macroglobulin. The remainder exists in the unbound or "free" form. Routine PSA assays detect all forms of PSA (Han *et al.*, 2004).

The normal range for PSA has generally been considered 0–4 ng ml^{-1}; however, age-specific cutoffs have been proposed (only for men <65 years) (Morgan *et al.*, 1996; Oesterling *et al.*, 1993). A comment should be made about the new data arising from the Prostate Cancer Prevention Trial. In this trial involving 18 882 men, patients were routinely biopsied at the end of the trial (Thompson *et al.*, 2004). It was found that men were diagnosed with high-grade cancers even with low PSA values (<1 ng ml^{-1}) raising

questions about the validity of PSA screening in general. A number of refinements in PSA have been explored to increase its sensitivity as a screening tool.

PSA velocity – It has been shown that PSA increases more rapidly in men with prostate cancer than in men without the disease (Carter *et al.*, 1992). Normal PSA velocity should be less than $0.75\,ng\,ml^{-1}\,year^{-1}$. In one series 72% of men with cancer had an increased PSA velocity compared with only 5% of men without cancer (Carter *et al.*, 1992). Other studies have supported this finding. Caution must be used with PSA velocity. The lab assays should be from the same laboratory over at least an 18-month period. In periods of less than 1 year, variations of up to 25% may occur in patients without prostate cancer (Riehmann *et al.*, 1993).

In addition to age-adjusted PSA (Table 6), physicians have also come to rely on free PSA and the ratio of free/total PSA to improve the specificity of PSA screening (Carter and Partin, 2002). Men with prostatic adenocarcinoma tend to have a larger percentage of PSA in the complexed or bound form and less in the unbound or free form when compared with men without prostate cancer (Carter and Partin, 2002).

The percentage of free PSA is only useful in men with a total PSA of $4-10\,ng\,ml^{-1}$. A number of studies have looked at the optimal cutoff for free PSA. Using a cutoff free/total PSA a ratio of 25% was shown to detect 95% of cancers while preventing 20% of unnecessary biopsies (Catalona *et al.*, 1998). If the ratio is less than 20–25% a biopsy is indicated. As the percentage of free/total PSA decreases, the odds increase that there is prostate cancer within the gland. For example, with a free PSA >25% there is an 8% chance of prostate cancer, with a free PSA ratio <10, there is a 56% chance of cancer within the gland (Carter and Partin, 2002).

Additional studies have looked at the free/total PSA ratio in the black population and in men on finasteride. There appears to be no difference in detection using a free cutoff of 25% in black-and-white men (Catalona *et al.*, 2000). Finasteride has been found to decrease the PSA by approximately 50%. However, it decreases the free PSA by an equal amount and is thereby still an effective screening tool in men on this medication (Carter and Partin, 2002).

As longevity increases in men, so will the duration of PSA screening and thus presumably the detection of prostate cancer. This will inevitably lead to the detection of clinically insignificant cancers. Treatment decisions will need to be discussed with the patient and a plan initiated. No therapy for prostate cancer is without side effects. As such, care must be taken to screen only those men whose comorbidities will likely permit at least 10 years of additional life expectancy.

One possible exception to this rule is in an elderly man with severe LUTS that the clinician suspects could be related to prostate cancer. In that instance, PSA and TRUS to diagnose and treat the prostate cancer may alleviate symptoms and improve quality of life.

Once a palpable nodule is found on exam, or a patient has an elevated PSA on screening, a transrectal ultrasound guided biopsy (TRUS) is recommended. The optimal number of cores to perform has been widely studied and debated and is beyond the scope of this chapter. Depending upon the size of the prostate 6–12 cores are usual.

The biopsy is usually performed in the office setting. The patient lies on the side with the knees drawn up. An ultrasound probe is inserted via the rectum and images and measurements of the prostate are obtained. Then a series of needle biopsy samples are obtained transrectally using the ultrasound probe. Most men tolerate the biopsies with minimal discomfort. There is always a risk of continued bleeding from the biopsy sites and as such men should hold their aspirin, vitamin E, herbals, and anticoagulation medications for 5–7 days prior to the biopsy. The use of enemas and antibiotics (fluoroquinoline) prior to the biopsy is usual.

Tumor Grade

The most widely utilized pathologic grading system is the Gleason grading system (Gleason and Mellinger, 1974). The pathologist looks at the prostate cancer under relatively low magnification and assigns a score based on the glandular architecture. Two scores of 1–5 are assigned: the first number being the predominant pattern, and the second number being the secondary pattern. A Gleason grade of 1 being well differentiated and 5 being poorly differentiated, the scores are then added together for a sum of 2–10. For example, two areas of totally undifferentiated tumor would represent a Gleason $5 + 5 = 10$ and, thus, portend a very poor prognosis. Overall, a score of <4 is well differentiated, 5–6 (7) moderately differentiated, and (7) 8–10 poorly differentiated. Any element of a Gleason pattern 4 or a total score of 8 or higher indicate poorly differentiated disease and a worse long-term prognosis.

Table 6 PSA thresholds based on age and race

	"Normal" PSA ranges ($ng\,mL^{-1}$)			
	Based on 95% specificity		Based on 95% sensitivity	
Age decade (Years)	White males	Black males	White males	Black males
40	0–2.5	0–2.4	0–2.5	0–2.0
50	0–3.5	0–6.5	0–3.5	0–4.0
60	0–4.5	0–11.3	0–3.5	0–4.5
70	0–6.5	0–12.5	0–3.5	0–5.5

Table 7 Prostate cancer staging

TNM	DESCRIPTION
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Nonpalpable tumor not evident by imaging
T1A	Tumor found in tissue removed at TUR; 5% or less is cancerous with histological grade ≤ 7
T1B	Tumor found in tissue removed at TUR; >5% is cancerous or histological grade >7
T1C	Tumor identified by prostate needle biopsy owing to elevation in PSA
T2	Palpable tumor confined to the prostate
T2A	Tumor involves one lobe or less
T2B	Tumor involves more than one lobe
T3	Palpable tumor beyond prostate
T3A	Unilateral extracapsular extension
T3B	Bilateral extracapsular extension
T3C	Tumor invaded seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures (not seminal vesicles)
T4A	Tumor invades bladder neck, external sphincter, and/or rectum
T4B	Tumor invades levator muscle and/or is fixed to pelvic wall
N (+)	Involvement of regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No lymph node metastases
N1	Metastases in single regional lymph node, ≤ 2 cm in dimension
N2	Metastases in single (>2 but ≤ 5 cm) or multiople nodes with none <5 cm
N3	Metastases in regional lymph node >5 cm in dimension
M (+)	Distant metatstatic spread
MX	Distant metastases cannot be assessed
M0	No evidence of distant metastases
M1	Distant metastases
M1A	Involvement of nonregional lymph nodes
M1B	Involvement of bones
M1C	Involvement of other distant sites

Staging of Prostate Cancer

Stage is determined using the TNM staging system. This is shown in Table 7. Once biopsy confirms prostate cancer, the clinician's goal is to accurately assign a clinical stage, which will predict prognosis and aid in selection of appropriate therapy. The clinical stage is based on the digital rectal exam (DRE), PSA, and pathologic information as well as imaging modalities if indicated. For patients with a Gleason score of 7 or greater, we will obtain a bone scan. For PSA's in excess of 20–25 ng ml^{-1} a CT scan may help identify pathologic lymph nodes.

The PSA, Gleason grade, and TNM stage can be utilized to predict final pathologic stage. There are complex nomograms to help predict the probability of organ confinement, seminal vesical invasion, lymph node involvement (Partin *et al.*, 1997), and extracapsular spread (Partin *et al.*, 1997).

Natural History

In general, prostate cancer is considered to be a slow growing tumor. Indeed, the cliché that most people die with prostate cancer rather than from it holds true. The need for treatment is very much predicated upon life expectancy with 10 years being the threshold defining need for treatment. Two papers have been published demonstrating the relatively benign course with no treatment (Johansson *et al.*, 1997; Albertsen *et al.*, 1998).

Patients with Gleason 6 cancers have a <10% risk of dying of their cancer within 5 years. At the same time, their overall risk of dying is 10–20%. However, even for patients 70–74 years, the risk of dying from a Gleason 8–10 cancer is approximately 30% at 5 years. Thus even for older patients, the diagnosis of a high-grade cancer supports active intervention.

Treatment

There are a number of treatment modalities available for prostate cancer today (Table 8). Each case must be considered individually and each patient (and their family) involved in the decision-making process. Patients who are involved in their decision making and who are fully apprised of the risks, benefits, and possible complications are generally more satisfied despite side effects.

Watchful Waiting

As with any disease process, the first step is to decide to treat or not to treat. Watchful waiting is the conservative approach to prostate cancer. It means that the man makes the decision to monitor the PSA and treat only if the disease spreads or causes symptoms. This decision is based on the natural history of prostate cancer, the patient's age, their comorbidities, and their wishes.

It is imperative that the patient understands that with watchful waiting there is no plan to perform one of the

Table 8 Treatment options for prostate cancer

	Pro	Con
Watchful waiting	• Noninvasive • No immediate side effects of treatment • Disease may never impact quality of life • Treatment unlikely to impact survival in less than 10 years	• Quality of life impacted by worry about cancer • PSA will rise • Tumor may spread and cause local symptoms • Metastatic disease possible
Surgery	• Removal of cancer • Pathology available on whole gland	• Major operation • Impotence in 60–75% of men over age 70 • Some incontinence in 5–15% with higher rate in older men
Radiation	• Less invasive than surgery	• Additional pathology not available • Impotenence • Incontinence • Irritative GI and GU side effects both early and delayed possible • Bleeding

potentially curative therapies listed below if or when the disease progresses. It is to monitor for disease progression and intervene if and when the disease progresses. The intervention at that point is to slow progression, not to cure. If the intent is to cure the disease and the patient is an acceptable candidate, one of the curative modalities discussed below should be utilized.

While this concept is seemingly simple, it is not necessarily easily accepted by all patients. Some men worry constantly about their next PSA. Their quality of life suffers because of the stress. Other patients readily accept this. The patient must be involved in any therapy decision, including the decision to perform watchful waiting.

Radical Prostatectomy

Radical prostatectomy, or removal of the prostate gland, is a potentially curative therapy for prostate cancer. Like any therapy it carries risks. Utilizing a retropubic (lower midline incision), perineal, or laparoscopic approach, the prostate gland is removed in its entirety and the urethra and bladder are sutured together. Goals in performing prostate surgery in order of importance are cancer control, urinary continence, and preservation of sexual potency (Walsh, 2002).

Radical retropubic prostatectomy is the approach most commonly performed today. With refinements in surgical technique and better anesthetic agents morbidity and mortality have been greatly reduced.

There are several advantages of retropubic prostatectomy. It allows for removal of the entire prostate gland and pelvic lymph nodes with accurate pathologic staging. It is not uncommon for the final pathology to differ from that of the needle biopsy with upgrading in about 30%. Patients found on pathologic evaluation to have positive margins may be considered for adjuvant radiation or antiandrogen therapy.

Complications include hemorrhage, incontinence, and impotence. Blood loss can be quite variable but has generally been falling over the last decade. It was quite common for patients to donate autologous blood prior to surgery during the 1990s. This is becoming less common as average intraoperative blood losses fall and transfusion is less often necessary.

Incontinence is another complication. Refined surgical techniques and a better understanding of the anatomy make this complication less common in contemporary series. Total continence rates vary from 80 to 95%. Age does appear to influence continence with younger men fairing slightly better than older men (Catalona *et al.*, 1999). A study of Medicare patients revealed that about one-third of patients had at least some degree of stress incontinence. Severe incontinence, when consideration for an artificial sphincter is given, should occur in 1–2% and certainly less than 5%.

Erectile dysfunction is less common in contemporary series owing to the advent of a nerve-sparing prostatectomy. Potency in large series ranged from 63 to 68% with bilateral nerve sparing and from 41 to 50% with unilateral nerve sparing. Erectile function and dysfunction are graded phenomena. The patient's erectile function prior to surgery, age, and comorbidities all impact the postoperative state.

Potency rates are generally better in younger men and men without significant vascular disease or comorbidities that would predispose to vascular disease. Potency following radical bilateral nerve-sparing prostatectomy varied from 86 to 91% in men under the age of 50, to 25–40% in men older than age 70 (Catalona *et al.*, 1999; Walsh *et al.*, 1994). It has been stated that erectile preservation is rare in men over 70 years. Additional complications to discuss with a patient when contemplating prostatectomy include rectal injury (<1–3.6%), deep venous thrombosis or pulmonary embolism (2–3.1%), and bladder neck contracture (5–10%) (Taneja and deKernion, 2001).

Postoperatively, patients remain in the hospital for 1–2 days and have a urinary catheter for 1–2 weeks. Full recovery takes about 2 months. A surgical option becomes less common for patients over 70 and rare for patients over 75 years.

External Beam Radiation Therapy

Radiation therapy is another potentially curative therapy for prostate cancer. Linear accelerators and 3D conformational techniques have improved delivery of radiation to the prostate gland and decreased radiation exposure to adjacent organs. Radiation treatments are typically delivered daily, Monday–Friday. Treatment protocols vary, but patients usually receive 6–7 weeks of therapy.

Advantages of external beam radiation therapy are that it does not require a general anesthetic, it is noninvasive, does not require a prolonged postoperative recovery period, it is a potentially curative therapy, and has lower risks of incontinence or impotence than prostatectomy. If PSA begins to rise after radiation therapy, patients may still be candidates for other therapies.

Potential disadvantages also exist for external beam radiation therapy as with all the discussed modalities. As the prostate gland is treated *in situ*, there is no additional pathology available to the clinician and no information about margin or lymph node status.

Complications of external beam therapy may be divided into early and late. Early toxicity often occurs during the course of treatment. Gastro intestinal (GI) distress is common occurring in up to 33% of patients (Selch, 2001). GI symptoms include diarrhea, rectal pain, and bleeding. Genitourinary (GU) symptoms are also common during treatment. Urinary symptoms include dysuria, occurring in 12%, and hematuria, frequency, and urgency in 1–5% (Selch, 2001).

Late toxicities may occur immediately after treatment, but more commonly occur years after the completion of therapy. Impotence, GI, and GU morbidity are common. Impotence is often a delayed effect after conclusion of therapy. Potency is retained in 40–76% of men at a follow-up of 12–24 months. Conformational therapy has had minimal

effect on potency (Roach *et al.*, 1996). Pretreatment level of function, as with prostatectomy is the most important determinant of posttreatment function.

The most complete analysis of late morbidity in radiation therapy was performed by RTOG (Pilepich *et al.*, 1984). Diarrhea ranged from 9–14%, proctitis 9–11%, and rectal bleeding from 8.7–13%. Additional late GI complications include rectal ulcer, anorectal stricture, and small bowel obstruction although these are much less common.

Delayed GU side effects from the RTOG study included cystitis 11–12%, hematuria 6–11%, and urethral stricture 3–7%. Ranges included are from three different protocols employed in the study.

Brachytherapy

Modern-day techniques have been refined significantly over those utilized in the 1970s. Improved imaging and delivery techniques have made the procedure safer and the disease free survival data more comparable to other techniques in properly selected patients with intermediate term results of nonrandomized trials (Blasko *et al.*, 1997).

Brachytherapy is the insertion of radioactive seeds into the prostate under general or spinal anesthesia. The prostate is imaged, usually by transrectal ultrasound. The prostate is mapped and a computer utilized to determine the dose and number of seeds needed to deliver optimal treatment to the prostate and minimal radiation to the adjacent tissues.

The advantages of brachytherapy include, rapid recovery period with the procedure performed as an outpatient or 23-hour observation, decreased erectile dysfunction and incontinence when compared with open surgery, and comparable results to external beam therapy in properly selected individuals (Jani and Hellman, 2003). Disadvantages include limitation of use to moderately differentiated tumors, lack of final pathologic specimen, erectile dysfunction, GU symptoms, and prostatitis (Jani and Hellman, 2003). Patients with anything but small low-grade tumors will be treated with additional external beam therapy to the pelvic nodes.

Irritative voiding symptoms are the most common side effects after implantation. Mild symptoms of urgency, frequency, dysuria, and hematuria occurred in up to 89% of patients in one large series in the first 4–8 months after the procedure. The symptoms continued after a year in 7% of that same group (Blasko *et al.*, 1993). Postprocedure urinary symptoms are related to the patient's pretreatment symptomatology.

Urinary retention occurs in 5–22% of patient's postimplant (Scherr *et al.*, 2001). Often the retention resolves with initiation of therapy and a temporary indwelling catheter; however, some patients will eventually require TURP. The degree of obstructive symptoms varies, but patients with preexisting obstructive symptoms are at higher risk for postprocedure complications. In fact, severe obstructive symptoms are a relative contraindication to brachytherapy.

A major problem exists for patients who remain in retention posttreatment. If this persists over several months it may be necessary to perform a TURP. When this is necessary, there is a significant risk for the patient having severe irritative LUTS, which can be quite debilitating (Scherr *et al.*, 2001).

Less than 1% of patients have postprocedure incontinence. The exception is in patients with a prior TURP whose risk in several large series was 11–17% (Scherr *et al.*, 2001). Erectile dysfunction after seed implantation was found to be 22% in one large series. Pretreatment potency was a predictor of posttreatment potency as was age. In men younger than 70, 85% were found to preserve potency compared with 50% of those older than 70 (Blasko *et al.*, 1997).

An additional phenomenon unique to brachytherapy is seed migration. One year after therapy, 18–20% of patients will have radiographic evidence of 1–3 seeds in the lungs (Scherr *et al.*, 2001). This is asymptomatic and does not cause clinical adverse outcomes. Additionally, seeds may migrate to the urethra and occasionally may require cystoscopic removal.

Cryotherapy

Cryotherapy of the prostate has been approved by the FDA for use in postradiation failures. Early use with the modality was hampered by problems with urethral and rectal injury. Efficacy in animal models has also been questioned. No good long-term trials are available.

Androgen Deprovation

For many elderly patients, watchful waiting will be the treatment of choice. Likewise, in this patient group (80+ years or younger with comorbidity) surgery and radiation carry greater risk for complications. Some patients will be diagnosed with high-grade tumors ($\geq$Gleason 7). For those patients, primary treatment with hormonal therapy will be appropriate. This is generally achieved with one of the 3–12-month depot injections of the GnRH agonists (Leuprolide, Goserelin Acetate). Bilateral orchiectomy is equally effective, but has largely fallen out of favor for social reasons. Estrogen (Diethylstilbestrol) is rarely if ever used because of cardiovascular toxicity and feminization: GnRH antagonists have recently been introduced and their use may increase in the future.

Treatment of Disease Progression

If the prostate cancer progresses (locally or distant) then initial treatment is hormonal, utilizing the drugs mentioned in the preceding text. Patients receiving hormonal therapy may suffer from osteoporosis with attendant risks for fractures (Krupski *et al.*, 2004; Diamond *et al.*, 2004). Caucasian patients and those of lower BMI are at increased risk for fractures. For these patients, it makes sense to consider a baseline screening for bone density. For patients at risk for bone loss or when it is demonstrated, treatment with a

bisphosphonate may be appropriate. At present these are not routinely indicated, but clearly the elderly (≥80 years) are at increased risk for osteoporosis and falls.

PROSTATITIS

Prostatitis is one of the most enigmatic disease labels in medicine. As a word, it implies inflammation of the prostate; yet in the current classification, one subcategory specifically excludes inflammation. The primary symptoms associated with this disease label are irritative LUTS and pelvic pain. It has often been associated with younger men (Moon *et al.*, 1997) though some recent data suggest increasing prevalence through old age (Roberts *et al.*, 1998; McNaughton Collins *et al.*, 2002).

Definition and Classification

The word prostatitis itself by traditional definition is one of inflammation (infection) of the prostate. The process has been subdivided into acute and chronic. Several decades ago it was recognized that not all patients had a bacterial infection and so the term nonbacterial prostatitis was coined. Next, there was a recognition that not all men with symptoms had either an infection or an inflammatory process and thus prostatodynia arose. Finally, in the current classification the recognition that men without symptoms often have histological prostatic inflammation led to the fourth category (Table 9). So what do these men have in common: essentially lower urinary tract symptomatology and pelvic pain. In the early 1990s, the National Institute of Diabetes and Digestive and Kidney Diseases brought together a group of experts and interested individuals to develop a consensus definition of prostatitis (Krieger *et al.*, 1999). This classification is now the basis for most research studies (Table 9). Categories 1 and 2 are fairly straightforward in that category 1 is acute bacterial prostatitis. Patients with this disease present with an acute urinary tract infection and frequently with systemic symptomatology. Patients with category 2 chronic bacterial prostatitis present with relapsing urinary tract infections. The primary requirement for category 3 prostatitis is pelvic pain. This is subdivided into 3a and 3b. 3a is inflammatory nonbacterial prostatitis for which expressed prostatic secretions demonstrate the presence of leukocytes. In category 3b, no leukocytes are present in the expressed prostatic secretions. Category 4 was introduced to cover the incidental finding of inflammation in the prostate in the absence of symptoms: for example, during a biopsy for possible prostate cancer.

Table 9 Classification of prostatitis

Category	Name	Factors
1	Acute Bacterial Prostatitis	Acute urinary tract Infection Systemic symptoms of fever, malaise, myalgia
2	Chronic Bacterial Prostatitis	Recurrent urinary tract infections Between symptomatic episodes cultures localize to prostate
3a	Inflammatory Chronic prostatitis/chronic pelvic pain syndrome	Pelvic Pain Leukocytes in expressed prostatic secretions usually with positive urinary symptomatology
3b	Noninflammatory CP/CPPS	Same as III a but no leukocytes in EPS
4	Asymptomatic inflammatory prostatitis	Incidental finding when prostate being evaluated for other reasons. For example, prostate cancer

Epidemiology

Until the last decade prostatitis was generally thought of as a young man's disease. Part of the reason for that belief occurs because there is significant overlap in the symptomatology between prostatitis symptoms and those of BPH/lower urinary tract symptomatology (Neal and Moon, 1994). However, various reviews of diagnostic coding and patient questionnaires have revealed an increasing incidence and prevalence with age (Roberts *et al.*, 1998; McNaughton Collins *et al.*, 2002). In one study reviewing physicians assigned prostatitis diagnoses in Olmsted County, MN, there were two age-associated peaks: patients aged 20–30 years had 4 cases per thousand person years and over 70 years at 5 cases per thousand person years (Roberts *et al.*, 1998). In another national health professional study, the overall prevalence was 16% with 75% of these patients being first treated before age 60 (McNaughton Collins *et al.*, 2002). Of interest, patients with a diagnosis of BPH had an eightfold increased likelihood of being diagnosed with prostatitis suggesting either a causal association between the two diagnoses, or alternatively that there is much overlap between the two entities making separation more difficult (more likely). Indeed, in a population-based study from Canada evaluating prostatitis symptom scores, no difference was seen in the prevalence rates for patients less than or over 50 years of age (11.5 vs 8.5%, respectively) (Nickel *et al.*, 2001).

Etiology

The etiology of category 3 prostatitis is one of the least understood diagnoses in medicine. Category 1 (acute bacterial) prostatitis is a lower urinary tract infection. In addition to the usual lower urinary tract symptomatology (frequency, urgency, dysuria) the patient is usually constitutionally sick with hesitancy, poor flow, feeling of incomplete emptying, high fever, chills, nausea, and vomiting. In most cases, there are also obstructive voiding symptoms. The most common infectious agents are *Escherichia coli*, *Klebsiella*, *Proteus*, and *Pseudomonas*. The prevalence of gram-positive bacteria is a debated subject. Certainly, *Staphylococcus aureus*, and *Enterococci* may on occasion cause infection but infections with *Staphylococcus epidermis*, and *Corynebacterium* are debated (Nickel *et al.*, 2003). Of interest, the FDA has recently accepted more gram-positive cultures as evidence

of chronic prostatitis than would earlier have been accepted (Bundrick *et al.*, 2003).

Category 2 (chronic bacterial) prostatitis presents as recurrent urinary tract infections where localization tests (performed between acute infections) would reveal prostatic infection. These patients account for only 5% of chronic prostatitis cases.

Category 3 chronic prostatitis (inflammatory 3a or non-inflammatory 3b) represents the majority of patients. The etiology for these patients is unclear, but a variety of etiologic possibilities have been postulated (Nickel, 2002). These include dysfunctional voiding, immunologic factors, pelvic floor abnormalities, and psychological factors. Category 4 prostatitis reflects an incidental finding of prostatitis.

Diagnosis/Evaluation

The diagnosis of patients with prostatitis consists of taking a history and physical exam (Table 10). The primary area concerns urinary symptomatology. However, an evaluation of back problems (*referred* pain) and bowel function are important. In 1999, the NIH published a chronic prostatitis symptom index (Litwin *et al.*, 1999) (Table 11) which while not essential for individual practitioners allows researches to uniformally compare data and also monitor changes in patient symptoms.

The physical examination should include a rectal examination and focused neurological examination to rule out other causes of lower urinary tract symptomatology. At the time of rectal examination prostatic massage is performed to obtain an expressed prostatic secretion (EPS) or at least a VB3 (postmassage urine). The one exception to prostatic massage is in the patient with acute bacterial prostatitis where such an examination could lead to septicemia.

Laboratory Testing

Traditionally the urine specimen was divided into 4 specimens (4 glass test). These were the initial stream urine (VB1 – to evaluate for urethral organisms), midstream urine (VB2 – to evaluate for cystitis), EPS, and VB3 urines as a surrogate for EPS, which is not obtainable in all patients, and is intended to define a prostatic infection/inflammation.

If hematuria is noted on the VB1 or 2 specimens then the patient will need an evaluation for hematuria to rule out upper urinary tract abnormalities. Generally, this will consist of a CT urogram and cystoscopy. A urine cytology is also appropriate for patients with hematuria or severe irritative lower urinary tract symptomatology, which could be caused by transitional cell carcinoma or carcinoma *in situ*.

If patients fail initial therapy and where voiding dysfunction is a problem then formal pressure flow urodynamic evaluation may be necessary and appropriate. In either case, a referral to a urologist will be necessary.

Prostatic ultrasound is rarely helpful in this disease. Occasionally, it may identify rare abnormalities such as prostatic cysts, prostatic abscess, or an obstructed seminal vesicle.

Table 10 Evaluation of patients with prostatitis

History		
Symptom index		
Physical Exam		
Including renal scan		
Prostatic massage for collection of EPS/Postmassage Urine		
NOT ACUTE PROSTATITIS PATIENTS		
Laboratory Tests		
4 glass test	VB1	Initial stream urine
	VB2	Mid stream urine
	EPS	Expressed prostatic secretions
	VB3	Post massage urine
2 glass test – VB2, VB3		
Urine culture		
Urine cytology – If hematuria present		
Urodynamics – May be required to evaluate voiding dysfunction-if initial treatment fails		

Treatment

Despite the fact that most urologists, let alone primary physicians, don't evaluate prostatic fluid/VB3 for bacteria or other microorganisms the majority will initiate antibiotic therapy (McNaughton Collins *et al.*, 2002) (Table 12). Clearly, with chronic bacterial prostatitis being present in only 5% of patients this treatment will not be very effective. In the absence of prostatic cultures persistence with antibiotics, filling one after the other (an all too often seen occurrence) is futile. Fluoroquinolones have become the treatment of choice for chronic bacterial prostatitis. Drugs should be given for 2–4 weeks. If a true infection is found then therapy in some cases will be necessary for up to 12 weeks to eradicate it completely. Trimethopim and Sulfamethoxazole (Bactrim) have been used for many years. However, increasing bacterial resistance is reducing the appropriateness for this drug. Doxycycline is considered a second-line drug. The place of fungal infections in prostatitis is unclear, but occasionally some patients may benefit from a trial with an antifungal agent such as diflucan.

α-Blockers

The prostate is innervated with α-1 adrenergic receptors ($\alpha 1_a$ on the smooth muscles and $\alpha 1_b$ on the blood vessels). The bladder body also has adrenergic innervation but primarily with $\alpha 1_d$ receptors. Thus, a drug, which blocks $\alpha 1_{a/d}$ receptors, should lead to a reduction in irritative bladder symptoms ($\alpha 1_d$) and improvement in obstructive symptoms ($\alpha 1_a$). As many prostatitis patients are thought to have voiding dysfunction with reflux of urine into the prostatic ducts, resection of the prostate should reduce this problem and likely reduce chemical inflammation and symptoms. The use of α-blockers has recently been reviewed (Moon, 2004). No good large randomized clinical trials have been performed but the general sense is that they have a place in the

Table 11 NIH–Chronic Prostatitis Symptom Index (NIH–CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	❑ 1	❑ 0
b. Testicles	❑ 1	❑ 0
c. Tip of the penis (not related to urination)	❑ 1	❑ 0
d. Below your waist, in your public or bladder area	❑ 1	❑ 0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	❑ 1	❑ 0
b. Pain or discomfort during or after sexual climax (ejaculation)?	❑ 1	❑ 0

3. How often have you had pain or discomfort in any of these areas over the last week?

❑ 0 Never
❑ 1 Rarely
❑ 2 Sometimes
❑ 3 Often
❑ 4 Usually
❑ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
0	1	2	3	4	5	6	7	8	9	10
NO PAIN									PAIN AS BAD AS YOU CAN IMAGINE	

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

❑ 0 Not at all
❑ 1 Less than 1 time in 5
❑ 2 Less than half the time
❑ 3 About half the time
❑ 4 More than half the time
❑ 5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

❑ 0 Not at all
❑ 1 Less than 1 time in 5
❑ 2 Less than half the time
❑ 3 About half the time
❑ 4 More than half the time
❑ 5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

❑ 0 None
❑ 1 Only a little
❑ 2 Some
❑ 3 A lot

8. How much did you think about your symptoms, over the last week?

❑ 0 None
❑ 1 Only a little
❑ 2 Some
❑ 3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

❑ 0 Delighted
❑ 1 Pleased
❑ 2 Mostly satisfied
❑ 3 Mixed (about equally satisfied and dissatisfied)
❑ 4 Mostly dissatisfied
❑ 5 Unhappy
❑ 6 Terrible

therapeutic armamentarium. Unfortunately, the largest randomized clinical trials recently conducted by the NIDDK failed to define a drug effect (Alexander *et al.*, 2004). However, as the authors point out, the population was heavily pretreated and resistant to other treatments.

The use of α-blockers has also been tried in conjunction with antibiotics for patients with chronic bacterial prostatitis. The general conclusion is that combining the two drugs and continuing the α-blocker for 6 months will reduce the likelihood of recurrence (Barbalias *et al.*, 1998).

Table 12 Treatment of prostatitis

Antibiotics	Commentary
Fluoroquinolines	If culture negative, one therapeutic trial is sufficient
α-blockers	Studies mixed but efficacy predicated upon voiding dysfunction amenable to α blockade
Anti-inflammatory drugs	Nonsteroidal anti-inflammatory drugs should reduce inflammatory parameters
Physical therapy	Pelvic flow massage and myofascial release
Microwave therapy	Although approved for benign prostatic hypertrophy small scale studies suggest efficacy

Physical Therapy

Physical therapy covers two main entities: prostatic massage and pelvic floor massage/myofascial trigger point release. Prostatic massage has mixed reviews. A recent publication by a panel of North American "prostatitis experts" could not come to a concensus as potential benefits (Nickel *et al.*, 1999).

Pelvic Floor Massage

It has been suggested that some patients develop chronic tension in the pelvic floor muscles as a result of many factors (Anderson, 1999). These include dysfunctional voiding, sexual abuse, constipation, and even stress and anxiety. These abnormalities may lead to pelvic trigger points causing pain. Physical therapy to release these trigger points has been reported to improve symptoms in patients. However, these methods have not been studied in a randomized clinical trial.

Minimally Invasive Therapy

Microwave thermotherapy has been reported to alleviate symptoms in patients with category 3a chronic prostatitis. The hypothesized mechanism of action is by possible denervation of the prostate by heat therapy. However, no large long-term randomized clinical trials have been performed.

Other Therapies

Because prostatitis is in many reports a symptom complex rather than a disease process, many different interventions have been utilized. These include anti-inflammatory agents, muscle relaxants, hormone therapy, and phytotherapeutics. These have been reviewed elsewhere (Nickel, 2002).

KEY POINTS

- Benign prostatic hyperplasia (as an histologic entity) may or may not be the cause of lower urinary tract symptoms in older men.
- The key issue for whether or not to treat men with BPH/LUTS is BOTHER.
- Screening for prostate cancer is only appropriate for men with more than 10 years' life expectancy.
- Older (>70 yrs) patients with high-grade prostate cancer will still die from cancer as well as competing comorbidities.
- Most patients (>95%) with prostatitis do not have an infection.
- Prostatitis is probably a catchbag for multiple pathologic entities.

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Urinary Incontinence

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Some men there are love not a gaping pig,
Some that are mad if they behold a cat,
And others when the bagpipe sings i'th' nose
Cannot contain their urine.

William Shakespeare (1564–1616),
Shylock, in The Merchant of Venice, act 4, sc. 1.

INTRODUCTION

Unlike other parameters of geriatric health, such as cognition, balance, and mood, continence is an attribute that is rarely appreciated until there is almost complete failure of the underlying physiological regulatory mechanisms. Additionally, despite the great strides that have been made in dissociating social stigma from a variety of diseases, including sexually transmitted diseases and acquired immune deficiency syndrome, urinary incontinence (UI) continues to suffer from the reluctance of both patient and provider to address the problem. Embarrassment, lack of awareness of the associated serious comorbidity and mortality, as well as ignorance regarding the availability and efficacy of several therapeutic options have been implicated as factors that deter due attention to this deadly disease (Dugan *et al.*, 2001; Horrocks *et al.*, 2004; Kinchen *et al.*, 2003; Shaw *et al.*, 2001). With the advent of the "baby boomers" and the projected increase in the proportion of older adults, UI and the attendant consequences will loom large on the horizon of geriatric disease. Thus, in this climate, health-care providers who fail to identify and adequately treat older adults with UI are delivering substandard care.

UI in older adults is a potentially devastating disease. Affected adults may exhibit significant functional decline and frailty, resulting in increased risk of institutionalization and death. Abundant data confirms the negative effect of UI on the quality of life of affected elders (Bradway, 2003; Johnson *et al.*, 2000).

Reported prevalence for UI varies from 15% among relatively healthy community-dwelling older adults to 65% among the frail elderly (Brandeis *et al.*, 1997; Holroyd-Leduc *et al.*, 2004; Landi *et al.*, 2003; Sgadari *et al.*, 1997). In the United States, more than 17 million adults suffer from UI (Hu *et al.*, 2004). However, available figures most likely underestimate the true prevalence of this syndrome for a variety of reasons. Major reasons identified for inaccurate reporting of the true prevalence of UI include failure to perceive the significance and ominous implications of UI by affected elders, and also the misconception that UI is an expected consequence of aging. Patient embarrassment, discomfort, and lack of awareness of effective treatment options are other barriers to self-reporting (Dugan *et al.*, 2001).

Annually, the direct cost of UI exceeds US $20 billion, with approximately 74% of this amount being spent on incontinence care in women. Two-thirds of the direct cost for UI care in women is spent on community-dwelling women (Hu *et al.*, 2004; Wilson *et al.*, 2001). Overall, the incremental lifetime medical cost of treating an older adult with UI approaches US $60 000 (Birnbaum *et al.*, 2003).

Indirect costs arising from factors such as reduced work productivity of the patient or the caregiver elevate the economic burden of UI even further. Of paramount importance in estimating the societal cost of UI is the recognition of associated intangible costs reflected in compromised quality of life, decreased feeling of well-being, psychological instability, and loss of self-esteem (Hu *et al.*, 2004).

RISK FACTORS

UI is less frequent in men. Zunzunegui Pastor *et al.* reported a prevalence of UI of 14% in older community-dwelling men compared to a prevalence of 30% among their female counterparts. Nevertheless, advancing age is associated with a higher frequency of UI in men, but not in women.

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Additional associated factors include coexisting morbidity, cognitive dysfunction, functional impairment, gait abnormality, diuretic therapy, and obesity (Zunzunegui Pastor *et al.*, 2003). Notably, most independent risk factors for UI are potentially reversible (Landi *et al.*, 2003). The onus lies with providers to identify and treat such risk factors in all patients being evaluated for UI.

PATHOPHYSIOLOGY OF URINARY INCONTINENCE IN THE ELDERLY

Several age-related changes threaten lower urinary tract function in the elderly. These include an increase in the frequency of uninhibited detrusor contractions, impaired bladder contractility, abnormal detrusor relaxation patterns, and reduced bladder capacity. An increase in nocturnal urine production also occurs. Anatomically, prostatic size increases in men, while urethral shortening and urethral sphincter weakening occurs in women. In addition to these physiological and anatomical age-related changes, the increased frequency of lower urinary tract disease in older patients further increases the risk of UI (Enriquez, 2004; Kevorkian, 2004; Klauser *et al.*, 2004; Lluel *et al.*, 2003; Patel *et al.*, 2002; Tan, 2003; Whishaw, 1998; Yoshida *et al.*, 2004).

Although providers tend to defer screening for UI until later in life, the framework for UI is often laid much earlier in life. Predisposing factors for UI should be sought in all patients regardless of age. Female gender is an irreversible predisposing factor and mandates routine enquiry for UI in all women regardless of age. The presence of structural congenital abnormalities such as hypospadias, epispadias, and ambiguous genitalia may also compromise bladder continence. With aging and the increased likelihood of disease, inciting factors such as cerebrovascular disease, radical pelvic surgery and autonomic degeneration further increase the risk of UI (Allen *et al.*, 2004; Ayed *et al.*, 1995; McLoughlin & Chew, 2000; Mouriquand *et al.*, 2003). Available data indicates that the occurrence of cerebrovascular disease doubles the risk of UI in older females. Obesity, frailty, and diabetes are other strong predictors of the occurrence of UI (Enriquez, 2004; Klausner and Vapnek, 2003; Landi *et al.*, 2003; Namikawa, 1999; Ouslander, 2000). Additionally, older adults are more likely to become incontinent following the onset of UI-promoting factors such as constipation, obesity, and polyuria from uncontrolled hyperglycemia, hypercalcemia, or diuretic therapy. Traditional geriatric pathophysiological factors such as impaired cognitive function, functional impairment, and frailty may also precipitate incontinence as a manifestation of global decompensation.

CLASSIFICATION

Accurate classification of UI should include reference to both the temporal course and the mechanistics of involuntary urine loss. Several mnemonics have been developed for the causes of transient or reversible incontinence (Figure 1; Table 1). Previously, continent patients who experience incontinence in the acute-care setting are likely to have underlying reversible causes of incontinence. Acute-care protocols that incorporate screening and detection of such risk factors are critical to reducing the incidence of incontinence in acutely hospitalized elders. Classification of UI in this manner also facilitates efficient and cost-effective intervention, as recognition and correction of causes of transient incontinence prevents unnecessary and expensive investigations and invasive studies.

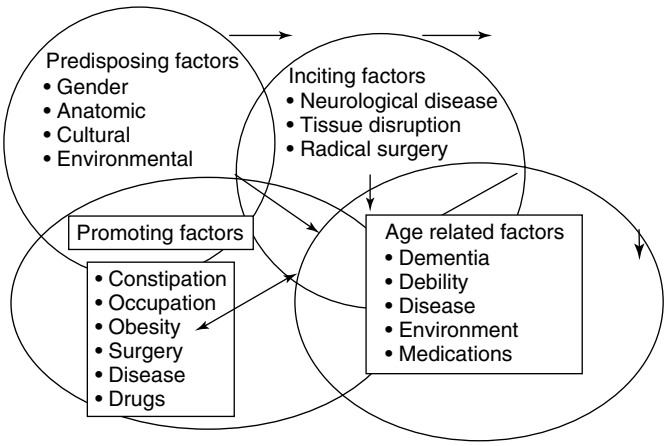

Figure 1 Risk factors for urinary incontinence

Table 1 Causes of reversible urinary incontinence

D Delirium	D Delirium
I Infection	R Restricted mobility, retention
A Atrophic vaginitis	I Infection, inflammation, impaction
P Pharmaceuticals	P Polyuria, pharmaceuticals
P Psychological disorders	
E Endocrine disorders	
R Restricted mobility	
S Stool impaction	

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Mechanistic classification of UI results in five major categories: UI associated with overactive bladder (OAB), stress incontinence, overflow incontinence, and functional incontinence. Combinations of these categories constitute the fifth category that is referred to as *mixed incontinence*. Bladder overactivity and impaired contractility frequently occur in conjunction in patients with diabetes mellitus. Similarly, benign prostatic enlargement often presents with symptoms of bladder overactivity as well as urinary retention (Johnson and Ouslander, 1999; Nasr and Ouslander, 1998; Ouslander, 2000; Ouslander and Schnelle, 1995).

Urinary Incontinence Associated with Overactive Bladder

Overactive bladder occurs in 1 of 4 adults over the age of 65, and is the most common cause of UI in the elderly,

accounting for 40–70% of all cases. Characteristically, overactive bladder results from involuntary contractions of the detrusor muscle, resulting in a strong urge to pass urine in unusually low volumes. Clinically, OAB manifests with urgency, frequency, and nocturia with or without urge incontinence (Newman, 2004; Teleman *et al.*, 2004; Tubaro, 2004; Yoshida *et al.*, 2004). Persons with urge incontinence present with involuntary urine loss preceded by a sudden, urgent, and strong desire to void.

Electrical field stimulation studies have identified at least three different mechanisms of detrusor muscle contraction. The major mechanism is cholinergic, and is mediated through the effect of acetylcholine (Ach) on muscarinic bladder receptors. A second mechanism (purinergic) involves adenosine triphosphate (ATP)-mediated bladder contraction. A third and poorly defined mechanism is thought to be nonneuronal and attributed to local urothelial Ach production and a paracrine effect on local muscarinic receptors located in the bladder. Age-related reduction in cholinergic and purinergic bladder transmission has been identified. However, purinergic transmission appears to play a greater role in bladder contraction in older adults, indicating disproportionate age-related compromise in cholinergic function. Available data also indicates an age-related compromise of nonneuronal uroepithelial Ach production (Wuest *et al.*, 2005; Yoshida *et al.*, 2004).

Stress Incontinence

Stress incontinence is the underlying cause in 25% of women with UI, and results from anatomical or pathological disruption of the angle between the bladder neck and the urethra, thereby disrupting continence. Causes of stress incontinence include vaginal childbirth, and pelvic surgery such as hysterectomy or prostate surgery (Jackson *et al.*, 2004; Molander *et al.*, 2002; Van der Varrt *et al.*, 2002).

Characteristically, stress incontinence presents with involuntary urine loss resulting from increases in intra-abdominal pressure in the presence of a relatively incompetent urethral sphincter mechanism. Thus, involuntary urine loss may occur when the patient laughs, coughs, or sneezes. In severe cases, UI may occur with a change in posture from supine or sitting to standing.

Overflow Incontinence

Overflow incontinence results from bladder outlet obstruction, resulting in massive bladder distension. Consequently, involuntary urine loss results from a buildup of intravesical pressure until the mechanical outlet obstruction is overcome by sheer pressure. Persons with overflow incontinence complain of persistent trickling of urine in the presence of suprapubic distension. In men, prostatic enlargement is the most common cause of overflow incontinence. Pelvic masses, such as uterine fibroids, or cystoceles may cause similar obstructive symptoms in women (Borrie *et al.*, 2001; Chapple, 2001; Grosshans *et al.*, 1993).

Functional Incontinence

Functional incontinence refers to involuntary urine loss resulting from inability to gain access to toileting facilities for a variety reasons including limited mobility, impaired cognition, lack of motivation, environmental barriers, or restricted access. This is a common cause of incontinence in frail elders with dementia, cerebrovascular disease, Parkinson's disease, or delirium. Altered mental status from narcotics, sedatives, or narcoleptic agents are also frequently implicated (Chadwick, 2005; Vickerman, 2002). Inappropriate use of physical or chemical restraints, poor vision, depression, reduced exercise tolerance, gait abnormality, or fear of falling are other miscellaneous causes of functional incontinence.

COMPLICATIONS AND CONSEQUENCES OF URINARY INCONTINENCE

Deleterious effects of UI are far reaching and multidimensional. Various aspects of quality of life are affected. Older adults with UI frequently suffer from embarrassment and loss of self-confidence and self-esteem. Sixty percent of older adults with UI develop depressive symptoms. Unpredictable involuntary urine loss frequently results in the affected elders becoming increasingly isolated as a result of voluntary restriction of social interaction and travel. Limitation of physical activity in affected elders may compromise functional status and hasten progression to frailty. Intimate relationships may also be adversely affected by the onset of incontinence, as affected persons avoid sexual activity with partners for fear of involuntary urine loss during intercourse. Indeed, available data highlights an independent association between sexual dysfunction and UI in older men (Bradway, 2003; Hogan, 1997; Johansson *et al.*, 1996; Miner, 2004; Saltvedt *et al.*, 2002).

Financially, the economic costs of UI may be extremely burdensome. Protective garments and beddings are relatively expensive, and are often not covered by insurance plans. The productivity of older adults in the workforce may be negatively affected by the threat of frequent and unpredictable episodes of incontinence. Likewise, the productivity of caregivers of patients with UI may be compromised by their inability to cope with the demands of a relative with UI. Indeed, available data highlights UI as the most common cause of institutionalization of elders. Likewise, in long-term care facilities, the resident with UI imposes an additional annual financial burden of approximately $5000 to total health-care costs (Bradway, 2003; Hogan, 1997; Johansson *et al.*, 1996; Miner, 2004; Saltvedt *et al.*, 2002).

Table 2 Complications of urinary incontinence

- Recurrent urinary tract infections
- Skin infections
- Balanitis
- Pressure ulcers
- Falls
- Fractures
- Depression
- Decreased libido and sexual dysfunction
- Acute hospitalization
- Social isolation
- Caregiver stress
- Reduced feeling of well-being
- Institutionalization
- Increased health-care costs

Medical complications further compromise health-care related quality of life. In women with incontinence aged over 65, the incidence of falls and fractures increases significantly. Approximately, 20–40% of women with UI will fall within 12 months and of these about 10% will result in fractures, usually of the hip. Available data also indicates a strong association between UI, acute hospitalization, and institutionalization (Gray, 2003; Wilson, 2003, 2004). Thirty percent of women with UI over the age of 65 are likely to be hospitalized within 12 months. Older men are twice as likely to be hospitalized over a 12-month period (Saltvedt *et al.*, 2002). Of the myriad complications associated with UI, the most alarming is the independent association between UI and increased mortality (Table 2).

CLINICAL DETECTION OF UI

Older adults with UI rarely volunteer this information as a presenting complaint. The onus is therefore on the providers to screen for UI in all older adults. Several older patients labor under the misconception that UI is part of the normal aging process. Other patients may be embarrassed by the nature of the complaint, especially when interacting with a health-care provider of the opposite gender. Decreased awareness of available therapeutic options may also discourage the patient from complaining. As a result of these factors, delayed presentation is typical, with most patients with severe continence, manifesting with loss of large volumes of urine, present themselves after 2 years or more after the onset of symptoms (Miller *et al.*, 1999; Resnick *et al.*, 1994; Rodriguez *et al.*, 2003).

In most cases, a detailed history will enable accurate classification of UI (Table 3). Specific inquiry should be made regarding volume of urine lost, strength of urinary stream, position in which urine loss is most likely to occur, number of pads used, and associated fecal incontinence. Quality of life and caregiver burden should also be assessed. Additional information should be sought regarding risk factors, and predisposing factors (Figure 1). Enquiry should also be made as to a coexisting history of diabetes mellitus, hypercalcemia, impaired cognition, functional disability, or impaired sensory perception. Medication history is critical (Table 4). Diuretics and hyperosmolar agents such as mannitol may contribute to polyuria. Anticholinergic agents may cause obstruction and consequent overflow incontinence. Narcotics, sedative, and hypnotics may impair cognition or cloud consciousness.

An accurate voiding diary is an important tool that facilitates the quantification of severity and classification of UI. Serial diaries also facilitate assessment of response to intervention. Although 7-day diaries are still done, available evidence indicates that shorter voiding diaries (48 or 72 hours) are comparable in reliability and validity to the 7-day diaries and are perceived as less burdensome by patients (Ku *et al.*, 2004; Nygaard & Holcomb, 2000; Singh *et al.*, 2004).

Physical examination of the patient with UI must include a complete neurological, abdominal, urogenital, pelvic, and rectal examination. The integrity of relevant superficial spinal reflexes, the anal and bulbocavernosus reflexes, should be assessed. Response to the cough reflex can easily be evaluated during pelvic examination, facilitating exclusion of stress incontinence. Persons with stress incontinence may actually be observed to lose urine during coughing. Patients with intact perineal sensation and reflexes will exhibit reflex tightening of the anal sphincter during coughing.

Bedside measurement of postvoid residual (PVR) volumes is helpful in the diagnosis or exclusion of overflow

Table 4 Some common medications that may cause incontinence

- Diuretics
- Anticholinergics
- Antihistamines
- Antipsychotics
- Antidepressants
- Sedatives/hypnotics
- Alcohol
- Narcotics
- α-adrenergic agonists/antagonists
- Calcium channel blockers
- Hyperosmolar intravenous infusions

Table 3 Clinical differentiation of urinary incontinence

Symptoms	OAB/urge	Stress	Overflow	Functional
Urgency	Yes	No	No	Variable
Leakage during activity or cough	No	Yes	Variable	No
Volume leaked	Large	Small	Small/dribble	Large
Ability to reach toilet in time	Reduced	Normal	Normal	Reduced
Nocturia	Yes	No	Variable	Yes

incontinence due to bladder outlet obstruction. Postresidual volumes greater than 150 cc in older adults suggest inadequate bladder emptying. PVR volumes greater than 200 cc are highly indicative of urinary retention. Where available, ultrasound measurements of PVR volumes are preferred over direct measurement using a urethral catheter due to the less invasive nature of bladder scans and the consequent lower risk of urinary tract infection (Lehman and Owen, 2001; Sullivan and Yalla, 1996).

PRACTICAL APPROACH TO THE INVESTIGATION AND MANAGEMENT OF UI

Diagnostic Evaluation

Comprehensive physical examination should yield preliminary information relating to PVR volumes and urethral sphincter competence. The primary care provider should also remain alert to other specific indications for specialist urological evaluation and ensure prompt referral. Thus, urinary retention due to obstructive uropathy, hematuria, prostate disease, recent pelvic surgery, recurrent urinary tract infections, and stress incontinence should prompt early referral for urological examination. However, the majority of older patients with functional UI or urge incontinence associated with overactive bladder can be effectively managed by geriatric or primary care providers.

Although urodynamic studies in the assessment of patients with UI are routinely conducted by urologists, available data indicates that results of this test are unlikely to alter management in a significant proportion of older adults. In older adults with UI, urodynamic studies are likely to be most helpful in patients being considered for surgical intervention or in patients in whom the diagnosis remains unclear after a thorough history and physical examination (Lovatsis *et al.*, 2002; Thompson *et al.*, 2000). Guidelines issued by the Agency for Healthcare Policy and Research recommend limitation of initial diagnostic work-up to urinalysis and measurement of PVR volumes. The American Medical Director Association's guidelines (AMDA) for the management of UI are even more conservative in recommending urinalysis only in patients with suspected urinary tract infection and new or worsening UI. AMDA guidelines recommend PVR measurements only in men and female patients at risk of retention due to coexistent neurologic disorders or diabetes mellitus (AMDA, 2000; Resnick *et al.*, 2004). Bedside cystometric studies have fallen out of favor mainly due to poor diagnostic accuracy, as evidenced by lack of correlation with results of urodynamic studies and failure of cystometry results to alter management initiatives based exclusively on clinical criteria (Byun *et al.*, 2003; Resnick *et al.*, 1996). The associated increased risk of urinary tract infection associated with urethral catheterization is an additional disadvantage of bedside cystometry (Hung *et al.*, 2005; Ouslander *et al.*, 1987).

Management

Effective management incorporates both nonpharmacological and pharmacological strategies. Although, traditionally, pharmacological therapy was withheld until nonpharmacological strategies proved effective, there is emerging controversial evidence that suggests that the parallel institution of both strategies may yield better results (Goode, 2004; Ouslander *et al.*, 2001). Nevertheless, the increased risk of adverse drug effects and interactions in older adults justifies caution with this approach. Thus, an initial trial of nonpharmacological therapy alone remains the conventional approach to treatment. However, inadequate response to nonpharmacological management should prompt consideration of drug therapy. Invasive procedures or definitive surgical intervention are occasionally warranted in older adults who can tolerate such procedures.

Nonpharmacological Intervention

The nature of nonpharmacological intervention varies with the type of incontinence. In patients diagnosed with overactive bladder, the mainstay of nonpharmacological management is behavior modification, tailored to suit the individual patient. Mentally competent, functional and highly motivated persons are good candidates for patient-dependent intervention such as biofeedback therapy. In dependent or cognitively impaired patients, caregiver-dependent toileting protocols are more appropriate and likely to be more effective. Prompted voiding is a caregiver-dependent strategy that offers the patient a regular opportunity to use the toilet. The designated caregiver offers toileting assistance at scheduled intervals, usually starting with a short period of about 2 hours. Prompted voiding has the added advantage of providing the patient an opportunity for social interaction and positive reinforcement. Habit training is a more complex variant of this method, where persons with UI are encouraged to link voiding to specific activities, such as meals, drinks, or just before outings. Eventually, regular toileting becomes a "habit", and involuntary urine loss is preempted.

Older adults who are more severely cognitively impaired may be unable to respond appropriately to communication, and thus a simple timed toileting schedule may be more appropriate. In such cases, the caregiver toilets the patient consistently at predetermined intervals. Prompted voiding and habit training are also helpful in the management of older adults with functional incontinence. Environmental assessment, and modification if indicated, is a pivotal component of the management of functional incompetence. Adaptive equipment and assistive appliances may help facilitate efficient toileting and reduce incontinent episodes.

Rehabilitative exercises focusing on pelvic muscles and biofeedback therapy may be helpful in patients with stress incontinence or mixed incontinence. In patients with mixed incontinence, a combination of pelvic floor exercises and bladder sphincter biofeedback therapy has been shown

to result in a reduction in episodes of involuntary loss (Teunissen *et al.*, 2004).

Pharmacological Therapy

Detrusor muscle contraction is dependent on the action of Ach on bladder muscarinic receptors. Thus, antimuscarinic drug treatment is appropriate for urge incontinence due to bladder overactivity being poorly responsive to nonpharmacological intervention. Traditionally, antimuscarinic drugs have formed the mainstay of management for this variant of UI. However, until recently, serious and prohibitive side effects such as delirium, cognitive impairment, orthostatic hypotension, falls, and cardiac arrhythmias have rendered this group of agents an unsafe choice to use in older adults. The emergence of selective antimuscarinic agents provides a safer alternative, although in older patients the occurrence of delirium, dry mouth, urinary retention, constipation, and blurring of vision are still troubling concerns.

Five different muscarinic receptor subtypes have been cloned (Table 5). M1, M4, and M5 receptor subtypes are found primarily, although not exclusively, in the nervous system. M2 and M3 receptors predominate in smooth muscle, although they are also present relatively small numbers in the brain and salivary glands. M2 and M3 receptors are also the major cholinergic receptors in the bladder. M3 receptors mediate direct detrusor muscle contraction, while M2 receptors appear to play a role in the inhibition of bladder relaxation and modulation of bladder contraction in pathological conditions, such as denervation injury or spinal cord disease. Differences in receptor subtype distribution are particularly important when considering adverse events associated with antimuscarinic agents in older adults.

Overall, oxybutynin and tolterodine are the two most commonly used antimuscarinic agents in the treatment of urge incontinence. Oxybutynin is a relatively nonselective antimuscarinic agent and acts primarily on M1, M2, and M3 receptor subtypes. Although oxybutynin has been shown to reduce episodes of UI by almost 50% in 60–80% of patients, there is a relatively high incidence of side effects, with approximately 75% of patients reporting discomfort arising from dry mouth. Tolerability is low, as evidenced by the high discontinuation rate (25%) due to peripheral anticholinergic side effects such as dry mouth, constipation, and blurred vision. Notably, central nervous system (CNS) side effects such as dizziness, cognitive dysfunction, delirium, and psychotic reactions have been reported in several studies, rendering oxybutynin a poor choice for the geriatric patient.

Table 5 Distribution of muscarinic receptors

- M1: Cortex, hippocampus, salivary glands
- M2: Hindbrain, heart, smooth muscle
- M3: Brain, salivary glands, heart, smooth muscle
- M4: Basal forebrain, striatum
- M5: Substantia nigra

Tolterodine is a more selective antimuscarinic agent that affects predominantly M2 and M3 receptor subtypes. Efficacy of tolterodine is comparable to oxybutynin. However, the incidence of peripheral anticholinergic side effects, such as dry mouth, is much lower. Additionally, only three case reports of cognitive dysfunction related to tolterodine use exist in the literature. Available data favor the use of the extended release formulations of tolterodine over the immediate release due to greater efficacy, higher tolerability, and higher adherence rates (Hartnett & Saver, 2001; Rovner and Wein, 2002).

More recently, two M3 selective inhibitors, darifenacin and solifenacin have emerged as viable pharmacological therapeutic options for overactive bladder. Available data suggests comparable efficacy with the older agents. However, adverse effects such as constipation and blurred vision, in conjunction with the notable paucity of safety and tolerability data in older adults preclude objective comment regarding prescription of these agents in geriatric practice (Jimenez Cidre, 2004; Robinson & Cardozo, 2004).

Trospium has recently been approved by the Federal Drug Administration in the United States for the treatment of overactive bladder in the elderly. However, this drug has been in use in Europe over the past three decades, and available literature indicates a relatively clean safety profile. Unlike the M2/M3 selective agents that are lipophilic, tertiary amines, trospium is a hydrophilic, quaternary amine. These unique biochemical properties render the blood-brain barrier relatively impermeable to trospium, thereby reducing the risk of unwanted CNS side effects. Additionally, available evidence indicates that trospium may exert a significant local effect on nonneuronal cholinergic receptors located in the detrusor muscle. Trospium is not metabolized by the cytochrome p450 system and, therefore, is less prone to drug interactions. Although available global data suggests that trospium is an effective agent and may be well suited for the treatment of urge incontinence in the elderly, further studies specifically relating to safety and tolerability in the frail elder are needed (Gaines, 2005; Rovner, 2004; Scheife and Takeda, 2005).

INVASIVE PROCEDURES AND SURGICAL MANAGEMENT

Periurethral sphincter collagen injections and vaginal pessaries are viable and reasonably effective options for older adults unable to tolerate surgery.

Sacral neuromodulation involves surgical implantation of a "bladder pacemaker" in the patient's hip attached to a lead wire that is threaded to a site within the sacral canal at the base of the spine. External programming results in the delivery of a painless electrical stimulus to the sacral nerves, which regulate bladder function. This allows patients to control urine storage and expulsion.

For some patients with stress or overflow incontinence, surgery may be the only effective treatment. Older men with

overflow incontinence due to obstructive uropathy arising from prostatic enlargement may experience considerable relief following prostatectomy. Although several techniques have been described to treat stress incontinence, none of them is entirely satisfactory. The best long-term success rate has been documented following bladder neck slings. Prolene suburethral sling insertion is a new promising technique, with a documented cure rate of more than 80%. However, published follow-up does not exceed 3 years. Surgical complications of this procedure include retropubic hematoma, urinary tract infections and fibrosis, pubic osteomyelitis, urinary fistula, and transient postoperative urinary retention. Late complications include dysuria, urinary retention and detrusor instability, genital prolapse, sexual disorders, chronic pain, chronic urinary tract infections, and complications related to the use of biomaterials, including screws, synthetic tape, and artificial urinary sphincter. Nevertheless, quality of life studies after surgery for stress incontinence in younger patients shows consistent improvement. Data in older adults is lacking.

Tension-free vaginal tape (TVT) surgery, is a highly effective and minimally invasive alternative for treating patients with stress UI. Surgical complications include bladder perforation, urinary retention, pelvic hematoma suprapubic wound infection, persistent suprapubic discomfort, and intravaginal tape erosion (Abouassaly *et al.*, 2004; Ayoub *et al.*, 2004; Krissi *et al.*, 2004; Ouslander *et al.*, 1987).

KEY POINTS

- Urinary incontinence is a highly prevalent syndrome in older adults. Age-related physiological changes in bladder regulation and lower urinary tract dysfunction in the presence of coexisting morbidity increase the likelihood of urinary incontinence with aging.
- Urinary incontinence is classified into five major types: urge, stress, functional, overflow, and mixed incontinence. The most common type of incontinence in older adults is urge incontinence resulting from bladder overactivity.
- Routine screening for urinary incontinence is a critical component of routine geriatric evaluation. A comprehensive history and physical examination usually enables accurate diagnosis and classification. Initial diagnostic work-up should include urinalysis and postvoid residual measurements. Urodynamic studies are not indicated routinely and should be reserved for selected cases only.
- Treatment modalities comprise nonpharmacological, pharmacological, and surgical modalities. Selective antimuscarinic agents are the preferred pharmacological therapeutic option. Invasive modalities include periurethral collagen injections, vaginal pessary insertion, and sling procedures for stress incontinence.

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Renal Diseases

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INTRODUCTION

As the term 'Giants' in Geriatric Medicine has been coined to define the most frequent clinical conditions, there is also a group of renal conditions that we believe deserve the term "Nephrogeriatric Giants". For instance, although more than 50% of aged kidneys are normal in appearance, not all of them are actually normal because approximately 14% display cortical scars scattered across their surface (Griffiths *et al.*, 1976). Usually, if these scars are detected in a young person, they suggest pathology such as pyelonephritis, but in the aged kidney, in the absence of other abnormalities, these scars are a consequence of the normal aging process. Another aspect of the renal aging process is the change in kidney weight and size. The weight of the kidney slowly decreases to less than 300 g in the ninth decade of life. Renal length diminishes by 2 cm between the age of 50 and 80 years. The cortex is more affected than the medulla. In the latter, an increase is seen in the interstitial tissue; this is accompanied by fibrosis and increased fat content at the level of the renal sinus (McLachlan, 1987). A constant finding is the presence of cysts along the distal nephron (Baert and Steg, 1977).

After the age of 30, there is a gradual reduction in renal functional capacity. By the age of 60, these functions decrease to half the value they were at the age of 30 (Musso *et al.*, 2001). The deterioration of renal function with age can be explained in terms of either the progressive loss of functioning nephrons alone, or a decrease in the number of energy-producing mitochondria, lower concentration of adenosine triphosphatase activity and other enzyme levels, or decreased tubular cell transport capacity as observed in kidneys of old animals (Beauchene *et al.*, 1965). It is important to understand that these changes are not representative of any pathology, but only the normal aging process leading to a reduction in kidney function.

As has been previously stated, all the structural and functional changes of the aged kidney may be summarized under the heading of "Nephrogeriatric Giants"; six conditions that are so called because they are conditions in which there are profound modifications of renal physiology which occur in the majority of the elderly population (Musso, 2002):

1. Senile hypofiltration
2. Renal vascular alterations
3. Tubular dysfunction
4. Tubular frailty
5. Medullary hypotonicity
6. Obstructive uropathy.

NEPHROGERIATRIC GIANTS

Senile Hypofiltration

Glomerular sclerosis begins at approximately 30 years of age. The percentage of obsolete glomeruli varies between 1 and 30% in persons aged 50 years or more (McLachlan *et al.*, 1977). The glomerular tuft appears partially or totally hyalinized, and this is the basis of glomerulosclerosis which accompanies aging (Rosen, 1976). With age, there is a reduction in the length and surface of the glomerulus, which affects the effective filtration surface (Goyal, 1982). On microangiographic examination, there is obliteration, particularly of juxtamedullary nephrons, but not of those sited more peripherally, with the formation of a direct channel between afferent and efferent arterioles in this area of the kidney (Takazakura *et al.*, 1972). This presumably contributes to the maintenance of medullary blood flow. The mesangium, which accounts for 8% of glomerular volume at 45 years, increases to nearly 12% at the age of 70 (McLachlan, 1987).

Owing to the aforementioned changes, aging is accompanied by a decrease of glomerular filtration rate (GFR), renal plasma flow (RPF) and renal blood flow (RBF) (Cohen

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and Ku, 1983). The GFR evaluation with ^{51}Cr EDTA confirms that the elderly have lower GFRs than the young. At the third decade of life, GFR reaches approximately 140 ml/minute/1.73 m^2, and from then on, GFR progressively declines at a rate of 8 ml/minute/1.73 m^2 per decade (Rowe *et al.*, 1976a). The fall in creatinine clearance (Ccr) is followed by a decrease in creatinine production, and the relationship between blood and urine creatinine levels changes with age (Swedko *et al.*, 2003). This may be the reason serum creatinine concentration of 1 mg dl^{-1} reflects a GFR of 120 ml/minute in a person 20 years old and 60 ml/minute at the age of 80. If an elderly person has a normal adult creatinine level, it should be remembered that the GFR is diminished and hence the dose of drugs metabolized/eliminated through the kidney should be corrected to the true GFR (Musso and Enz, 1996). To calculate the Ccr in the elderly, the nomogram of Cockcroft and Gault is quite useful in daily clinical practice (Cockcroft and Gault, 1976):

$$\text{Ccr} = \frac{(140 - \text{age}) \times (\text{body weight})}{72 \times \text{serum creatinine}}$$

In women, it is 15% lower. It is of paramount importance to know that although creatinine clearance diminishes with age, the value of plasma creatinine remains stable and comparable to young adults, ranging from 0.9 to 1.3 mg dl^{-1}. Therefore, if we only take into account plasma creatinine levels without calculating creatinine clearance, we may falsely interpret the GFR as normal, thereby failing to recognize reduced renal function. For patients with a normal plasma creatinine level, one simple way to calculate GFR is 130 – age in years, but for patients with plasma creatinine >1.5 mg dl^{-1}, it is mandatory to calculate GFR according to the nomograms or 24-hour urine collection.

Renal Vascular Alteration

In apparently normal elderly individuals, prearterioles, from which afferent arterioles arise, show subendothelial deposition of hyaline and collagen fibers resulting in an intimal thickening (McLachlan *et al.*, 1977). Small arteries exhibit a thickening of the intima due to proliferation of the elastic tissue. This is associated with atrophy of the media, which virtually disappears when intimal thickening is prominent. Afferent arterioles show reduplication of elastic tissue, with thickening of the intima preceding the subendothelial deposition of hyaline material. Another characteristic of the aging kidney is the formation of anastomoses among afferent and efferent arterioles of the capillary tuft (Darmady *et al.*, 1973).

Ischemic nephropathy from nonmalignant nephrosclerosis has emerged as an important cause of terminal renal failure in the elderly patient with essential hypertension (Ritz and Fliser, 1992). Antihypertensive agents may impair renal blood flow (through plasma volume contraction) and further aggravate the age-related decline in renal perfusion. A worsening of renal perfusion may activate counterregulatory neurohormonal mechanisms, such as the renin-angiotensin-aldosterone system, which in turn may place the patient at increased risk for the development of glomerulosclerosis through promotion of vascular or mesangial hypertrophic changes or increased intraglomerular pressure, despite an associated reduction in systemic blood pressure (Weir, 1992).

Sometimes, renal function deteriorates suddenly and unexpectedly in hypertensive patients. This condition is commonly due to destruction of main renal arteries by atheroma, a cause of so-called *renovascular* renal failure. In hypertensive patients, poorly controlled blood pressure on several medications or rapid acceleration of hypertension can suggest renovascular disease. The classic association is a reversible renal failure after use of angiotensin-converting enzyme (ACE) inhibitors and unequal sized kidneys on echography. The importance of making the diagnosis is that it is often possible to regain some renal function, even in end-stage renal disease (ESRD), by intervention on the renal artery (Meyrier, 1996).

Tubular Dysfunction

Renal tubules undergo fatty degeneration with age, showing an irregular thickening of their basal membrane (McLachlan, 1987). By microdissection, the existence of diverticulae arising from the distal and convoluted tubules has been demonstrated, and this becomes more frequent with age. It has been suggested that these may serve as reservoirs for recurrent urinary tract infections in the elderly (Darmady *et al.*, 1973). There are also increasing zones of tubular atrophy and fibrosis, which may relate to the defects in concentration and dilution observed as part of the normal renal aging process (McLachlan, 1987).

Sodium (see Chapter 117, Water and Electrolyte Balance in Health and Disease)

Hypernatremia and hyponatremia are probably the commonest and most well known disturbances of the internal milieu in the elderly. In spite of the lower sodium tubular load, 24-hour urinary sodium output and fractional excretion of sodium are significantly greater in old and very old people (Macias *et al.*, 1987; Musso *et al.*, 2000). This suggests that the renal tubule of the elderly is unable to retain sodium adequately, either in absolute terms or when corrected to glomerular filtration. The mean half-time for a reduction of sodium excretion is 17.7 hours in persons under 30 years, reaching 30.9 hours in persons over 60, apparently mediated by the concomitant reduction in GFR (Meyer, 1989). As GFR declines with age and the amount of filtered sodium is lower than in young subjects; a salt load given to an elderly person takes longer to eliminate (Fish *et al.*, 1994). However, when sodium is restricted to 50 mmol/day, the period required to achieve equilibrium is 5 days in the young and 9 days in the elderly. As a result of these slow adaptations, both hypernatremia and hyponatremia are frequent findings in patients in geriatric wards (Solomon and Lye, 1990; Roberts and

Robinson, 1993). Under normal conditions, the elderly are not salt depleted because of replacement of renal sodium losses by salt contained in the diet. Problems may arise when patients are salt restricted for therapeutic reasons or when they become ill and lose their appetite. Both situations may easily lead to salt and volume depletion and even to acute renal failure (ARF). The incompetence of the aging kidney to conserve sodium may explain the facility with which the aged develop volume depletion (Macias *et al.*, 1980). The capacity of the aging kidney to adapt to a low salt intake (50 mmol/24 hour) is clearly blunted (Macias *et al.*, 1978). The proximal nephron behaves similarly in the young, old, and very old, whereas in the "distal nephron" (thick ascending limb of Henle's loop), a clear-cut difference in the handling of sodium in the elderly is evident, present in 85% of a study population of healthy elderly people (De Santo *et al.*, 1991; Musso *et al.*, 2004). The diminished capacity to reabsorb sodium by the ascending limb of Henle's loop in healthy elderly people has two direct important consequences. First, the amount of sodium arriving at more distal segments of the nephron (distal convoluted and collecting tubules) increases; and second, the capacity to concentrate in the medullary interstitium is also diminished, causing elderly subjects to exhibit both increased sodium excretion and an inability to maximally concentrate urine. Despite the elderly being more prone to an exaggerated natriuresis, total body sodium is not significantly decreased with age (Fulop *et al.*, 1985). Kirkland *et al.* (1983) found greater urinary elimination of water and electrolytes during the night in the elderly, which can, at least in part, explain the nocturia observed in 70% of elderly persons. Basal plasma concentrations of renin and aldosterone and the response to stimuli such as walking and salt restriction are also diminished in old age (Macias *et al.*, 1987). Thus, a dual effect of low aldosterone secretion and a relative insensitivity of the distal nephron to the hormone could account for diminished sodium reabsorption at this site. Atriopeptin in the elderly elicits a greater increase in natriuresis, calciuresis, diuresis, urinary, and plasma cyclic Guanydine monophosphate (cGMP) concentrations than in the young (Heim *et al.*, 1989).

Potassium (see Chapter 117, Water and Electrolyte Balance in Health and Disease)

Potassium content of the body is lower in the old than in the young and the correlation with age is linear (Cox and Shalaby, 1981). As 85% of potassium is deposited in muscle, and muscular mass diminishes with age, this may largely account for the fall in total body potassium, with other factors such as poor intake also playing some role (Lye, 1981). Under normal conditions, plasma potassium is normal in the elderly, but when diuretics are taken, they develop hypokalemia more rapidly than do the young (Kirkland *et al.*, 1983). The possible explanation for the tendency to develop potassium deficiency is an inability of the kidney to conserve potassium. On the other hand, it has been observed that the total renal excretion of potassium is significantly lower in the aged population than in the young. The clinical consequence of the tendency to excrete less potassium by the aging kidney, when total potassium urinary output is considered, is the vulnerability of elderly people to develop hyperkalemia (Lowental, 1994). This electrolyte disturbance is particularly frequent when elderly individuals are treated (either alone or in combination) with the following drugs: nonsteroidal antiinflammatory drugs (NSAIDs), ACE inhibitors, nonselective β-blockers (particularly during exercise) or potassium-sparing diuretics (especially in diabetics) (Andreucci *et al.*, 1996). Recently, a hyperfunction of the H+-K+ ATPase of the intercalar cells in the collecting tubules was described in old rats, generating a greater excretion of H+, and a greater reabsorption of potassium. This mechanism may also explain the trend in old people to develop hyperkalemia (Eiam-Ong and Sabatini, 2002).

Urinary Acidification

Macias *et al.* did not find differences in titratable acid, ammonia, or net acid excretion in response to an acute acid overload in old people, with respect to young controls. The maximal values of ammonia and titratable acid excretion, however, were reached four hours following the acid load in the young, and between six and eight hours in the old. The elderly subjects took longer to reach peak excretion, and experienced a greater fall in blood bicarbonate following the same dose of ammonium chloride (Macias *et al.*, 1983). Lindeman (1990) suggests that renal ammonium ion secretion in response to acid load is not different in healthy elderly subjects.

Calcium, Phosphate, and Magnesium

In general, it is a usual clinical finding to observe relatively low blood calcium and high phosphate levels in old age. In the urine, hyperphosphaturia is often found. Regarding calcium urinary output, some authors refer to the same range as for the young population, others have observed a tendency for it to be higher and other groups have found hypocalciuria (Galinsky *et al.*, 1987). These discrepancies may be explained by different calcium intake (dairy products) with or without the addition of vitamin D in these products. These changes in the metabolism of calcium and phosphate may be related to low levels of 1,25-dihydroxy-vitamin D found in the elderly, probably as a result of a deficit of renal 1-α-hydroxylase as an expression of the normal aging process. Serum levels of 24,25-dihydroxy-vitamin D are also low in the elderly. In addition, low plasma phosphate may lead to mild hyperparathyroidism, with further loss of bone mass (Perez del Molino and Alvarez, 2002; De Toro Casado and Macías Núñez, 1995). It is known that in old age, magnesium supplements are often required, probably because of a combination of diminished spontaneous intake of magnesium, poor intestinal absorption and increased urinary output. Approximately 80% of magnesium is filtered, 25% reabsorbed by proximal tubuli, and 65% by the thick

ascending limb of Henle's loop, which is functionally altered in the elderly. Consequently, a diminution of the reabsorptive capacity of the ascending limb may account for the negative balance of magnesium if oral intake is lower than optimal (Seeling and Preuss, 1994).

Erythropoietin Hormone

Erythropoietin hormone is mainly produced by the peritubular interstitial cells near the proximal convoluted tubules. There is no difference in plasma erythropoietin levels among healthy young, old, and very old people (Musso *et al.*, 2004).

Urea

In healthy old and very old people, fractional excretion of urea (FEU) is increased in comparison to the younger population: 65 and 50% respectively. This phenomenon could be secondary to a senile alteration in the UT1 (urea channels) that perhaps produces an increase in urea permeability at the collecting tubules (Musso *et al.*, 2004).

Medullary Hypotonicity

Aging reduces the capacity of the kidney to concentrate the urine (Rowe *et al.*, 1976b). The maximum urinary concentration remains constant until about the third decade and then falls by about 30 mosmol/kg for each subsequent decade. The diminution of the concentrating ability has been related to the decrease in GFR that occurs with age. The relative increase in medullary blood flow could contribute to the impairment of renal concentration capacity. The defect in sodium chloride reabsorption in the ascending limb of Henle's loop, which is the basic mechanism for the adequate function of the countercurrent concentration mechanism, may be an important factor for the decrease in the capacity to concentrate urine, as seen in the aged. Moreover, the increased FEU in this group of people could contribute to their medullary hypotonicity, since normally urea accounts for 50% of the interstitial tonicity (Musso *et al.*, 2004). The decrease in responsiveness of collecting duct tubular epithelium to circulatory antidiuretic hormone (ADH), is another explanation for impairment of urine concentrating ability, and it may also explain why plasma vasopressin levels are higher in the elderly compared to the younger population (Bengele *et al.*, 1981; Andreucci *et al.*, 1996). When healthy active elderly volunteers are water restricted for 24 hours, the threshold for thirst is found to be increased and water intake reduced in comparison with a control group of younger subjects (Phillips *et al.*, 1984). Dryness of the mouth, a decrease of taste, alteration in mental capacity or cortical cerebral dysfunction, and a reduction in the sensitivity of both osmoreceptors and baroreceptors may all contribute to the increased threshold for thirst. Finally, angiotensin concentration, a powerful generator of thirst, is lower in the elderly (Andreucci *et al.*, 1996). Total body water is slightly diminished with age, so that it comprises only 54% of total body weight, probably because old people have a greater proportion of body fat than the young. The diminution seems to be predominantly intracellular. Males have a higher volume than females, regardless of age (Macias *et al.*, 1987; Andreucci *et al.*, 1996; Shannon *et al.*, 1984). Thus, a low plasma volume in an elderly subject is almost always the result of disease (Macias *et al.*, 1987). Urinary dilution has not been extensively investigated in the old, but it has been found to be decreased. There is a minimum urine concentration of only 92 mosmol kg^{-1} in the elderly compared with 52 mosmol kg^{-1} in the young (Dontas *et al.*, 1972). Maximum free water clearance was also reduced in the elderly from 16.2 ml/minute to 5.9 ml/minute. Again, the functional impairment of the diluting segment of the thick ascending limb described above seems to account for the remainder of the diminution in the capacity to dilute urine as observed in the aged (Macias *et al.*, 1978).

Tubular Frailty

Tubular cells are frail in the elderly, and because of that they progress easily to acute tubular necrosis (ATN), and they also recover slowly from this histological alteration. Owing to these reasons, ARF is a frequent disturbance in the elderly (Musso, 2002; Macías Núñez *et al.*, 1996). The commonest causes of ARF in the old population are (Macías Núñez *et al.*, 1996; Musso and Macías Núñez, 2002):

1. *Prerenal causes*: loss of fluids (vomiting and diarrhea, diuretics); inadequate fluid intake; loss of plasma (burns); loss of blood (hemorrhage); shock (cardiogenic and septicemic).

2. *Renal causes*: ATN due to the persistence of the state of prerenal uremia and/or to nephrotoxins; rapidly progressive damage due to collagen disorders, Goodpasture's syndrome, Henoch-Schonlein purpura; arterial or venous thrombosis; acute interstitial nephritis (toxicity with drugs).

3. *Postrenal (obstructive) causes*: stones, clot, tumor, stricture, prostatic hypertrophy.

Prerenal and postrenal causes of ARF are of particular importance since their early identification and treatment may prevent the development of established ATN (Musso and Macías Núñez, 2002). The incidence of ARF in the elderly is higher than in the young, because of the frequency of systemic illnesses, poly pharmacy, and because of the renal aging process itself (Kafetz, 1983). There is also the intriguing role played by accumulation of superoxide radicals with aging. Some illnesses may predispose the aged kidney to develop ARF: cardiac insufficiency, diabetes mellitus, myeloma, prostatic enlargement, vasculitis, rapidly progressive idiopathic glomerulonephritis (GN), mesangiocapillary GN, and the proliferative variety of systemic lupus erythematosus (Frocht and Fillit, 1984). Other etiological agents are septic shock, postsurgical ARF and cardiogenic

shock. Poly pharmacy includes the use of diuretics, laxatives, analgesics, NSAIDs, and ACE inhibitors, which are all frequently taken by the elderly. The cause of ARF in a particular individual is often multifactorial, that is, inadequate fluid replacement before surgery, followed by dehydration, hypotension, infection, or inappropriate antibiotics (particularly aminoglycosides).

In the old, the renal indices for diagnosing ARF may be slightly different from those accepted for younger populations. For instance, in the elderly, a urinary sodium output lower than $70\,\text{mmol}\,l^{-1}$ in a patient with clinical and biochemical findings of ARF suggest a prerenal cause or acute reversible renal hypoperfusion. When urinary sodium output is higher than $70\,\text{mmol}\,l^{-1}$ one should think in terms of ATN (Macías Núñez *et al.*, 1996; Musso and Macías Núñez, 2002; Musso *et al.*, 1996). Initial treatment involves rapid correction of fluid and electrolyte balance. If diuresis is not restored with volume expansion, frusemide can be administered. Other measures, such as administration of low dose dopamine infusion (2–7 μg/kg/minute), may be employed to increase renal tubular flow and promote glomerular vasodilation (Musso and Macías Núñez, 2002). Sometimes renal replacement therapy is needed. A greater than 40% survival was achieved in critically ill elderly patients with severe ARF by the use of continuous hemodiafiltration (Bellomo *et al.*, 1994). These findings support an aggressive renal replacement approach in such patients and suggest that continuous hemodiafiltration may be ideally suited to their management. Age *per se* is not an important determinant of survival in patients with ARF (Druml *et al.*, 1994). Prophylaxis is of paramount importance: maintenance of an adequate extracellular volume and drug dosage regimen tailored to the patient's GFR are essential (Macías Núñez *et al.*, 1996; Musso and Macías Núñez, 2002).

Obstructive Uropathy (*see* Chapter 125, Prostate Diseases)

Prostatic hypertrophy occurs to some extent in almost all aging males, but in a proportion it provides a slow obstruction to urinary outflow, with entry into uremia. It is often not recognized until it is too late, largely because the patient becomes polyuric rather than oliguric (Sacks *et al.*, 1989). By the time it is diagnosed, irreversible damage may have taken place, so that even with the relief of obstruction, renal function recovers only partially. The use of α-blockers may help to relieve bladder outlet obstruction and reduce the need for catheterization. Other causes of urinary tract obstruction include uterine prolapse, stones, strictures, and neurogenic bladder due to diabetes mellitus and posterior column dysfunction (Klahr, 1987).

Urinary Tract Infection in the Elderly

Urinary tract infection is the most common infectious disease of the elderly and is especially prevalent in debilitated, institutionalized old individuals. The pathogenesis is strongly related to obstructive uropathy or its treatment: abnormal bladder function, bladder outlet obstruction, urolithiasis, tumors, use of long-term indwelling catheters. Moreover, the incidence of bacteriuria increases with advancing age since there are nonobstructive mechanisms that predispose aged people to urinary infection such as: vaginal and urethral atrophy and puddling related to bed rest. Infection is usually asymptomatic, and there is currently no indication for the treatment of usually asymptomatic bacteriuria except before invasive genitourinary procedures. Catheter-acquired bacteriuria should probably be treated following catheter removal. These individuals are always bacteriuric, usually with a complex polymicrobial flora. For symptomatic infection, the goal of treatment is relief of symptoms and not sterilization of the urine. Treatment has not been shown to prevent subsequent symptomatic episodes, is associated with antimicrobial adverse effects, and promotes the emergence of resistant organisms. Overuse of antimicrobials should be avoided (Rodríguez Pascual and Olcoz Chiva, 2002; Nicolle, 1994).

CHRONIC RENAL FAILURE (CRF)

Introduction

CRF is a syndrome characterized by progressive and generally irreversible deterioration of renal competence due to destruction of nephronal mass. CRF is predominantly a disease of the elderly, because the population incidence of CRF rises steadily with age, being at least 10 times more common at the age of 75 than at 15–45 years (Feest *et al.*, 1990). The causes of ESRD in the elderly differ substantially from those in younger populations (Verbeelen *et al.*, 1993). The most common disorders that lead to renal failure in old age are hypertension, diabetes mellitus, nephrosclerosis, and obstructive uropathy although in as many as one-third of cases it proves impossible to identify any specific cause. Two common causes of ESRD in the elderly are vascular disease of the main renal arteries and prostatic. A further problem worth noting is that of amyloidosis (Labeeuw *et al.*, 1996). Pathogenic mechanisms by which the failing kidney may produce specific clinical features are as follows:

(1) As the sclerosis of the glomeruli advances, glomerular hyperfiltration appears in the remaining nephrons. In this manner, it is possible to eliminate more intoxicating products per functioning nephron. This mechanism appears beneficial in the first instance, but the price paid for hyperfiltrating is an acceleration of glomerular sclerosis (Anderson and Brenner, 1987).
(2) Retention of uremic toxins (polyamines, guanidines, middle molecules, and hormonal peptides).
(3) High levels of parathormone (PTH) is currently accepted as the major uremic toxin-Erythropoietin and 1,25-dihydroxycholecalciferol deficiencies result in anemia and low calcium, respectively.

(4) Phosphate retention leads to secondary hyperparathyroidism and renal osteodystrophy. Clinically, it is convenient to divide CRF into three phases. In the early phase, until GFR reaches 50 ml/minute, there are no clear clinical symptoms. The reduction of creatinine clearance is a laboratory finding. As CRF progresses and creatinine clearance falls to about 25 ml/minute, the clinical picture of CRF appears. During this period, polyuria with clear urines and nocturia are present in nearly all patients. With GFR lower than 15 ml/minute, the full clinical picture becomes evident. The skin acquires a characteristic yellow–brown pallor and pruritus is frequent. Soft-tissue calcifications due to high calcium phosphate production are very common. In the eyes, conjunctival and corneal calcifications occur when the calcium phosphate product is raised, producing the "red eye of renal failure". Patients complain of asthenia, anorexia, and vomiting. In the cardiorespiratory system, pulmonary edema, hypertension, heart failure, coronary disease, and arrhythmia may be seen. The nervous system shows polyneuropathy, clonus, and even uremic coma in the most advanced period of the disease. Secondary hyperparathyroidism, carbohydrate intolerance, hypothyroidism, hyperprolactinemia, and hypogonadism are frequent endocrinological disturbances. A deficit of cellular immunity, polynuclear dysfunction, and clotting alterations are also present. In the late phase, all the above problems increase and when creatinine clearance is lower than 10 ml/minute, it is necessary to start replacement therapy (Musso and Macías Núñez, 2002; Glickman *et al.*, 1987).

Management

A low protein diet, proposed to relieve uremic symptoms, has shown little effect, and protein restriction in the elderly is associated with a high risk of malnutrition; as a result, we should provide a diet with a protein content between $0.6–1\,g\,kg^{-1}$ body weight.

Concerning secondary hyperparathyroidism, it remains necessary to suppress PTH secretion with calcitriol, a low-phosphate diet, and phosphate binders. Calcium acetate is preferable as a phosphate binder, because calcium carbonate needs hydrochloric acid to get converted into active calcium chloride, so there is a risk that this drug will remain ineffective in the elderly, who are frequently affected by low gastric acid secretion. The new calci-mimetic drugs should also be of value, although at the moment there is no clinical experience in aged patients. When urinary output falls below 2 l/day, sodium and potassium intake must be restricted, adding loop diuretics. Calcium blockers and ACE inhibitors are recommended to lower high blood pressure and to slow down the progression of renal disease (Vendemia and D'Amico, 1995).

Dialysis

During the 1970s, older patients with ESRD were almost never considered as candidates for renal replacement therapy (RRT), due to limited resources, whereas during the last decade, patients aged 75 and over with ESRD have been accepted routinely on to dialysis programs. Up to one-third of new patients entering dialysis throughout the world are now older than 65 years (D'Amico, 1995). Today, almost all clinicians believe that the majority of elderly uremics can be rehabilitated satisfactorily, and that age by itself does not constitute a major impediment to dialysis and/or transplantation (Piccoli *et al.*, 1993). Elderly patients on dialysis are prone to develop more serious forms of bone disease than the young, because of osteopenia, unbalanced diet, reduced physical activity and lack of exposure to sunlight. Malnutrition is frequently present and cachexia may contribute to death. Of routine laboratory tests, a low serum albumin is the most powerful independent risk factor for mortality. To prevent this, it is advisable to provide more than $1\,g\,kg^{-1}$ body weight of proteins for patients on hemodialysis (HD), and more than 1.2 g for those on chronic ambulatory peritoneal dialysis (CAPD), with a diet containing more than 6.3 g/day of essential amino acids(Musso and Macías Núñez, 2002).

The most common practical problems during treatment by HD of people aged 65 or more are (Ismail *et al.*, 1993; Lerma *et al.*, 1995; Vandelli *et al.*, 1996):

1. Difficulty in surgical fashioning of the arteriovenous fistula due to concomitant arteriosclerosis or insufficient venous dilatation. As a general rule, it is wise to plan surgery for fistula early, when the creatinine clearance is around 20–15 ml/minute. If all local access fails, transposition of a saphenous vein graft to the radial or cubital artery in a loop may allow hemodialysis, and seems to give better results than other artificial grafts.
2. Some 50–60% of elderly patients complain of weakness, hypotension, headaches and vomiting, cramps, and cardiovascular instability in the first two hours of HD. Such episodes can be alleviated by maintenance of a hemoglobin level over $10\,g\,dl^{-1}$ and an albumin level about $4\,g\,dl^{-1}$, careful titration of "dry weight", gentle and slow ultrafiltration, avoidance of vasodilator drugs in the predialysis period, and of course, the use of bicarbonate instead of acetate will also help.
3. Angina is frequent in older patients with coronary artery disease, and this may be facilitated by anemia, left ventricular hypertrophy and perhaps the higher free radical production exhibited by the elderly treated by hemodialysis. To prevent these episodes, it may be useful to maintain a high hematocrit above 30% by transfusion, intravenous iron, androgens, and/or administration of erythropoietin hormone.
4. Arrhythmias are very frequent in the elderly during dialysis because metastatic calcification, amyloid infiltration, cardiac hypertrophy and hypertension are more frequent than in younger patients. Hypokalemia and acidosis are contributory factors to the development of supraventricular and ventricular rhythm disturbances.

5. The commonest causes of gastrointestinal bleeding in elderly patients are angiodysplasia and gastritis provoked by uremia and worsened by intake of NSAID.
6. Impaired cellular immunity may lead to a higher incidence of viral infections and malignant tumors.

CAPD is also not without complications in the aged (Ismail *et al.*, 1993; Grapsa *et al.*, 2000):

1. dialysate leakage and formation of hernias;
2. peritonitis is the most common complication, but its incidence is not significantly different in elderly and young patients. The use of a Y-connector reduces the risk of infection, even in handicapped elderly patients;
3. exit site and tunnel infections requiring antibiotic treatment occur with the same frequency in young and in elderly patients, and catheter survival is also similar in both groups;
4. diverticulitis due to the frequency of intestinal diverticulosis in the elderly. Constipation is common, and is almost invariable in the elderly on dialysis;
5. backache, probably related to increased lordosis, secondary to carrying 21 of dialysate fluid in the peritoneal cavity;
6. hypotension and worsening of peripheral vascular disease, particularly in those with preexisting ischemia of the lower limbs;
7. peritoneal dialysis imposes a nutritional stress in that from 8 to 15 g of first-class protein, mainly albumin, are lost each day in dialysate, and this amount increases during and following episodes of peritonitis.

CAPD is better for patients with residual diuresis, severe hypotension, complicated and/or short-lived vascular access, intradialytic arrhythmias, angina, or cardiovascular instability. CAPD is a satisfactory alternative treatment for elderly ESRD patients. Most studies confirm that survival of elderly patients on CAPD and HD is similar. Other forms of peritoneal dialysis include chronic cycling peritoneal dialysis (CCPD) and nightly automated peritoneal dialysis (APD); the latter can be an alternative treatment for more vulnerable elderly patients (Grapsa and Oreopoulos, 2000; Carrasco *et al.*, 1999).

Transplantation

Renal transplantation in the elderly remains controversial, despite being recognized as the most successful and cheapest treatment for patients with ESRD. Until the beginning of the 1980s, patients as young as 45 years were considered to be a "high-risk" group: allograft survival in this age-group was only 20% at 1 year, due to a high incidence of infections and cardiovascular complications (Simmonds *et al.*, 1971). These ideas are no longer present due to improved care of transplant recipients and the introduction of cyclosporin. However, the reality is that only 4% of patients aged 65–74 under treatment for ESRD receive a renal transplant. The USRDS report for 1991 notes that the actual 10-year survival for transplant recipients aged 55–59 was only 22%, only 10.5% for those aged 60–64, and 8% for those aged 65–69 years (Cameron *et al.*, 1994; USRDS, 1991). Triple therapy regimen (prednisolone, azathioprine, and cyclosporin A, all in relatively low doses) used in most European transplant units can be used in the elderly almost without modification. It is prudent to lower the dose of both cyclosporin, to avoid toxicity, and prednisolone, to avoid the many side effects of these drugs, especially on skin and bone. Elderly patients have decreased hepatic enzyme activity, especially the P450 system, and therefore require a lower cyclosporin dose. Because of that, other new drugs such as mycofenolate or rapamycine may be of help although clinical trials of the effect of these drugs in renal transplant in persons aged over 65 are lacking. It is unclear whether antilymphocyte globulin or monoclonal antibodies such as OKT3 should be used in the elderly. The success of transplantation in geriatric ESRD patients over the last decade is due to improved patient selection as well as the use of cyclosporin A and lower doses of corticosteroids, with achievement of 1-year patient and graft survival rates of 85 and 75%, respectively. For patients older than 60 or 65 years, the 5-year "functional" graft survival is 55–60%. Although overall results are excellent, the management of transplantation in the elderly requires an understanding of pharmacology, immunology and physiology peculiar to this age-group. Although elderly patients experience fewer rejection episodes than younger patients, graft loss in the elderly transplant recipient is due mainly to patient death. Most common causes of death in the elderly transplant recipient are cardiovascular disease and infection related to peaks of immunosuppression (Morris *et al.*, 1991; Ismail *et al.*, 1994).

AGED KIDNEY ALTERATIONS

Secondary to Systemic Diseases

Many features of common renal syndromes are different in elderly subjects. In a comparison of the elderly with patients of younger age-groups, it appeared that amyloidosis, MN, vasculitis, hypertension, and diabetes mellitus had a significantly higher incidence in the elderly. However, apart from greater critical water and electrolyte balance and tendency to develop cardiac failure, the causes, symptomatology, and investigations are largely the same as in the young.

Hypertension (see Chapter 48, Hypertension)

Renal diseases, including acute and chronic failure, may cause hypertension but on the other hand, hypertension itself can result in renal damage (Parfrey *et al.*, 1981). It accounts for 33% of ESRD in the elderly (Labeeuw *et al.*, 1996). A pathological rise in arterial pressure with age in Western society may result from an increase in dietary sodium or

decreased dietary potassium, or both. A renal lesion develops later, possibly as a consequence of this primary increase in blood pressure. This is associated with resetting of pressure natriuresis, so that higher blood pressure is needed to maintain a given sodium excretion. It seems that renal hemodynamics in essential hypertension are adjusted mainly to ensure a consistent GFR. Albuminuria and renal dysfunction have recently been recognized as important complications in the patient with essential hypertension. Albuminuria is associated with more severe hypertension, with evidence of more advanced target organ damage (e.g. left ventricular hypertrophy), and is more prevalent in high-risk groups (e.g. older people). Ischemic nephropathy from nonmalignant nephrosclerosis has emerged as an important cause of terminal renal failure in the elderly patient with essential hypertension (Ritz and Fliser, 1992). Antihypertensive agents may impair renal blood flow (through plasma volume contraction or reduction) and further aggravate the age-related decline in renal perfusion. An understanding of the antihypertensive actions in an elderly patient may have a significant influence on renal function. A worsening of renal perfusion may activate counterregulatory neurohormonal mechanisms, such as the renin-angiotensin-aldosterone system, which in turn may place the patient at increased risk for the development of glomerulosclerosis through promotion of vascular or mesangial hypertrophic changes or increased intraglomerular pressure, despite an associated reduction in systemic blood pressure (Weir, 1992).

Atheroembolic Disease of the Elderly

Atheroembolism of the kidney occurs when plaque material breaks free from the diseased vessel and enters the distal microcirculation. Cholesterol crystals are the most easily recognizable of the embolic material, and usually vessels of about 80 mm diameter are affected. Diagnosis is made in a vasculopathic patient aged over 60 years, who has undergone an angiographic procedure or vascular surgery, and fever, muscle pain, weight loss, leucocytosis with eosinophilia, consumption of platelets, hypocomplementemia, and appearance of autoantibodies. Livedo reticularis and digital infarcts occurred in more than 30% of patients. Skin, muscle, and kidney biopsies remain the main tools for diagnosis. Confusion with vasculitis is not rare. Recovery of renal function rarely occurs and the mortality is very high (Cameron, 1995).

Diabetic Nephropathy (see Chapter 122, Type 2 Diabetes Mellitus in Senior Citizens)

Renal disease is now one of the commonest fatal complications of diabetes, especially in the elderly, where it causes about 22% of the ESRD cases (Labeeuw *et al.*, 1996). The condition of intercapillary glomerulosclerosis was first described by Kimmelstein and Wilson. Clinically, longstanding proteinuria with gradual decline in renal function leads to development of nephrotic syndrome, hypertension, and heart failure (Airoldi and Campanini, 1993). Results of treatment of ESRD in patients with non-insulin-dependent diabetes mellitus (type 2) showed a survival rate of 58% at 1 year and 14% at 5 years, independent of treatment modality. Patients who received a renal allograft had a higher survival rate as compared with patients on HD treatment (5-year survival, 59 vs 2%, $P < 0.005$). Renal transplantation improved survival of elderly diabetic patients without vascular complications and should be the treatment of choice in this specific group of patients (Hirschl *et al.*, 1992).

Collagen Disorders

These are chronic multisystem inflammatory diseases that commonly involve the kidney. The lesion is always some form of vasculitis. In systemic lupus erythematosus, necrosis and thrombosis of small vessels lead to ischemic changes. In progressive systemic sclerosis, there is obliterative thickening of the interior of small arteries and thickening of basement membrane due to fibroblastic proliferation and deposition of collagen. Rheumatoid arthritis commonly affects the kidney with proteinuria and renal impairment. In systemic vasculitis in elderly patients, it is not uncommon that kidney involvement, glomerulitis or necrotizing vasculitis, and circulating antineutrophil cytoplasm activity (ANCA), is what leads to diagnosis of the disease. Hematuria is almost a constant in vasculitis nephropathy. ANCA-related renal disease can be treated successfully with cyclophosphamide and steroids, and elderly patients should not be excluded from treatment, including dialysis if necessary (Musso and Macías Núñez, 2002; Garrett *et al.*, 1992).

Primary Glomerulopathies and Nephrotic Syndrome

During the past decade, controversy has raged about the necessity of renal biopsy for the management of the idiopathic nephrotic syndrome. The debate has centered on whether a precise diagnosis is imperative for steroid treatment or whether such therapy can be given blindly. There is a positive approach to the performance of a renal biopsy in the management of the nephrotic syndrome in the elderly (Moran *et al.*, 1993). Firstly, because at present it is known that the indications for renal biopsy, and the incidence of biopsy complications are the same for elderly and young adults. Secondly, because steroid therapy is not free of complications in the old population, it is therefore better to use this medication with histological support. Consequently, renal biopsy and histological observations are useful aids in estimating the prognosis and therapy selection for renal disorders even in elderly patients (Labeeuw *et al.*, 1996; Moulin *et al.*, 1991). When the number of glomerulopathy cases are properly related to the size of the general population of corresponding age-group, primary GN in the elderly was found to be the most diffuse biopsy-proven renal disease, even more frequent than primary GN in the adult (Vendemia *et al.*, 2001). Incidence of immunoglobulin A (IgA) nephropathy is three- to fourfold higher in patients aged 20–60 years than in the elderly. In contrast,

membranous nephropathy (MN) is 3 times more frequent in the elderly than in young people (Simon *et al.*, 1995). Nephrotic syndrome accounts for 50% of renal biopsy indications in elderly patients, with its most frequent causes being: MN, minimal change disease and amyloidosis (Labeeuw *et al.*, 1996). MN in some patients is related to drugs or an underlying malignancy (20%). Usually the tumor, most commonly adenocarcinoma of the lung or colon, is obvious at the time of presentation (Labeeuw *et al.*, 1996; Vendemia *et al.*, 2001). Regarding minimal changes disease, it has some particular characteristics when it appears in the elderly: senile structural renal changes make its histological diagnosis difficult; its clinical presentation is usually "atypical", that means in the context of hypertension, microhematuria and/or renal failure; it may be associated with drugs (NSAID) or malignancies (lymphoma) (Labeeuw *et al.*, 1996). Crescentic GN reaches its greatest incidence in older people aged 60–79 years, and its typical clinical presentation is an ARF of rapid evolution. Steroids and other immunosuppressive drugs (cyclophosphamide, etc.) can be used in the old as in the young, though paying special attention to its side effects (Labeeuw *et al.*, 1996; Vendemia *et al.*, 2001).

Plasma Cell Dyscrasias and Primary Amyloidosis

Myeloma has been recognized for many years as a cause of renal disease in the elderly, usually ARF or CRF accompanied by proteinuria. Recovery from ARF is common in myeloma, perhaps because dehydration and desalination plays a role, itself the result of mobilization hypercalcemia. However, once ESRD has been reached, return of renal function is rare. Other types associated with abnormal plasma cell products are light chain nephropathy and fibrillary or immunotactoid nephropathy. In both conditions, the marrow is usually of normal to ordinary cytology, but there are often paraprotein spikes in serum or light chains in the urine. Finally, in primary amyloidosis patients are nephrotic and often develop renal failure (Musso and Macías Núñez, 2002; Kafetz, 1983; Frocht and Fillit, 1984; Musso *et al.*, 1996; Bellomo *et al.*, 1994; Druml *et al.*, 1994; Sacks *et al.*, 1989; Klahr, 1987; Rodríguez Pascual and Olcoz Chiva, 2002; Nicolle, 1994; Feest *et al.*, 1990; Verbeelen *et al.*, 1993; Labeeuw *et al.*, 1996; Anderson and Brenner, 1987; Glickman *et al.*, 1987; Vendemia and D'Amico, 1995; D'Amico, 1995; Piccoli *et al.*, 1993; Ismail *et al.*, 1993; Lerma *et al.*, 1995; Vandelli *et al.*, 1996; Grapsa and Oreopoulos 2000; Carrasco *et al.*, 1999; Simmonds *et al.*, 1971; Cameron *et al.*, 1994; USRDS, 1991; Morris *et al.*, 1991; Ismail *et al.*, 1994; Parfrey *et al.*, 1981; Cameron, 1995).

DRUGS AND THE KIDNEY

The kidneys in elderly subjects are particularly susceptible to the toxic effect of drugs and other chemical agent for the following reasons: (1) there is a rich blood supply; (2) drugs are concentrated in the hypertonic medulla; (3) drug accumulation is associated with impaired renal function; (4) hypersensitivity reaction with vasculitis is common in the kidney; (5) concomitant inhibition of hepatic enzymes increases drug toxicity. There is evidence that metabolic activation of some drugs within the kidney is responsible for nephrotoxicity while other drug reactions seem to be immunologically mediated (Evans, 1980).

The high rates of drug-induced ARF, worsening chronic renal dysfunction and systemic toxicity of renal excreted drugs can be minimized by carefully assessing renal function, avoiding potentially nephrotoxic drugs as much as possible and closely monitoring drug concentrations and renal function when drugs must be used (Thomson, 1995). NSAIDs may induce a variety of acute and chronic renal lesions. Acute interstitial nephritis can follow the use of nearly all NSAIDs, but the number of reported cases is low. Most of these patients are elderly and develop a nephrotic syndrome with ARF while taking NSAIDs for months. Renal biopsy shows acute tubulo-interstitial lesions with minimal changes in the glomeruli. The renal signs usually improve after discontinuing the drug, with or without steroid therapy, but chronic renal insufficiency or even ESRD are possible hazards. Interstitial nephritis results mainly from a delayed hypersensitivity response to NSAID, and nephrotic syndrome results from changes in glomerular permeability mediated by prostaglandins and other hormones. Patients taking NSAIDs for months or years may develop papillary necrosis, chronic interstitial nephritis, or even ESRD (Kleinknecht, 1995). The use of ACE inhibitors has increased greatly during recent years, and they are used in the treatment of elderly patients who often have generalized atherosclerosis. During treatment with ACE inhibitors, kidney function must be controlled before and following 1 to 2 weeks of treatment, since treatment with ACE inhibitors can cause pronounced changes in renal hemodynamics and kidney function (Rasmussen *et al.*, 1995). ACE inhibitors reduce angiotensin II production, with a decrease in total renal vascular resistance. The mechanism of ARF involves two major factors: sodium depletion and reduction in renal perfusion pressure. ARF is usually asymptomatic, nonoliguric, associated with hyperkalemia, and in nearly every case, completely reversible after discontinuation of the ACE inhibitors. The use of ACE inhibitors in the elderly should be practised with caution (Toto, 1994).

Toxicity of Drugs Administered to Patients with Renal Impairment

This depends on multiple factors, particularly the proportion of the drug normally excreted by the kidneys and the likely toxic effect of drugs. Thus the elderly are more susceptible to ototoxicity and nephrotoxicity with aminoglycosides, neuropathy with nitrofurantoin, and hypoglycemia with chlorpropamide (Castleden, 1978). Digoxin is mainly excreted by the kidney and, consequently, the same dose of

digoxin produces higher blood levels and a longer blood half-life in old subjects than in the young. Its cardiac toxicity is enhanced by hypokalemia, a very common association due to the concomitant use of diuretics and the known tendency of the elderly to take a diet deficient in potassium. Dose adjustment may be achieved by reducing the amount given at the same intervals or by giving the same dose at longer intervals (Musso and Enz, 1996).

CONCLUSIONS

The aging kidney becomes less efficient in coping with stressful situations such as overload or deprivation. If attention is not paid to this decrease in functional capacity, it is possible to predispose elderly patients to situations such as ARF or congestive cardiac failure. In elderly patients, drug abuse is frequent, dehydration is very common, and renal artery stenosis and urinary outflow obstruction are important but often symptomless. With clinical experience, it is possible to overcome these difficulties and prevent renal failure. Kidney transplantation in elderly patients shows that long-term survival is at least as good, quality of life is improved and treatment is cheaper than HD or CAPD.

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KEY POINTS

- The "Nephrogeriatric Giants" are six conditions that represent profound structural and physiological renal modifications which occur in the majority of the elderly population. These conditions are senile hypofiltration, renal vascular alteration, medullary hypotonicity, obstructive uropathy, tubular dysfunction, and frailty.
- Indications for renal biopsy, and the incidence of biopsy complications are the same for elderly and young adults.
- Main causes of renal failure in the old population are hypertension, atheroembolic disease, diabetes mellitus, vasculitis, plasma cell dyscrasias, and nephrotoxic drugs.
- CRF is predominantly a disease of the elderly and age by itself does not constitute a major impediment to dialysis and/or transplantation.

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PART III

Medicine in Old Age

Section 12

Cancer

Cancer and Aging

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Cancer is the second most common cause of death and a major cause of disability for individuals aged 65 and older (Yancik and Ries, 2004). Cancer control is a key to a more prolonged and more active survival. After reviewing the epidemiology of cancer in the elderly and the biologic interactions of cancer and age, we will examine effectiveness and safety of cancer prevention and treatment in the older aged person.

EPIDEMIOLOGY

The incidence of most common cancers increases with age (Figure 1) up to age 80–85 and plateaus thereafter (Yancik and Ries, 2004). Autopsy studies suggest that after age 95 cancer ceases to be a major cause of morbidity and mortality, and even the incidence of occult malignancies may decrease (Stanta *et al.*, 1997). Seemingly, the prevalence of common cancers increases also with age, as early diagnosis and new forms of treatment have transformed many neoplasms into chronic diseases that may influence the function and the quality of life of older individuals. This area deserves more investigation (Caranasos, 1997).

Four epidemiological facts may have clinical implications. First, while cancer incidence has increased both among people younger than 65 and those 65 and older since 1950, cancer-related mortality has decreased for the young but increased for the old ones (Wingo *et al.*, 2003). This may be due in part to remediable causes, including the fact that older individuals are less likely to undergo cancer screening and to receive aggressive antineoplastic treatment. For example, breast cancer is diagnosed at a more advanced stage in women over 70 despite the fact that this neoplasm becomes more indolent with age (Randolph *et al.*, 2002).

Second, the incidence of some neoplasms, including non-Hodgkin's lymphomas and malignant brain tumors, has increased since 1970 mainly in older individuals (Yancik and Ries, 2004; Wingo *et al.*, 2003). This phenomenon, that so far is unexplained, should alert the practitioner that with the aging of the population certain diseases may become more common and that age may be associated with increased susceptibility to certain neoplasias.

Third, an age-related shift in incidence and mortality has been seen for some cancers. For example, lung cancer–related mortality has declined by more than 10% in individuals 50 and younger, but has increased around 20% for those 70 and older (Wingo *et al.*, 2003). Nowadays, lung cancer in elderly ex-smokers is becoming progressively more common. Smoking cessation has likely resulted in reduced death rate from cardiovascular and chronic obstructive lung diseases, and in reduced growth rate of occult cancer. In support of this hypothesis, lung cancer may be more indolent in older individuals. The emergence of more indolent lung cancer with a prolonged preclinical phase justifies new studies of early detection of lung cancer in ex-smokers.

Fourth, cancer may affect preferentially older individuals in good general condition. In Italy, Ferrucci *et al.*, (2003) and Repetto *et al.*, (1998) demonstrated that cancer patients aged 70 and older were less likely to present functional dependence or comorbidity than age-matched individuals without cancer. The Surveillance, Epidemiology and End Result study (SEER) showed that women aged 80 and older with breast cancer had a more prolonged survival than women of the same age without breast cancer (Diab *et al.*, 2000). These findings support cancer prevention and treatment in older individuals as they indicate that cancer is indeed a cause of death and morbidity for the elderly.

BIOLOGICAL INTERACTIONS OF CANCER AND AGING

These interactions may occur in two areas: carcinogenesis, and tumor biology.

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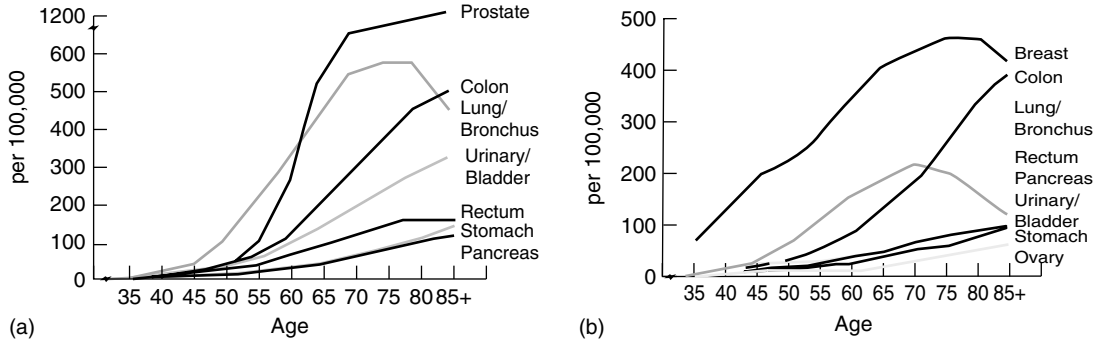

Figure 1 (a) Cancer incidence rates in men. (b) Cancer incidence rates in women

Aging and Carcinogenesis

Carcinogenesis is a stepwise process that involves a number of serial genomic changes, including activation of cellular oncogenes and inhibition of antiproliferative genes (antioncogenes) (Anisimov, 2005). These changes are effected by substances called *carcinogens* that in experimental models have been distinguished into early- and late-stage carcinogens. The action of the latter is reversible and is the focus of a modern strategy of cancer control, chemoprevention.

The association of aging and cancer may be explained by three, nonmutually exclusive mechanisms. First, as carcinogenesis is time consuming, cancer is more likely to become manifest late in life. Second, aging is associated with molecular changes similar to those of carcinogenesis, including formation of DNA adducts and DNA hypermethylation. Older individuals harbor a larger concentration of cells primed to the action of late-phase environmental carcinogens. Both experimental and clinical data support this hypothesis (Anisimov, 2005). A possible explanation for the increased incidence of lymphoma and malignant brain tumors recently observed in older individuals is that these individuals are a natural monitoring system for new environmental carcinogens, that is, in the presence of new carcinogens older individuals develop cancer at an earlier time. Third, paradoxically, proliferative senescence, that is the loss of self-replicative ability of the aging cells, may predispose to cancer, as senescent cells may become immortalized (Hornsby, 2004). The pathogenesis of slowly growing neoplasms, such as follicular lymphoma, may be traced to the loss of programmed cell death (apoptosis) by the aging lymphocytes (Balducci and Aapro, 2004).

Age and Tumor Biology

The clinical behavior of some neoplasms may change with the age of the patient (Table 1) (Balducci and Aapro, 2004). At least two mechanisms may explain these changes. If one thinks of a tumor as a plant, the growth of the plant may be determined by the nature of the seed (the tumor cell), and of the soil (the tumor host). In the case of acute myelogenous leukemia (AML), the prevalence of resistance to cytotoxic chemotherapy increases after age 60, which may explain the poor outcome of AML in the elderly (Lancet *et al.*, 2000). The prognosis of NHL (Non Hodgkin's Lymphoma) may worsen through a "soil" mechanism: age is associated with increased circulating concentrations of interleukin-6 (IL-6), an independent poor prognostic factor (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993; Preti *et al.*, 1997), as IL-6 stimulates lymphoid proliferation. In the case of breast cancer, both a "seed" and a "soil" mechanism may conspire to

Table 1 Example of neoplasms whose biology may change with aging

Cancer	Change in prognosis	Mechanism
Acute myelogenous leukemia	Worse, increased resistance to chemotherapy	Seed: 1. Increased prevalence of MDR1 2. Increased prevalence of stem-cell leukemia
Non-Hodgkin's lymphoma	Worse, decreased response rate to chemotherapy, decreased disease-free survival	Soil: Increased circulating concentration of IL-6
Breast	Better: More indolent disease	Seed: 1. Higher prevalence of hormone-responsive tumors 2. Lower proliferation rate 3. Higher prevalence of well-differentiated tumors Soil: 1. Endocrine senescence 2. Immune senescence
Ovary	Worse: reduced response to chemotherapy and disease-free survival	Unknown
Lung, nonsmall cell	Better, presentation at earlier stages, more indolent disease	Seed: More differentiated, slowly growing tumor

Note: MDR, multi drug resistance.

generate a more indolent tumor (Balducci *et al.*, 2004): the prevalence of well-differentiated-hormone-receptor-rich tumors increases with age, and at the same time endocrine senescence may disfavor the growth of hormone-responsive neoplasms. As already mentioned, lung cancer is more likely to affect elderly ex-smokers, whose tumor has undergone a lower number of mutations and is less aggressive.

A major breakthrough in tumor biology has been the development of microarray techniques, able to reveal the full genetic profile of a tumor. The overexpression of certain genes has been associated with different biologic behaviors, including growth rate and susceptibility to cytotoxic chemotherapy (Sikic, 1999). Microarrays may allow identification of biologic differences between the tumor cells of younger and older patients.

Little is known about the host-related changes that may influence tumor growth. In addition to endocrine senescence, immune senescence and proliferative senescence of the stromal cells may play a role. Immune senescence may favor the growth of highly immunogenic tumors, while proliferative senescence of fibroblasts is associated with increased production of tumor growth factors (Hornsby, 2004). It is also worthwhile remembering that frailty is associated with increased concentration of catabolic cytokines in the circulation (Cohen *et al.*, 2003) and with sarcopenia (Stanta *et al.*, 1997) that may inhibit tumor growth.

The mechanisms by which age may influence tumor aggressiveness represent a widely open research area.

Two considerations are clinically pertinent: (i) Aging may be associated with more indolent as well as more aggressive tumors. (ii) Age itself is a poor predictor of tumor behavior and each cancer should be managed according to the individual characteristics of the tumor and of the patient. If it is true that 67% of AML in individuals aged 60 and older present MDR (Multi Drug resistance), it is also true that 33% of these patients have a neoplasm sensitive to chemotherapy. If 80% of breast cancer patients aged 65 and older have a hormone-receptor-rich tumor for which cytotoxic chemotherapy produces limited benefits, 20% of these women have aggressive hormone-receptor-poor tumors that may need front-line cytotoxic chemotherapy.

CANCER PREVENTION

Cancer prevention represents the most obvious way to reduce the impact of cancer on mortality, disability, and quality of life. Primary prevention involves elimination of environmental carcinogens or block and reversal of carcinogenesis with chemoprevention. Secondary prevention involves early detection of cancer at a curable stage by screening asymptomatic individuals at risk.

Chemoprevention of Cancer

Chemoprevention appears the most practical form of primary cancer prevention (Beghe' and Balducci, 2004). Potential drawbacks include cost and toxicity of treatment. Figure 2 illustrates the possible mechanisms of action of chemopreventative agents. Chemoprevention may inhibit the reactions that activate procarciongens into carcinogens and facilitate those that catabolize carcinogens. The crossroad of chemical, radiation, and light-induced carcinogenesis, electrophylic DNA adducts, may be reversed by DNA repairing enzymes, whose activity is enhanced by selenium, calorie restriction, and epigallocatechin galate (Hursting *et al.*, 1999). Endogenous substances that influence carcinogenesis, such as reactive oxygen species, hormones, growth factors, and eicosenoids, represent another target of chemoprevention.

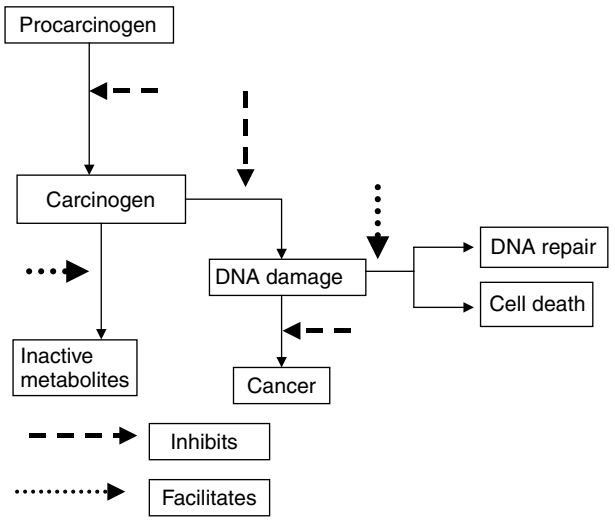

Figure 2 Mechanism of action of chemoprevention

Three groups of agents were proven to prevent cancer in humans: hormonal agents, retinoids, and NSAIDs. In randomized controlled studies, the SERM tamoxifen (Lippman and Brown, 1999) has prevented breast cancer, and the reductase inhibitor finasteride prostate cancer (Thompson *et al.*, 2003). Other hormonal agents of interest for the prevention of breast cancer include the SERM raloxifen that unlike tamoxifen does not cause endometrial cancer, and the aromatase inhibitors. In randomized controlled studies, retinoic acid has reversed preneoplastic lesions and delayed the occurrence of secondary cancers in the upper airways (Oridate *et al.*, 1986). In a prospective study, the COX-2 inhibitor rofecoxib has caused regression of preneoplastic polyps (Steinbach *et al.*, 2000); two large retrospective studies suggest that aspirin may prevent death from cancer of the large bowel (Thun *et al.*, 1991; Chemoprevention Working Group, 1999) and another retrospective study that it may reduce the risk of breast cancer (Terry *et al.*, 2004). Furthermore, NSAIDs and aromatase inhibitors appear synergistic *in vitro*.

These encouraging results cannot be translated as yet into clinical indications. Tamoxifen prevents only indolent well-differentiated hormone-responsive tumors and has not reduced breast cancer-related mortality. Though rare, the complications of tamoxifen have been potentially serious, including endometrial cancer, deep vein thrombosis, and

cerebrovascular accidents (Lippman and Brown, 1999). Finsteride has reduced the incidence of, but not the mortality from, prostate cancer, may have enhanced the risk of poorly differentiated aggressive neoplasms, and causes hot flushes and loss of libido (Thompson *et al.*, 2003). Retinoic acid has caused severe cutaneous and hepatic toxicity, and has delayed rather than prevented cancer of the upper airways (Oridate *et al.*, 1986). For what concerns the NSAIDs, there is no information related to the dose, the treatment duration, and the potential complications.

Secondary Cancer Prevention

Secondary prevention of cancer is based on a threefold assumption (Beghe' and Balducci, 2004):

- Clinical manifestations of cancer are preceded by a prolonged preclinical phase, including invasive cancer and premalignant lesions.
- Screening tests may diagnose cancer in the preclinical and even the premalignant phase.
- Early diagnosis of cancer is associated with improved chances of surgical curability.

A reduction in cancer-related deaths in randomized clinical trials is considered the definitive proof that secondary prevention is effective. This end point has been criticized for two reasons. First, it may take several years and result in unnecessary loss of lives and the conclusions of the trial may be obsolete, because by the time of completion new and more sensitive screening techniques might have been developed. Second, one may wonder how meaningful a reduction of cancer-related mortality is in elderly individuals when overall mortality is unaffected. This issue is exemplified by a randomized study of radical prostatectomy versus observation in men up to age 75 in Sweden that demonstrated radical prostatectomy is associated with a reduction in cancer-related but not overall mortality (Holmberg *et al.*, 2002). For a number of older men with prostate cancer, maybe the majority, prostatectomy is costly, dangerous, and without appreciable benefit. At the same time, however, screening may improve patient quality of life even when it does not seem to affect mortality. It is possible that early detection of some cancers, such as breast cancer, might reduce the risk of cancer-related complications.

Age itself has diverging effects on the outcome of screening (Beghe' and Balducci, 2004). On one hand, the positive predictive value of screening tests may increase with age, owing to increased prevalence of common cancers. On the other hand, reduced life expectancy and development of more indolent tumors may lessen the benefits of screening. Also, the yield of screening tests decreases with the number of times they have been performed, as the initial tests have eliminated most prevalence cases.

Two combined approaches may help identify asymptomatic older individuals for whom cancer screening is indicated. The first involves an estimate of the effects of screening on quality of life. Chen *et al.* have identified a profile of older patients for whom the benefits of screening may overwhelm the risk of complications (Chen *et al.*, 2003). These are the so-called risk takers, who are willing to undergo dangerous forms of cancer treatment even when the benefits are minimal. The second approach identifies patients at higher risk of development of a certain type of cancer. In a decision analysis, Kerlikowske *et al.* demonstrated that mammography is most beneficial for women in the upper quintile of bone density, who are those at higher breast cancer risk (Kerlikowske *et al.*, 1999).

Randomized and controlled clinical trials have demonstrated that screening mammography reduces the mortality of breast cancer in women aged 50–70 (Kerlikowske *et al.*, 1995) and screening for colorectal cancer with fecal occult blood reduces the mortality for individuals aged 50–80 (Frazier *et al.*, 2000). Presumably, serial endoscopies may be at least as effective as examination of stools for occult blood, and are the preferred form of screening in many centers (Frazier *et al.*, 2000). In the absence of data, it appears prudent to screen persons with a life expectancy of five years or longer for breast and colorectal cancer, as the earliest benefits of screening have been observed five years after the institution of the screening program (Walter *et al.*, 2004). Controversy lingers on the benefits of screening asymptomatic men for prostate cancer: in any case it is unlikely that this intervention may reduce cancer-related mortality in men over 70. Screening for cervical cancer after age 60 is another area of controversy. It is recommended in women at risk, because they are sexually active, especially if they have multiple partners, and for those who have never been screened before age 60. No proof exists of the value of screening for lung, ovarian, or endometrial cancer. In these cases, screening is justified only in the context of clinical trials.

CANCER TREATMENT

Local treatment of cancer involves surgery and radiation therapy; systemic treatment involves cytotoxic chemotherapy, and hormonal, biological, and targeted therapy. Cancer therapy may have different goals including curative, adjuvant, and palliative. Adjuvant treatment is administered to prevent recurrence of cancer in patients at high risk of recurrence after definitive therapy: Palliative treatment is aimed at relieving symptoms and prolonging the survival of patients with incurable cancer.

Two new treatment approaches deserve mention: neoadjuvant and combined modality treatment. Neoadjuvant treatment mainly involves chemo and hormonal therapy and is administered prior to definitive therapy, with the goal of making this more effective and less radical. Neoadjuvant chemotherapy of breast cancer has allowed breast preservation in the majority of patients. Combined modality treatment that generally involves a combination of cytotoxic chemotherapy and radiation therapy has been used to allow organ preservation and to obtain better outcome than with

either individual forms of treatment. Combined modality treatment has allowed organ preservation in patients with resectable cancer of the head and neck area, of the esophagus, and of the anus, and has prolonged the survival of patients with locally advanced cancer of the lung and of the head and neck.

Surgery

The incidence of surgical complications, including mortality, increases after age 70, according to Medicare data (Berger and Roslyn, 1997). The majority of these complications should be ascribed to emergency surgery, however, mainly related to large bowel obstruction and resulting Gram-negative sepsis (Berger and Roslyn, 1997). With the exception of pneumonectomy, most elective surgical procedures appear well tolerated by older individuals (Berger and Roslyn, 1997; Kemeny *et al.*, 2000). Unfortunately, the risk of emergency abdominal surgery increases with age, which underlines the importance of regular screening for colorectal cancer, as early detection would minimize the risk of colonic obstruction.

Recent advances in anesthesia and in surgical techniques have reduced the risk of postoperative complications in the elderly. The addition of amnesic drugs to the anesthetic cocktail has allowed reducing the dose of traditional anesthetics and opioids, and has minimized the risk of respiratory and cardiovascular complications of anesthesia even in centenarians (Miguel and Vila, 2004). Furthermore, a number of procedures, including mastectomy, may be performed under local anesthesia and are accessible also to patients with severe respiratory diseases. The advent of sentinel lymph-node mapping to recognize patients at risk for lymph-node metastases has allowed the foregoing of full lymph-node dissection in patients with cancer of the breast and melanoma (Singletary *et al.*, 2004). The value of this approach is being explored also in cancer of the head and neck areas and in gynecological cancer. The extent of surgery has become more limited for several cancers, including rectal cancer that seldom requires nowadays an abdominal-perineal resection. Laser endoscopic surgery may be curative in early stages of esophageal and bronchial cancer and may maintain the patency of these organs through the latest stages of the disease. Radiosurgery (γ knife) proved as effective as standard surgery for small brain tumors and is investigated in other malignancies (Hevezi, 2003). Radio-frequency ablation (RFA) that may be performed in many patients without general anesthesia and under CT guidance was proven effective in the management of primary and secondary liver tumors, and may be utilized also for small kidney cancers (Tranberg, 2004).

Radiation Therapy

A number of retrospective studies in Europe and in the United States have shown that external beam irradiation is well tolerated even in individuals over 80, more than three-quarters of whom are able to receive full doses of radiation (Zachariah and Balducci, 2000). The risk of mucositis may increase with age during radiation of the chest, involving the esophagus, and of the pelvis. In these cases it is extremely important to assure hydration and nutrition. Prophylactic peg tubes are recommended in patients undergoing treatment of the upper digestive tract and of the esophagus.

The advent of conformational radiation therapy has minimized toxicity of normal tissues and maximized therapeutic efficacy. Brachytherapy, that is delivering of radiation by implant of radioactive material, is another safe and effective form of treatment. Of special interest for older men is brachytherapy of prostate cancer (Zachariah and Balducci, 2000).

New forms of radiation therapy include hyper fractionated radiation therapy that may improve therapeutic efficacy by reducing the time intervals between treatments, and also lead to reduced treatment duration. The safety of this form of treatment in elderly patients is being explored.

Together with radiation therapy one should mention *radioisotopes* that have gained new momentum in the last few years. Radioactive strontium and sumerium relieve pain from multiple bone metastases and are generally well tolerated, though they may cause myelosuppression and limit the use of cytotoxic chemotherapy (Roque *et al.*, 2003). In addition, monoclonal antibodies targeted to the CD20 antigens, in combination with radioactive yttrium (Zevelin) or Iodine (Bexaar), induce remission in 40% of patients with low-grade lymphomas resistant to cytotoxic chemotherapy (Harris, 2004). The use of these agents as front-line treatment is being explored. These compounds may cause prolonged and substantial myelodepression.

Hormonal Therapy

Breast, prostate, and endometrial cancer may respond to hormonal therapy.

Estrogen deprivation is the mainstay breast cancer treatment. For almost 30 years this has been achieved with SERM, tamoxifen, and toremifene. These compounds have reduced the recurrence rate of breast cancer after surgery and the development of contralateral breast cancer by almost 50%, and have relieved the symptoms and prolonged the survival of 50–60% of patients with metastatic breast cancer (Buluwela *et al.*, 2004). SERMs still represent the preferred form of hormonal treatment of breast cancer in men. Tamoxifen and toremifene prevent bone loss, but cause hot flushes and vaginal discharge in the majority of patients. In addition, they increase the risk of endometrial cancer, deep vein thrombosis and ischemic strokes, especially in presence of obesity, but these complications are rare. In postmenopausal women, the aromatase inhibitors that prevent the transformation of androgen into estrogen were proven superior to tamoxifen both in the adjuvant and the metastatic setting (Arora and Potter, 2004). These compounds appear better tolerated than the SERMs in terms of vasomotor and genitourinary

complications, and have not been associated with endometrial cancer, thrombosis, or stroke. The nonsteroidal aromatase inhibitors anastrozole and letrozol increase the rate of bone loss and bone fracture, while examestane, which has a steroidal configuration, may delay bone loss. A new SERM, faslodex, is also available. Unlike tamoxifen and toremifene, faslodex is a complete estrogen antagonist and does not cause endometrial cancer or hypercoagulability, and is effective in about a fourth of the patients whose disease has progressed while taking tamoxifen (Buluwela *et al.*, 2004). Though the role of this compound vis-a-vis the aromatase inhibitors is not clear, parenteral (intramuscular) administration every 4 weeks makes faslodex particularly suitable for older women with poor compliance for oral medications. Progestins are still used as third line treatment of metastatic breast cancer, while the role of estrogen at high doses and androgen has become extremely limited.

The mainstay treatment of prostate cancer is androgen deprivation that may be effected by orchiectomy, oral estrogen, LH-RH (luteinizing hormone-releasing hormone) analogs, LH-RH antagonists (abarelix), and ketoconazol in high doses (Hellerstedt and Pienta, 2003). Currently, the LH-RH analogs are almost universally used as front-line treatment of metastatic prostate cancer, whereas ketoconazol is indicated for patients whose disease has progressed with LH-RH analogs. The only current indication for the use of abarelix is metastasis causing impending urinary obstruction or epidural compression. In these cases, the LH-RH analogs, which cause initially a spate in testosterone concentration, may stimulate tumor growth and precipitate a life-threatening complication. Long-term complications of androgen deprivation including osteoporosis, fatigue, and hot flushes (Holzbeierlein *et al.*, 2003) are seen with increased frequency as androgen deprivation is initiated in patients experiencing a PSA recurrence of prostate cancer whose life expectancy is in excess of 10 years (Han *et al.*, 2001).

Cytotoxic Chemotherapy

Cytotoxic chemotherapy destroys preferentially tissues with high concentration of proliferating cells (Cova and Balducci, 2004). While preferentially harmful to neoplastic tissues, chemotherapy may also affect a number of normal tissues.

Age is associated with a number of pharmacologic changes affecting effectiveness and toxicity of chemotherapy. These include pharmacokinetics, pharmacodynamics, and susceptibility of normal tissues to antineoplastic drugs (Table 2). Biological availability of oral drugs does not appear to change at least up to age 80 (Carreca and Balducci, 2002). Oral formulation of antineoplastic agents is becoming increasingly common, and appears particularly suitable for older individuals, thanks to home administration and more flexible dose titration. As the GFR declines almost universally with age, it is recommended to adjust the doses of medication to renal function, with the provision to increase the dose in subsequent treatment cycles in absence of toxicity, to avoid the risk of undertreatment (Balducci, in press). The volume of distribution of hydrosoluble agents declines owing to reduced water content; consequently, the shape of the AUC (Area Under Curve) is changed with higher peak concentrations of free drug. Anemia may exacerbate this problem, as many agents are bound to red blood cells. For this reason, it is recommended that the hemoglobin of older patients receiving chemotherapy be maintained at 12 gm dl^{-1} or higher (Balducci, in press).

Table 2 Pharmacologic changes of age

Pharmacokinetics	1. Reduced intestinal absorption 2. Reduced renal excretion 3. Reduced volume of distribution of hydrosoluble drugs 4. Reduced hepatic uptake and reduced activity of cytochrome p450 reactions
Pharmacodynamics	1. Reduced rate of DNA repair 2. Reduced intracellular catabolism of drugs
Susceptibility of normal tissues	1. Increased duration and severity of myelotoxicity 2. Increased risk of cardiomyopathy from anthracyclines 3. Increased risk of peripheral (platinol, alkaloids, taxanes, epipodophyllotoxins), and central nervous toxicity (cytarabine in high doses) 4. Increased risk of mucositis (fluorouracil, fluorouridine, anthracyclines)

Myelosuppression, mucositis, peripheral neuropathy, and cardiomyopathy are the complications of chemotherapy that become more common with age. The risk of neutropenic infections as well as the duration and complications of hospitalization from neutropenic infections increase after age 65. Fortunately, hemopoietic growth factors and, in particular, flilgrastim are effective also in older individuals. A pegylated form of filgrastim, peg-filgrastim, is particularly suitable for older individuals, as it requires a single administration per cycle of chemotherapy (Balducci, in press). Anemia is also a common manifestation of myelosuppression that is associated with fatigue and functional dependence (Balducci, 2003; Knight *et al.*, 2004), and may enhance the risk of chemotherapy related toxicity. Epoietin or darbepoietin ameliorate anemia in 60–70% of the patient. Mucositis may lead to dehydration from lack of fluid intake and diarrhea, with serious and even lethal consequences (Stein *et al.*, 1995). Prevention of mucositis may involve the use of oral capecitabine in lieu of intravenous fluorouracil and management with an oral solution of lysine. A keratynocute growth factor is undergoing clinical trials with promising results. In any case, an older person presenting with dehydration should be immediately admitted to the hospital for aggressive fluid resuscitation. No antidotes to neurotoxicity are available. Precautions include avoidance of combination of neurotoxic drugs (e.g. cisplatin and paclitaxel), and timely discontinuance of a neurotoxic drug in the presence of weakness. Age is a risk factor for anthracycline induced cardiomyopathy (Hequet *et al.*, 2004). Though this

complication is rare for total doses of doxorubicin lower than $300\,mg\,m^{-2}$, it increases steeply with higher doses. Furthermore, a recent study in patients with lymphoma revealed that asymptomatic myocardial dysfunction may affect up to one-fourth of patients treated with doxorubicin. Cardiomyopathy may be prevented by infusional doxorubicin (which is cumbersome), by concomitant administration of the antidote desrazoxane, which may increase the risk of myelodepression and mucositis, and by substitution of doxorubicin by pegylated liposomal doxorubicin (doxil) with a much more favorable toxicity profile (Theodoulou and Hudis, 2004).

Finally, it should be underlined that a number of new cytotoxic agents are particularly suitable for older individuals, even for frail individuals. These include capecitabine, vinorelbine, gemcitabine, weekly taxanes, and pegylated liposomal doxorubicin (doxil).

Most of these medications do not cause alopecia or severe nausea and vomiting or myelotoxicity.

Targeted Therapy

These agents target specific components or processes of the neoplastic cells, leading to their destruction or to inhibition of their proliferation. As the targets are specific to or overexpressed in neoplastic cells, these compounds promise to spare normal tissues. For practical purposes, we may distinguish monoclonal antibodies and small molecules antagonizing specific processes (Table 3).

Monoclonal antibodies may be naked or tagged (Harris, 2004). Naked antibodies may cause immune destruction of the cells or antagonize growth factor receptors. Tagged antibodies are used as carriers of toxins, cytotoxic agents, and radioisotopes. Rituximab targets the CD20 antigen, mainly expressed on B-lymphocytes. As single agent, rituximab induces a response rate of approximately 40% in low-grade lymphoma; in combination with chemotherapy, it improves the response rate in virtually all forms of B-cell lymphomas Alemtuzumab is directed against the CD52 antigen, overexpressed on B-lymphocytes, but also in normal hemopoietic precursors. This drug has an approximately 30% response rate in patients with CLL (Chronic Lymphocytic Leukemia) refractory to chemotherapy, but is associated with significant myelotoxicity. Tositumomab (Bexaar) and Ibitumomab tiuxetan (Zevalin) are also monoclonal antibodies targeting CD20 and they are bound respectively to radioactive iodine and Yttrium. They have produced prolonged remissions in patients with low-grade lymphomas, refractory to other forms of treatment, including rituximab, but their use has been complicated by substantial myelotoxicity. Mylotarg targets the CD33 antigen of myelopoietic cells and is active in patients with AML refractory to chemotherapy, but induces substantial myelosuppression

Table 3 Targeted therapies

Group of compounds	Target	Indication(s)
Monoclonal antibodies		
a. Naked		
Rituximab	CD20	B-cell lymphoma
Trastuzumab (Herceptin)	HER-2 neu	Breast cancer
Alemtuzumab (CamPath)	CD52	CLL; low-grade lymphoma
Cetuximab	EGFR	Colorectal cancer
Bevacizumab	VEGF	Colorectal cancer
b. Tagged		
Gemtuzumab ozogamicin (Mylotarg)	CD33	Acute myelogenous leukemia
I-131 tositumomab (Bexaar)	CD20	Low-grade lymphoma
Ibitumomab tiuxetan (Zevalin)	CD20	Low-grade lymphoma
Small molecules		
Imanitib mesylate (Gleevec)	Tyrosine kinase	CML, Gastric stromal cell tumors
Gefitinib (Iressa)	EGFR-TK	Lung cancer
Bortezomib (Velcade)	26-S proteasome	Multiple myeloma
Thalidomide (Talidomid)	Angiogenesis	Multiple myeloma, myelodysplasia, malignant gliomas

Note: EGFR-TL, epithelial growth factor receptor–associated tyrosine kinase.

Cell proliferation may be inhibited by targeting the growth factor receptors (Trastuzumab, Herceptin), the activation of these receptors (cetuximab, erbitux), the intracellular signal transduction (gefitinib, Iressa, farnesyl transferase inhibitors), and the surface tyrosine phosphokinase (Imanitib) (Herbst, 2004; Ravandi *et al.*, 2004).

Imanitib, an inhibitor of the tyrosine phosphokinase encoded by the hybrid Bcr/abl oncogene, has resulted in higher rate of hematological remission and improved survival in patients with chronic myelogenous leukemia (CML) (Sledge, 2004). Trastuzumab has shown significant activity in those 30% of women with breast cancer that overexpress the growth factor receptor, genfitinib is indicated in a small group of patients with adenocarcinoma of the lung (Murray *et al.*, 2004), and cetuximab is indicated in carcinoma of colon and rectum (Folprecht and Kohne, 2004).

Proteosome inhibition may also lead through cell destruction through apoptosis (Adams, 2004) or programmed cell death. Bortezomib (velcade) produces a response in approximately 40% of multiple myeloma patients refractory to other forms of treatment.

Another important target of antineoplastic therapy is angiogenesis, as tumor cells cannot survive without the production of new vessels (Drevs *et al.*, 2002). Thalidomide, an inhibitor of angiogenesis, proved effective in patients with multiple myeloma and those with myelodysplasia, whereas bevacizumab (Avastin), a monoclonal antibody directed against the vascular endothelial growth factor (VEGF), in combination with chemotherapy, has prolonged the survival of patients with colorectal cancer (Hurwitz *et al.*, 2004).

CONCLUSIONS

Cancer in the older person is an increasingly common problem, to the point that it has been proposed to consider cancer

a geriatric syndrome. Preventative and treatment strategies should be tailored to the situation of each patient, based on life expectancy and treatment tolerance.

Chemoprevention is a promising cancer prevention strategy that may benefit older individuals, but its clinical use at present is limited. Screening for breast and colorectal cancer appear beneficial for people with a life expectancy of 5 years and longer; screening for other common cancers (prostate, lung, cervix, ovary) is the object of ongoing studies.

Elective surgery, with the possible exception of pneumonectomy, and radiotherapy appear well tolerated by persons of any age, while the risks of emergency surgery increase with age. Early detection of colorectal cancer may minimize the need of emergency surgery.

A number of advances have improved the tolerance of cytotoxic chemotherapy by older individuals: these include myelopoietic growth factors, that minimize neutroopenia and neutropenic infections, recombinant epoietin and darbepoietin for the treatment of anemia and the prevention of functional dependence, and the development of newer and safer drugs. In particular, capecitabine should be used in lieu of fluorouracil in older individuals and pegylated liposomal doxorubicin "in lieu" of other anthracyclines, when indicated.

Targeted therapy represents a very promising and novel approach to the treatment of cancer that may be particularly beneficial to older individuals.

With proper patient selection and adequate support, antineoplastic treatment may be as effective in older patients as it is in younger patients and age should not be considered a contraindication.

KEY POINTS

- The biologic interactions of cancer and age include carcinogenesis and tumor biology. Older individuals may be more susceptible to environmental carcinogens as they harbor a higher concentration of cells in advanced carcinogenetic stages than younger individuals. Breast and lung cancer are more indolent; AML, B-cell lymphoma and ovarian cancer are less responsive to treatment.
- Chemoprevention is promising, but clinical indications are wanted. Screening for breast and colorectal cancer is indicated for persons with a life expectancy of 5 and more years.
- New surgical techniques (radiosurgery, RFA) and radiation therapy techniques (brachytherapy) are minimally invasive and may prove particularly beneficial for older patients.
- Patients aged 65 and older receiving moderately cytotoxic chemotherapy should receive support with hemopoietic growth factors (filgrastim, pegfilgrastim, epoietin α, darbepoietin).
- New chemotherapy drugs, including capecitabine, pegylated liposomal doxorubicin, weekly taxanes, vinorelbine, and gemcitabine, may be safely used even in frail individuals.

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Oncological Emergencies and Urgencies

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INTRODUCTION

Studies of cancer in the "very old" (older than 80 years) have been hampered by several factors including inaccuracies in death certificates, failure to diagnose malignancy in the setting of multiple illnesses, and a reduction in frequency of seeking medical attention in this age-group. It is known that nearly half of all cancers and almost two-thirds of all cancer deaths in the United States occur in people more than 65 years old (Yancik, 1983). Moreover, the incidence appears to be increasing with age.

During the past three decades there has been a noteworthy increase in our desire as well as the technology to treat some cancers (Bailar and Smith, 1986). Extrapolating from therapeutic progress in the 1980s and 1990s, we should anticipate further enhancement in our capacity to treat an even larger number of individuals with malignant disease, especially those with somewhat more resistant solid tumors, which are most common at older ages. These facts, coupled with steady growth in the size of the elderly population, indicate a need to prepare for more oncological crises. Moreover, a predominance of certain neoplasms, particularly solid tumors of breast, lung, colon, and prostate, with their particular attendant acute complications, could swell the number of emergencies even further.

Simultaneously, physicians have witnessed a remarkable gain in the ability to deal with and effectively manage the intensive care needs of patients with any disease. Early on, as intensive care units (ICU) attempted to cope with unmanageable numbers of referrals, there developed an unwritten and sometimes unspoken attitude about rationing beds, a policy which not infrequently precluded individuals with incurable forms of malignancy, especially if the patient was "old". With enlightenment and an increase in the numbers of ICU beds, this obstacle to heroic clinical management in the setting of cancer has begun to disappear (Pontoppidin *et al.*, 1976), especially for young patients who have leukemia or lymphoma.

Neoplastic diseases can bring about both acute and chronic complications either by their natural progression or by our treatment of them. They have the capacity to invade contiguous structures, such as blood vessels or viscus organs; cause a host of mechanical events by obstruction or compression; secrete a variety of ectopic hormones, some resulting in severe metabolic effects; and proliferate so extensively that vital organs are literally replaced. In addition, we have a therapeutic armamentarium that can irreversibly damage any of the vital organs or severely compromise the host's defenses. These statements prevail no matter what age-group one is discussing. There appears to be nothing particularly different in this regard about elderly patients. Although older patients may have more obvious cerebral dysfunction in the setting of fever, sepsis, hypotension, or hypercalcemia, and their marrow reserve may be less robust, there is no valid evidence that age alone is a criterion for withholding intensive life support or for that matter withholding treatment of the basic disease process (Cohen *et al.*, 1983; Peterson, 1982; Kennedy, 1985).

A growing volume of literature (Vaeth and Meyer, 1985) discusses cancer and its management in the elderly. There is also literature now written specifically about the concept of malignant disease in the emergency department (Brown *et al.*, 1983) but few publications specifically address the management of medical or surgical emergencies that occur in people over 65 as a consequence of a malignancy.

From experience in our own emergency departments, it is possible to list in order of decreasing frequency the more common reasons for attendance by adult patients with a known neoplasm. There is first fever and a close second is fever with granulocytopenia already defined by their referring physician; inability to eat or drink; pain; dyspnea from advancing cancer in the lung, nausea and/or vomiting following recent chemotherapy; general decline in performance status due to several factors ("failure to thrive"); weakness associated with severe anemia in need of blood transfusion; demonstrated thrombocytopenia in need of platelet transfusion; hypercalcemia; intestinal dysfunction

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(including gastric outlet obstruction and partial or complete obstruction of small more often than large bowel); request by the family that the patient be allowed to die in the hospital; gastrointestinal bleeding from various sites and for several different reasons; altered mental status; spinal cord compression; and hemoptysis. Some, of course, come for a second opinion about their diagnosis of cancer and are already under therapy by a physician at another university or community hospital.

In this chapter, we discuss the life-threatening complications associated with cancer in the elderly and how to manage such events. Both the reader and the author must be mindful of those potentially fatal intercurrent problems that are independent of neoplasia and that occur more frequently in the old than in the young. Urosepsis with shock, myocardial infarction, pulmonary embolism, rupture of an abdominal or thoracic aortic aneurysm, upper gastrointestinal hemorrhage, perforation of large bowel, cardiac arrhythmias, and massive stroke with aspiration are specific examples. They require consideration in differential diagnosis far more often than in the young.

From a review of several major treatises on the subject of oncological emergencies (Yarboro and Bornstein, 1981; Yarboro *et al.*, 1978), it is clear that urgencies, true emergencies, and various serious problems are usually extensively intermixed. Although there is room for debate about the definition of the term medical emergency, most can agree about what items should be included in that category. For example, ventricular fibrillation, respiratory arrest, status epilepticus, intracranial (transtentorial) herniation, tension pneumothorax, septic shock, hemorrhagic shock, advanced pulmonary edema, pericardial tamponade, and massive hemoptysis all demand therapeutic action within seconds to minutes. We think about malignant tumors being capable of occasionally producing many of these events, but certain ones in particular are more commonly associated. Cancers erode into a carotid artery with exsanguination or into a pulmonary artery with death by asphyxiation. Intracranial metastases have been relatively silent until their size produces intractable seizures or uncal herniation. Pericardial involvement can cause a gradual filling of the pericardial space by fluid with modest symptoms until a critical volume rapidly results in total compromise of cardiac dynamics. And severe granulocytopenia, especially during cytotoxic chemotherapy, may lead to sepsis with profound hypotension. Only a few entities in emergency medicine are unique to malignancy: cerebral and pulmonary leukostasis (McKee and Collins, 1974), tumor lysis syndrome (Kalemkerian *et al.*, 1997; Zusman *et al.*, 1973) and, usually, superior vena cava (SVC) syndrome (Bell *et al.*, 1986).

The situations selected for inclusion are not unique to the older population, although some are more commonly seen in the later years of life. Disseminated intravascular coagulation (DIC) is frequently associated with advanced carcinoma of the prostate, clearly an older man's affliction. Hyperviscosity syndrome, with its attendant cerebral and cardiac consequences, generally is less well tolerated in the elderly patient.

It should be pointed out that there are two distinct settings in which one of these acute changes in clinical course might occur. The ideal would be for the patient to appear first in his/her personal physician's office. That doctor, thoroughly familiar with the clinical course to date, is quite prepared to decide about the appropriate intensity of investigation and support for the patient, and dispatches the patient to the hospital, calling ahead with orders and a plan of action. The second common scenario takes place in an emergency department and is more difficult for the patient and the physician, who has neither knowledge about this person's course to date nor about the many other factors that might bear on a decision to intervene in heroic ways. Because the latter setting is a more typical arena for the suddenness that characterizes emergencies and because of the extra challenge created by seeing a new physician, we have elected to discuss recognition and management of many oncological emergencies as though the reader is a physician in an emergency room (ER) seeing each patient for the first time.

FIRST TIME PRESENTATION BECAUSE OF ACUTE SYMPTOMS

Even though it is much less common that patients present with an urgent manifestation of a heretofore undiagnosed neoplasm, it certainly can and still does happen. In that situation it is always best to treat aggressively since critical questions about the quality of life or the reversibility of the acute process usually cannot be answered quickly in the emergency setting (Kalia and Tintinalli, 1984). Such is clearly the case for acute cecal dilatation as occurs in patients with a competent ileocecal valve and distal colonic occlusion by an adenocarcinoma. This is not an insignificant matter when one considers that the incidence of colorectal cancer is highest in the elderly; that the disease can be relatively "silent", especially if one ignores constipation; and that localized "potentially curable disease" is found in nearly two-thirds of patients presenting as emergencies although the perioperative mortality is twice as high as in those who undergo elective operation (Waldron *et al.*, 1986).

There are other instances wherein a combination of denial and minimal morbidity during early stages of a primary malignancy has resulted in presentation of an acute manifestation due to advanced disease before patient or clinician is aware of the diagnosis. This certainly happens with breast cancer, which, for example, can metastasize to pericardium causing tamponade. Another example of an unusual first time presentation of acute symptoms has been reported for previously undetected laryngeal carcinoma that declared itself by impending obstruction of the airway that was successfully managed by an "emergency" laryngectomy (Griebie and Adams, 1987). Fortunately, physicians who work principally or only in large and busy accident rooms have a practiced, sensible approach to these types of unusual presentations, that is, rapid formulation of a differential

diagnosis while quickly mobilizing urgent procedures and consultations.

SPINAL CORD COMPRESSION

A diagnosis of this catastrophe is an easy matter by the time paraplegia and loss of sphincter control have occurred, but an optimal outcome requires much earlier recognition. In the face of vague or isolated symptoms, one must have much more clinical acumen in order to prevent one of the worst disasters that can befall a patient with cancer, namely, loss of locomotion and continence. Such deficits could be even more devastating for the widow or widower who had until that moment been able to manage an independent existence despite having a malignant disease.

Presenting symptoms of metastatic cord compression are generally shared by all primary tumors (Mullins *et al.*, 1971; Torma, 1957). A prodromal phase, present in almost every case, is characterized by pain somewhere along the spinal axis, with or without an accompanying radicular pattern. More importantly, many patients have a sense of dysfunction in their lower extremities even when there are no definite neurological findings. This subtle awareness by the patient may not be volunteered, or worse, if reported may be discounted as an acceleration in a natural process of aging because of the general systemic effects by a tumor with attendant weight loss and decrease in activity. Pain can antedate rapid deterioration of spinal cord function by days, weeks, and even months while other symptoms typically occur days to weeks before the critical sign that brings the patient to an ER. If these early subtle warnings were recognized it could turn emergency medicine into elective medicine.

Once clinical suspicions are aroused, one must follow through the appropriate diagnostic pathway. Although at least two-thirds of plain radiographs of the spine will show bony abnormalities, such as erosion of pedicles, partial to complete vertebral collapse, or a paraspinous soft-tissue abnormality, they do not establish the exact boundaries of cord compression. For appropriate neurosurgery or irradiation treatment, the exact boundaries of the compression must be known. This is easily determined by magnetic resonance imaging (MRI) when it is available. If MRI is unavailable, then myelography (either routine or with computed tomography) is needed.

Selection of the appropriate treatment depends upon the rapidity of onset, the severity as well as the duration of neurological deficit, the level of block, and the primary tumor. A first step in therapy of every case is relief of probable edema with corticosteroids. Dexamethasone, 100 mg intravenously as an initial "bolus" is probably excessive and unproved in any scientific study but has become accepted as standard in many places. That large dose is followed by 20 mg every six hours (by mouth or intravenously). A radioresponsive tumor detected early on predicts for excellent outcome using radiation therapy plus corticosteroids (Gilbert *et al.*, 1978; Ushio *et al.*, 1977). More importantly, that approach avoids surgery with risk of mortality ranging between 6 and 13% and the prolonged debility or lengthy incapacitation that often characterizes the postoperative course of elderly individuals who undergo laminectomy. Chemotherapy is often useful in cases due to lymphomas or other chemotherapy responsive malignancies.

Obviously, laminectomy should be performed in four situations: malignancy is suspected but the tumor type is unknown (needle biopsy may suffice for diagnosis); prior high dose radiation at that level of the cord; individuals with rapidly progressing or acute as well as severe neurological deficits found to have a complete block at myelography; and patients who fail to show a rapid response to radiation. Because laminectomy rarely results in complete removal of tumor, postoperative irradiation should be considered in all cases (Wild and Porter, 1963; Wright, 1963).

MASSIVE HEMOPTYSIS

Infectious disorders have dominated any listing by etiology for causes of massive hemoptysis, but the oncological category is becoming more important along with pulmonary tuberculosis, bronchiectasis, and chronic necrotizing pneumonia (Conlan *et al.*, 1983). Emergency physicians readily consider tuberculosis when confronted with hemoptysis, particularly in older patients and especially in residents of or refugees from underdeveloped countries. However, the elderly represent that fraction of the world's population which is enlarging the fastest; and they are the most likely to get cancer. At the current time, they may (hopefully they do) represent the last male generation of heavy smokers but it is recognized that a history of smoking combined with advanced age increases the incidence of lung cancer.

It is noteworthy that the definition used to quantify serious hemoptysis by such terms as significant or massive varies from 2 dl (Yoh *et al.*, 1967) to more than 3 dl or up to 5–6 dl (Crocco *et al.*, 1968). Clearly some patients can survive quite striking episodes of expectoration of blood, up to 600 ml in 12 hours, while others have instantaneous death with sudden first hemoptysis even when the cause is not neoplastic (Bobrowitz *et al.*, 1983). Regardless of the definition used for massive, the danger is asphyxiation due to obstruction of the tracheobronchial tree rather than exsanguination, although that too can occur. Finally, any amount of hemoptysis can be excessive to the patient with underlying lung disease who has also sustained loss of parenchyma by tumor, surgery, and/or irradiation. In that setting, even as little as 150 ml can lead to a clot capable of occluding a mainstem bronchus with resultant lethal pulmonary insufficiency.

In rare cases, a patient may present with life-threatening bronchial hemorrhage that is due to previously undiagnosed pulmonary neoplasms. However, the probable etiologic diagnosis should be obvious in almost all patients with profuse hemoptysis due to lung cancer because bleeding directly from bronchogenic carcinoma early on is rarely brisk and tumor erosion into a major blood vessel is usually a late sign. In

any event, except in the unusual situation where a patient has a living will or durable power of attorney and can express or has previously expressed wishes that no further intervention take place, emergency management should proceed as for any critical patient: the ABCs (airway, breathing, circulation) must be secured. Whereas in an elective surgical situation an experienced anesthetist may selectively intubate each lung with a double lumen Carlen's or Robertshaw tube, in the most urgent setting with severe respiratory distress, intubation of the mainstem bronchus of the nonbleeding lung must be achieved as rapidly as possible. The patient is then positioned with the "suspected" side dependent. That, combined with suctioning, affords the only opportunity to prevent further drowning of the normal lung. Next, large bore intravenous catheters are inserted for resuscitation by crystalloid followed by blood products. Then and only then can one be more deliberate about further studies.

There are differences of opinion in the literature about surgical versus medical approaches to treatment even when the etiology of pulmonary hemorrhage is infectious (Bobrowitz *et al.*, 1983). However, even for the most aggressive thoracic surgeon there are some contraindications to resection including inadequate pulmonary reserves and very late stage disease, while cancer itself poses special problems, especially if it was deemed irresectable at the time of initial diagnosis and there has been subsequent radiation. All of these compromising descriptors are frequently the rule for lung cancer patients over age 70. So, after resuscitation with both the patient and the situation under control, there may be time for more definitive study of the site that is hemorrhaging and time to consider a nonsurgical therapeutic intervention such as bronchial artery embolization or laser bronchoscopy if the endobronchial growth itself is bleeding.

The expectoration of huge quantities of blood is usually much more frightening than hematemesis or copious hematochezia for both the patient and family, but also for the physician. There is nothing more distressing or taxing than trying to have a meaningful dialogue in an ER about a patient's wishes when that person is repeatedly coughing up large amounts of blood. Yet, our staff has had to do just that on several occasions in order to help the individual and/or family sort out whether they wanted heroic measures including intubation or merely sedation because it was clear that the malignancy was very advanced and no longer amenable to standard modalities of therapy.

In general, both geriatricians and oncologists should be urging upon almost all patients the concept and the execution of two legal instruments, a living will and a durable power of attorney. Hopefully, one or both would be in place when and if this cataclysmic event of massive hemoptysis occurs in any patient with advanced lung cancer.

HYPERCALCEMIA (*see* Chapter 108, Age-related Changes in Calcium Homeostasis and Bone Loss)

Hypercalcemia is a common complication of a number of neoplasms, whether associated with skeletal metastases, ectopic parathyroid hormone (PTH), PTH-like substances, interleukin-1 (as in adult T-cell leukemia/lymphoma), other humoral factors, or coincidental hyperparathyroidism. Although hypercalcemia occurring during the course of malignancy is usually attributable to the neoplasm, one must not forget to consider benign causes such as primary hyperparathyroidism, vitamin D intoxication and sarcoidosis. In any case, treatment in an emergency is similar, with definitive management requiring a later diagnosis.

Once a clinician considers hypercalcemia in the differential diagnosis of apathy, depression, malaise, somnolence, confusion, personality change, new polyuria–polydipsia, or rapidly evolving anorexia with nausea plus constipation, it is easy to establish the presence of a significant elevation in serum calcium. Changes in mental faculties and strength are more easily recognized in younger individuals, whereas in the elderly such events can be too easily blamed on many things including their poor tolerance of analgesics, anxiolytics, hypnotics, and antiemetics. This is especially true when symptoms occur very gradually. On rare occasion, elevations in serum calcium can appear with such rapidity that the event can be fatal within a few days (Cornbleet *et al.*, 1977).

Because normal serum calcium is maintained with 95% confidence limits of 2.24 to 2.58 mmol l^{-1} (9.0–10.5 mg dl^{-1}) for men and 2.22 to 2.57 (8.9–10.4 mg dl^{-1}) for women, it is important to consider a level of 2.64 mmol l^{-1} (10.6 mg dl^{-1}) as a signal of abnormal calcium homeostasis. Values above 2.74 mmol l (11.0 mg dl^{-1}) should be considered an indication to initiate treatment. (Each local laboratory confirms its own range of normal values, so that the above should be taken only as a guideline.) Although the hypercalcemic crisis is still reversible, it is easier to treat earlier before renal effects, with azotemia, or cardiovascular effects, with Mobitz II and other arrhythmias, have developed. It should be remembered that both the inotropic and toxic effects of digitalis preparations are potentiated by calcium and that digitalis preparations are commonly prescribed for elderly patients.

Essentially all patients will have become dehydrated and benefit from intravenous saline to restore vascular volume, with a consequent improvement in calcium excretion. Unless clearly contraindicated, this approach should be initiated immediately. Since large volumes of saline may be required and are usually administered rapidly, there is a need for careful monitoring of cardiac status. Potassium balance must be observed carefully. Once adequate hydration is assured, frusemide (furosemide) augments the calciuresis by decreasing renal tubular resorption of sodium and calcium. Thiazides should not be used since they inhibit calciuresis. Before the availability of potent antiresorptive agents it was common to suggest a fluid intake and output of 4–6 l daily. We now aim to maintain normovolemia and a more modest fluid flux. This minimizes the risk of volume overload in the debilitated patient and edema in the hypoalbuminemic patient.

Glucocorticoids can be helpful in the management of hypercalcemia caused by lymphoma, myeloma, and sometimes breast cancer. It is usual to prescribe prednisone in a

dose of 60 mg daily, but the response is slower than with saline and diuretics, occurring over several days, so that this agent should be started promptly along with rehydration. We are less dependent on glucocorticoids since the advent of potent antiresorptive agents.

Salmon calcitonin in a dose of 8 IU kg^{-1} body weight, by intramuscular injection every six hours for several days, has been useful in controlling hypercalcemia in some patients. Intramuscular administration gives more reliable absorption than the subcutaneous route. Tachyphylaxis may occur, limiting the effectiveness of this treatment. However, the efficacy of calcitonin in managing hypercalcemia due to epidermoid carcinoma has been questioned (Warrell *et al.*, 1988).

The use of bisphosphonates such as pamidronate and zolendronate has been a major advance in management of hypercalcemia of malignancy (Harvey, 1995). These agents very effectively reduce bone resorption. Increases in serum phosphate may occur during treatment, a potentially useful side effect in those patients with hypophosphatemia. Pamidronate 60–90 mg is administered intravenously over 2–4 hours, after rehydration. Zolendronate 4 mg iv may be administered over 15 minutes. Adequate saline should be used to ensure continued calciuresis. The dose can be repeated if required. Bisphosphonates are now our first line of therapy after rehydration.

The most recent addition to our armamentarium is gallium nitrate, administered at a dose of 200 mg m^{-2} day^{-1} over 24 hours for five consecutive days. Its use is contraindicated in patients with significant renal insufficiency. Although some combination of the measures discussed will generally control the excessive serum calcium, occasionally for prolonged periods of time, ultimately the underlying disease must be managed. One must consider early administration of specific treatment for the malignant tumor.

Following the early clinical recognition of its ability to lower serum calcium in most patients with hypercalcemia caused by malignancy, plicamycin (mithramycin) became a standard therapy. The availability of bisphosphonates has greatly reduced its use. Whereas most texts recommend a dose of 25 μg kg^{-1} body weight by intravenous "push" every 24 hours for two to three doses, often we find a lower dose of 15 μg kg^{-1} body weight will suffice. It can be useful in older patients in whom fluid balance is precarious. Plicamycin may be difficult to obtain, and is myelosuppressive. It is no longer a part of our armamentarium.

For patients in the truly terminal stage of a tumor refractory to standard therapy, especially if complicated by skeletal pain, hypercalcemia may contribute to analgesia and on occasion may allow a more comfortable, dignified demise. Knowledge of a patient's wishes and clinical course to date therefore assumes critical importance.

HYPONATREMIA (*see* Chapter 117, Water and Electrolyte Balance in Health and Disease)

At serum sodium levels below 115 mmol l^{-1} (115 mEq l^{-1}), especially when the fall is rapid, brain edema can occur. Hyponatremia of this severity leads to alteration in mental status with lethargy and, in severe cases, coma, seizures, and death. The elderly are more susceptible to the effects of hyponatremia, and may manifest mental status impairment at higher levels of serum sodium. Other physical findings are generally unhelpful in the diagnosis, and routine evaluation of serum electrolytes is mandatory in patients with otherwise unexplained alterations of mental status.

Hyponatremia may be seen in several situations: water redistribution associated with mannitol infusions; pseudohyponatremia due to hyperparaproteinemia or hyperlipidemia; and acute water intoxication. More common causes are renal sodium loss due to diuretic therapy, extrarenal sodium loss during vomiting/diarrhea, and sudden withdrawal of glucocorticoid therapy. The hyponatremia in these situations is usually not life threatening.

The syndrome of inappropriate antidiuretic hormone (SIADH) secretion can cause a severe decrease in sodium that may be life threatening. Diagnostic features include (i) hypo-osmolality of serum; (ii) inappropriately high osmolality of urine for the concomitant plasma hypo-osmolality; (iii) normal renal function; (iv) continued renal excretion of sodium; (v) clinical normovolemia; and (vi) normal adrenal function. SIADH is most frequently seen with small cell undifferentiated carcinoma of the lung, but abnormalities in water homeostasis have been reported with many neoplasms, and especially in association with pulmonary or central nervous system metastases.

Optimal therapy is to correct the underlying disease by chemotherapy and/or radiotherapy while restricting "free water" intake to 500–1000 ml day^{-1}. Correction by this method may take 7 to 10 days. More serious hyponatremia can be reversed in an average of three to four days with the addition of demeclocycline, an antidiuretic hormone (ADH) antagonist (Trump, 1981). For potentially fatal hyponatremia, such as in patients with seizures, coma, or other neurological abnormalities, more rapid correction is required. We utilize infusions of 3% saline combined with frusemide 0.5–1.0 mg kg^{-1} intravenously, with careful attention to intravascular volume, until the serum sodium is above a critical level (Hantman *et al.*, 1973).

SUPERIOR VENA CAVA (SVC) SYNDROME

Although SVC obstruction was seen with benign disease (such as tuberculosis and aneurysms) in the past, most cases in the developed world are now due to malignancy. Most neoplastic SVC obstruction is due to bronchogenic carcinoma, but Hodgkin's disease, non-Hodgkin's lymphoma, and other malignancies may be associated. Benign causes include thrombosis complicating central venous catheters (becoming more common as permanently implanted catheter use is increasing), and mediastinal fibrosis (primary, or secondary to radiation or surgery). The SVC and tributaries are easily compressed by expanding

masses, causing impaired venous return and eventually tracheal, facial, and arm edema. Cerebral edema may occur in severe cases. With gradual obstruction a rich collateral circulation develops, and signs and symptoms may be subtle. With more rapid obstruction, the patient may present as a true emergency. Signs and their frequency of appearance at presentation include: thoracic vein distention (67%), neck vein distention (59%), facial edema (56%), tachypnea (40%), facial plethora (19%), cyanosis (15%), upper extremity edema (10%), vocal cord paralysis (4%), and Horner's syndrome (2%). Vocal cord paralysis and Horner's syndrome usually imply involvement of adjacent structures.

The syndrome is rarely so severe that immediate definitive treatment is necessary. For patients who initially present with SVC obstruction, there is usually time to search for a diagnosis. Sputum cytology and bronchoscopy usually provide a diagnosis. Often easily biopsied masses are found elsewhere in the body. In patients without tracheal edema, mediastinoscopy or even thoracotomy may be performed safely, notwithstanding older literature which suggests that an unacceptable risk of bleeding accompanies these procedures. "Blind" supraclavicular node biopsies may afford a diagnosis in up to 60% of cases.

Emergency treatment, without awaiting a diagnosis, is indicated when there is cerebral dysfunction, symptomatic impairment of cardiac output or upper airway edema. Adequate oxygenation and circulation should be obtained. If intubation of the edematous trachea is required, it should be performed by an experienced anesthetist under controlled conditions to avoid trauma. For patients known to have small cell carcinoma of the lung or lymphoma, chemotherapy is the treatment of choice (unless the tumor is known to be resistant). When the history is unknown, radiation therapy is promptly administered. We proceed with diagnostic maneuvers during the initial stages of radiation. Responses are usually seen within seven days, and are obtained in 70% of patients with bronchogenic carcinoma and 95% of patients with lymphoma. Lack of improvement in spite of tumor regression on radiographic studies suggests that thrombosis of the SVC may have developed. The usefulness of prophylactic anticoagulation in preventing SVC thrombosis must be weighed against the risk of hemorrhage in a venous system under increased pressure. We do not routinely anticoagulate patients with SVC obstruction. Corticosteroids have been recommended to reduce accompanying inflammation and edema, but there are no controlled trials to support their use.

A recent advance has been the development of intravascular SVC stents to relieve obstruction (Stock *et al.*, 1995). Relief is typically rapid. We have found this approach useful in patients who have previously received mediastinal radiation, and who lack other life-threatening comorbid conditions. Catheter-associated SVC thrombosis is best treated by immediate thrombolytic therapy, administered when possible directly to the thrombus to minimize systemic fibrinolysis. An alternative is anticoagulation and catheter removal.

MALIGNANT PERICARDIAL EFFUSIONS AND CARDIAC TAMPONADE

Although many patients with metastatic cancer are found to have cardiac or pericardial metastases at autopsy, only about 30% of these patients had symptoms attributable to this involvement, and in less than 10% was the diagnosis of malignant pericardial effusion made before death. The most common tumors associated with tamponade are bronchogenic carcinoma, breast cancer, lymphoma, leukemia, melanoma, gastrointestinal malignancy, and sarcomas. Occasionally tamponade may be due to cardiac encasement by tumor or to postirradiation pericarditis.

Eventually there is interference with diastolic filling and the stroke volume decreases, with subsequent fall in blood pressure and compensatory tachycardia. As ventricular pressure rises, the mean pressures rise and eventually equalize in the left atrium, the pulmonary circulation, and the vena cava. The major complaint of patients is typically dyspnea, often with cough, or retrosternal chest pain. Hiccups, hoarseness, nausea, vomiting, and epigastric pain are occasional complaints. Eventually there is a decrease in cerebral blood flow which may result in seizures or altered mental status. There is often peripheral cyanosis, engorged neck veins, pulsus paradoxus, facial plethora, low systemic and pulse pressures, and distant heart sounds. With persistent increases in venous pressure, edema, ascites, and hepatosplenomegaly may occur. A chest radiograph is abnormal in most patients, showing either an enlarged cardiac shadow, mediastinal widening, or hilar adenopathy. The electrocardiogram may be normal or show sinus tachycardia, low QRS voltage, ST segment elevation, T wave changes, or electrical alternans. If any suspicion of tamponade arises, an echocardiogram is the test of choice. With optimal techniques of echocardiography, right heart catheterization is rarely necessary to differentiate tamponade or constriction from cardiomyopathy.

Immediate removal of pericardial fluid should be performed as an emergency if there is cyanosis, shock, dyspnea, a pulse pressure less than 20 mm Hg, a paradox greater than 50% of pulse pressure, or peripheral venous pressure greater than 13 mm Hg (Spodick, 1967). Typically, this has been performed by pericardiocentesis using a subxiphoid approach and insertion of a Silastic catheter over a guide wire (Davis *et al.*, 1984). This is a temporary measure, but may allow stabilization of a patient, as well as a diagnosis by pericardial fluid cytology.

Pericardiectomy with creation of a pericardial window, generally utilizing a subxiphoid approach, provides long-term control of the tamponade, and provides diagnostic material in cases in which tumor cells are not shed into the pericardial fluid (Osuch *et al.*, 1985). In our center, this is also the preferred method for emergency management of tamponade, since an experienced surgical team is immediately available. Pericardiocentesis remains a viable temporary measure for situations in which access to pericardiectomy is not immediately available.

HYPERVISCOSITY SYNDROME

Emergency department visits because of altered mental status, visual disturbance, ischemic neurological symptoms, purpura, ecchymoses, epistaxis, or gastrointestinal bleeding are common for older patients. One cause to be considered, especially in elderly patients, is hyperviscosity syndrome due to high serum levels of an abnormal monoclonal immunoglobulin (McGrath and Penny, 1976). Plasma cell neoplasms, multiple myeloma, and Waldenström's macroglobulinemia occur predominantly in the elderly. In these patients, there is frequently expansion of plasma volume, which can create an appearance of congestive heart failure. There is also renal dysfunction in many individuals.

Usually plasma viscosity must be increased to four times normal before disturbances in hemostasis or circulation becomes evident (Crawford *et al.*, 1985). Ancillary laboratory abnormalities often include varying degrees of cytopenia with the expanded plasma volume contributing to the reduction in packed red cell volume. Examination of a blood film always demonstrates rouleaux formation; and the sedimentation rate is elevated. Diagnosis is completed by examination of the bone marrow aspirate and by serum protein electrophoresis and immunofixation electrophoresis. One should not delay treatment while waiting for results of laboratory studies. Physical examination is usually unhelpful in diagnosis, since the classic "boxcar" pattern of circulation in the retinal vessels is seen only in the most severe forms of hyperviscosity syndrome. Plasma viscosity may be rapidly and acutely reduced by plasmapheresis. Despite anemia, patients with hyperviscosity syndrome must undergo plasmapheresis before transfusion since red cell infusions will increase viscosity and may aggravate disturbances in perfusion.

PATHOLOGICAL FRACTURES

Fractures of weight-bearing bones are common in the elderly due to osteopenia. This tendency is enhanced in patients with cancer due to local metastatic disease or to tumor enhanced osteopenia. In pathological fractures of the axial skeleton, there is danger of neurological damage due to bony instability, and patients should be immobilized until surgical consultation is obtained. Pain control with rapidly acting narcotic analgesics is usually required. In these situations, particularly with vertebral pedicle involvement, surgical stabilization may be required (Drew and Dickson, 1980).

Long bone lesions often cause pain with weight bearing on use of that extremity and there is always a risk of pathological fracture. In the lower extremity, we consider prophylactic internal fixation and/or radiation therapy for areas of destruction more than 3 cm in length or when involvement exceeds 30% of the thickness of the cortex. (For the upper extremity, the corresponding dimensions are 5 cm and 50%.) Once a pathological fracture occurs, internal fixation is usually necessary for adequate healing and pain relief. In patients who present with pathological fractures, one immobilizes the affected extremity, provides adequate analgesia, establishes an intravenous line to ensure adequate hydration, estimates blood loss around the fracture site, and prepares for internal fixation as soon as practical if the patient's general condition is stable. Rapid fixation permits rapid mobilization. Radiation therapy to the involved site is begun as soon as feasible.

HEMATOLOGICAL EMERGENCIES

Leukostasis

This is an uncommon problem in a general medical setting, essentially occurs primarily in the situation of previously undiagnosed acute leukemia, and must be recognized rapidly for appropriate therapy. Patients present with varying degrees of mental confusion, and are sometimes even comatose; they may have respiratory insufficiency and often demonstrate evidence of inadequate peripheral perfusion. White blood cell counts are greater than 100×10^9/l and composed predominantly of blasts indicative of acute leukemia. This syndrome is rarely if ever a problem in chronic leukemia with similar leukocyte counts, since cells are smaller and possibly have greater deformability.

Therapy is directed toward reduction of circulating blasts and maintenance of perfusion. Patients should not be transfused initially, even if profound anemia is present. It is better to wait until leukocyte counts are falling and the clinical condition is improving, since early red cell transfusions can increase blood viscosity at presentation and even be fatal. While maintaining careful fluid balance, arrangements should be made for urgent therapeutic leukopheresis under the care of an oncologist or hematologist. Chemotherapy should be instituted promptly after diagnosis, to help prevent the progression of leukostasis after leukopheresis. In the case of acute promyelocytic leukemia, chemotherapy may induce a coagulopathy, and the combination of leukopheresis and retinoid therapy may be appropriate as well.

Thrombocytopenia (*see* Chapter 38, Disorders of Hemostasis)

There is no consensus regarding precise platelet counts below which transfusion of platelets is mandatory. Thrombocytopenia predisposes to bleeding at platelet counts less than 50×10^9/l but especially below 20×10^9/l if the level has fallen rapidly. If platelet function is abnormal, bleeding is frequently seen in this range, and is an indication for platelet transfusion. If platelet function is normal, then lower counts may be tolerated. Thrombocytopenia may occur because of marrow suppression by drugs, other marrow dysfunction or peripheral platelet destruction. When uncertain, a bone marrow aspirate is required for evaluation. Acutely, one transfuses platelets immediately for any bleeding or significant headache (which may be due to an early intracranial

hemorrhage) and avoids salicylates or nonsteroidal anti-inflammatory agents that interfere with platelet function. Six pooled platelet concentrates or a single donor platelet aphereis collection will usually raise the platelet count some $40-60 \times 10^9$/l in an average sized adult (Kruskall *et al.*, 1988). Definitive therapy then is directed toward the cause of the thrombocytopenia.

Neutropenia

This is relatively uncommon except in acute leukemia or a setting of cytotoxic drug therapy, although extensive marrow involvement with tumor may also be a cause. Bone marrow failure in the elderly may also present in this manner. Definitive diagnosis and treatment of the underlying cause may require specialty consultation. Once the granulocyte count falls below 1×10^9/l, risk of infection increases dramatically. Therefore, any fever should prompt immediate examination; culture of blood, urine, and sputum; a chest radiograph; and prompt empiric broad-spectrum antibiotic therapy. Evaluation of the cerebrospinal fluid may be advisable in selected cases.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

DIC crosses several clinical boundaries including infection, obstetrical catastrophes, neoplasia, shock, acidosis, and even heat stroke. DIC is certainly a well-recognized complication of malignant neoplasm. Cancer of the lung, pancreas, breast, prostate, stomach, and colon are particularly likely to precipitate a disturbance of coagulation by release of thromboplastic material from tumor tissue (Levi, 2004). The one hematological malignancy most likely to trigger DIC is acute promyelocytic leukemia and of all the neoplastic processes, it should be the most easily recognized.

Between 13 and 25% of patients with chronic DIC have underlying prostate carcinoma (Sack *et al.*, 1977). Moreover, prostate cancer is the second most common form of malignancy in American males over the age of 50 years and the incidence increases each decade thereafter. Therefore, since prostate cancer increases with age, and because DIC is a frequent complication of that malignancy, physicians in ERs should expect occasionally to see an elderly man with a life-threatening bleeding disorder or thrombotic disorder that is clearly related to cancer only.

Inclusion of this topic in a chapter devoted to oncological emergencies is appropriate but much more difficult to discuss than other problems because its clinical presentation can be variable and quite enigmatic; well-defined criteria for the diagnosis of acute and chronic DIC do not exist; coagulation tests are not infrequently deranged in random studies of patients with a broad spectrum of cancers (Peck and Reizuam, 1973); and treatment of this intricate coagulopathy remains controversial. Either thrombotic or fibrinolytic events may predominate in a patient with DIC, resulting in a picture of either thrombosis or of bleeding. The balance may shift from time to time, and, not infrequently, sites of thrombosis and of bleeding exist simultaneously.

Clinically significant expressions of the syndrome are usually manifest by bleeding, often from a combination of sites. Systemic signs of consumption coagulopathy can be quite inconstant since they reflect both the cause of the disordered clotting scheme and the organ dysfunctions that are secondary to defibrination as well as thrombosis. In a patient with cancer, one should evaluate primary roles for sepsis, shock, hemorrhage, venous thrombosis, embolism, thromboembolism, or the tumor itself, not to mention potential intra-abdominal disasters such as a perforated viscus of more rarely acute pancreatitis.

This disorder is an extremely complex disarray of the hemostatic mechanisms, in which there can be evidence of accelerated coagulation without overt bleeding such that the formation of microthrombi overshadows activation of fibrinolysis. Although criteria for diagnosis vary, basic tests for DIC center around three areas: assays for clotting factors, studies of cellular elements, and determination of fibrinolysis. We initially evaluate the prothrombin time, activated partial thromboplastin time, thrombin clot time, and serum fibrinogen level. These may be abnormal in DIC and the degree of abnormality is a clue to the severity of the condition. Fibrin D-dimer measurement detects the lysis of cross-linked fibrin, and if elevated confirms the presence of a fibrinolytic component in the clinical situation. Inspection of the blood film is mandatory to evaluate the presence of schistocytes, which connote microvascular thrombosis with intravascular red cell fragmentation. The platelet count is also often depressed due to consumption in the coagulation process. These studies do not usually define the exact pathophysiologic processes underway in the patient, but provide a "snapshot" of the situation at a single moment. Observation of changes in these tests over several hours or days is necessary to appropriately treat the hemostatic abnormalities.

Aggressive effort to trace and treat the underlying precipitating disorder is the best method to initiate therapy. Septicemia and shock may be difficult to treat but disseminated cancer is even less easily ablated. We strive to maintain reasonably normal levels of clotting factors, by transfusions if necessary, but also by anticoagulation if it appears that factors are being consumed due to extensive intravascular thrombosis. For situations in which excessive fibrinolysis plays a role, antifibrinolytic agents might be appropriate. The target is a moving one, and expert hematological consultation and access to a capable coagulation laboratory greatly facilitate managing patients with clinically significant DIC.

CENTRAL NERVOUS SYSTEM EVENTS

Mass lesions of the brain in patients with cancer may be due to a primary brain tumor, metastatic disease, postirradiation

brain necrosis, hemorrhage, or abscess. Lung and breast primaries account for most metastases and symptoms are related to location of masses and the rate of increase in intracranial pressure.

Headache is often throbbing and present on awakening, clearing in hours but recurring periodically during the day. It is exacerbated by cough, Valsalva, or sudden movements. Headaches of a fleeting or stabbing nature, or those that increase in severity throughout the day, are unusual for tumor.

Any new onset of seizures (usually focal) without obvious cause in a patient over 30 years of age suggests tumor, especially in an individual known to have malignant disease. Other more classical findings in brain metastasis are focal neurological deficits or papilledema.

Computed tomography (CT) of the brain is generally the initial test. MRI scans are less readily available, and more expensive, although more sensitive. MRI scans may be most helpful in determining the exact number of lesions in patients being considered for excision of brain metastases or for stereotactic radiation. Once a mass lesion is identified, its origin must still be determined. At 6–12 months posttherapy, postirradiation brain necrosis can mimic a return of the original tumor but papilledema is not present. A biopsy may be required to distinguish between them. Positron-emission tomography is helpful in this situation but its availability is limited. In the setting of long-term steroid therapy or recurrent neutropenia, an abscess may present merely as a mass lesion without fever. A variety of disorders can mimic potential brain metastasis upon presentation, including: other kinds of headaches; ethanol withdrawal seizures; cerebrovascular accidents; pseudotumor cerebri; subdural hematomia; encephalitis and arachnoiditis. All should be evaluated appropriately.

If a mass lesion felt to be a tumor is demonstrated, initial therapy with dexamethasone is begun as for spinal cord compression. If herniation is imminent, then mannitol 12.5–25 g is given intravenously along with dexamethasone and neurosurgery and radiation oncology are consulted immediately.

Cerebrovascular complications in patients with cancer originate from several different causes, have been well described, and will be overlooked if not considered in the appropriate setting (Graus *et al.*, 1985). Nonbacterial thrombotic endocarditis and attendant cerebral infarction should not have any age dependence but atherosclerosis is the most frequent cause of cerebral infarction found at autopsy and certainly is more age related. Usual risk factors for cerebrovascular disease are often overshadowed in a patient with malignancy because frequently there are several other things going on. There are perhaps two clues in the approach to the diagnosis of cerebrovascular disease in patients with cancer: first, the clinical presentation is often a diffuse encephalopathy rather than an acute focal deficit and secondly, the type of event is related sometimes to the primary tumor, but also to the extent of cancer, evidence of central nervous system infiltration, or the presence of superimposed complications such as immunosuppression, infection, coagulopathy, and any recent invasive procedures (Graus *et al.*, 1985).

GASTROINTESTINAL EMERGENCIES

Major gastrointestinal calamities in the setting of cancer are related to obstruction, perforation, hemorrhage, and inflammation. These may be due to effects of tumor or therapy. Obstruction of the bowel may result from primary tumor, recurrent or metastatic tumor, adhesions, or scarring from radiation. Patients present with combinations of pain, nausea, vomiting, constipation, and distention. The greatest threat is in those individuals with a competent ileocecal valve and a distal obstruction wherein cecal perforation may occur. Immediate surgical decompression is indicated should cecal dilatation to 12–14 cm be seen on a plain film of the abdomen. When the ileocecal valve is not competent, large bowel obstruction as well as small bowel dilatation respond well to suction, along with fluid and electrolyte replacement, such that surgery can be delayed or sometimes avoided.

In patients presenting to an ER with abdominal pain, 2% were discovered to have cancer (usually of the colon) and there was rarely obstruction or perforation (DeDombal *et al.*, 1980). Of patients older than 50 years presenting with abdominal pain, 7% developed cancer. Data from a cooperative study in Scotland, England, and Denmark suggest that 10% of all patients with gastrointestinal malignancies present to an ER and 3% do so with an intra-abdominal catastrophe. The remainder present as acute "unexplained" abdominal pain. Characteristics more common in those found to have cancer were pain lasting longer than 48 hours, intermittent pain, worsening pain, constipation, abdominal distention, and an abdominal mass (DeDombal *et al.*, 1980). Surgery, when performed as an emergency in the elderly, especially for gastrointestinal malignancies, was believed to carry a higher risk. However, recent studies have shown no change in morbidity or mortality by decade if patients of similar nutritional status without coexisting organ system disease are compared (Boyd *et al.*, 1980). Complications are less related to age than to preoperative nutritional status and preoperative impairment of other organ systems. However, emergent surgery overall does have a higher risk than for similar procedures performed electively. The lesson here is that with proper attention, the elderly can undergo appropriate procedures with similar morbidity and mortality as patients who are younger but with similar coexisting conditions. Conditions that adversely affect risk include pulmonary insufficiency, cardiac dysfunction, hypertension, renal insufficiency, hepatic disease, diabetes, or previous major surgery (Boyd *et al.*, 1980).

VENOUS THROMBOSIS AND EMBOLISM (*see* Chapter 55, Venous Thromboembolism)

Thromboembolic events are common in patients with malignancies and can be attributed to a lack of activity and to a

hypercoagulable state which characterizes some neoplasms (Di Nisio *et al.*, 2004). It is important to realize that a predisposition to thrombosis may be present and that the presentation may be gradual. For instance, multiple small pulmonary emboli may be responsible for worsening pulmonary insufficiency. Yet in patients with malignancies one sometimes avoids thrombolytic therapy since many patients have had surgery, have structural lesions, or have coexisting cytopenias, and often life expectancy as well as mobility are greatly limited such that prevention of a postphlebitic syndrome is of less concern than in other patients.

Age alone is not a contraindication to appropriate thrombolytic therapy or anticoagulation, although it may complicate management. The elderly patient is more likely to fall, complicating anticoagulation. The appetite and diet may be variable, complicating control of oral anticoagulation. There may also be an increased risk of gastrointestinal bleeding in these patients. If anticoagulation is contraindicated or unsuccessful, then insertion of a caval filter may at least prevent subsequent pulmonary embolism.

EMERGENCIES DUE TO NEOPLASMS OF THE HEAD AND NECK

Squamous cell carcinomas of the floor of the mouth, the tongue, the tonsils, and the larynx essentially occur during middle and older life. Therefore, two disasters, upper airway obstruction and external massive hemorrhage from the carotid system, are not unusual in the elderly. However, the usually slow growth of epidermoid carcinoma in the head and neck region provides ample warning of such complications, and more than enough time to decide how or whether to treat it. Unfortunately, a specific plan for such an exigency is uncommon or rarely transcribed.

Tracheostomy is indicated in every patient in whom there is or it is expected that there will be airway compromise. By following this principle, it should be possible to perform tracheostomy under controlled circumstances in the operating room, thereby avoiding having to do it under emergency and uncontrolled circumstances. There are rare exceptions, such as patients with bilateral thyroid cancer and primary or metastatic pulmonary neoplasms that might be seen with airway obstruction at the glottic level due to bilateral vocal cord paralysis in the adducted position. In that setting, it is possible to have more subtle signs and the etiology of the recurrent laryngeal nerve dysfunction might not be immediately apparent.

For the patient with a tracheostomy tube already in place, there are still two more threats. Rarely a life is lost because of the inability to reinsert tubes during the changing of them before the tract is well defined or when there is high-grade airway obstruction. Finally, dislodgement of a tube can be catastrophic and has characteristic signs including recurrent airway obstruction, despite an earlier tracheostomy; absence of airflow via the tube during attempts at deep respiration; inability to suction pulmonary secretions from it; and a normal voice. A proper instruction sheet warns of these signs and advises the patient and/or family to alert their physician promptly or to call for help through a number for emergency medical services.

Hemorrhage may ensue from extensive cancers that erode major vessels or because of necrosis of vessel walls subsequent to injury by some combination of exposure, radiation, surgery, cytotoxic chemotherapy, and oral cutaneous fistula formation. Attempts at local control or grafting of the vessel are of no avail. Carotid artery hemorrhage by tumor erosion is the most life-threatening emergency seen in oncological disorders. However, it rarely occurs de novo, being heralded by a small transient bleed prior to the final disruption. Certainly there is more than enough time for the physician of a patient with head and neck cancer to decide whether hemorrhage from the carotid system is going to be accepted as the terminal event should it occur. Unfortunately, decisions like that are both painful and distasteful, resulting in heroic attempts by emergency teams in the absence of such decision making and in the absence of written orders.

A deeply invasive tumor at the base of the tongue, with erosion of branches of the external carotid system, is one of the most common causes of major arterial hemorrhage from the mouth. This type of hemorrhage may require ligation of both external carotid arteries in order to stop the bleeding, since there is such extensive cross circulation.

UTILIZATION OF INTENSIVE CARE UNITS (ICUs)

Early in the course of neoplastic disease, when expectations of a successful outcome are real, there is almost never any reason to withhold supportive measures, including an ICU, in order to overcome an early complication of the disease *per se* or its treatment. On the other hand, it is legitimate to ask what to do about that patient with advanced cancer who is in the third trimester of the illness and whose intercurrent problems suddenly escalate. There appears to be no simple stopping point in the progression of attempts at diagnostic or therapeutic intervention. Often there is a clinical temptation to believe that just a bit more intervention, such as endotracheal intubation, open lung biopsy and aggressive support on an ICU, will surmount the complication. This is a scene played out frequently, leading to marginally useful results and extraordinarily high costs. Of the many controversies that attend this highly charged decision about admitting cancer patients to intensive care wards is one still incompletely resolved even by the courts: which patient has the right to refuse life-saving extraordinary therapy (Emanuel, 1988). Another challenge faced by critical care specialists who often control access to these units is the matter of unattainable certainty in formulating prognosis upon which life-and-death decisions should be based (Reuben *et al.*, 1988). It is impossible to give specific advice in this area of the practice of medicine since physicians are waiting for a societal commitment to the solution of certain problems (Bayer *et al.*, 1983). Nevertheless, physicians should not practice emergency medicine in

the field of oncology without first carefully reflecting about the issues involved in the use of ICUs, and without examining/understanding the policies for control of the ICUs at their own hospital.

EMERGENCY MEDICAL SERVICES AND CANCER

The interface between emergency medical services and the dying patient is both complex and difficult. It ranges from the extreme, where an ambulance delivers paramedical staff to the bedside of a patient experiencing dyspnea, coma, or shock, to the appearance of a patient in an ER with varied or several complaints (usually reported by a relative or caregiver rather than the individual who has the malignancy). In the first scenario, the paramedical staff may be told about a living will, but the existence of such cannot be immediately documented. Sometimes a family member might just report that this individual patient would not want to be resuscitated. At such times, there is not comfortable agreement about what to do and in many states living wills were designed for use in hospital rather than as instruments to instruct medical technicians after a request for emergency care has already been initiated. Today general legal and ethical standards offer these paramedical personnel no truly safe alternative than to initiate life-saving techniques upon encountering an unresponsive patient or one in severe physiological distress. In the second setting, a visit to an ER, the reason for attendance may turn out to be plural, something we call a multifactorial presentation. Everything seems to be going a little bit wrong and actually it is a matter of family or caregivers wearing out or refusing to cope any longer. The problem then becomes one of dealing with a chronic disease in an inappropriate setting, by a busy physician who has limited knowledge about the patient's previous course.

Our capabilities for intervening are great and increase steadily with each decade. One challenge is to intervene appropriately and not let a potentially reversible crisis progress to irreversibility. We also must be wise enough not to make a bad situation worse. All of this requires an intense effort toward preventing individual pieces of the medical care system from becoming disconnected. Physicians can do that by remaining aware of their responsibilities especially in the area of communication. Certainly patients having an acute event during a chronic illness should rarely turn up in an ER unannounced. Finally, in the realm of therapy, we should all do well to remember the words of Max Born (Born, 1968): "intellect distinguishes between the possible and the impossible; reason distinguishes between the sensible and the senseless; even the possible can be senseless". There should be no real doubt about some of the sensible goals of treatment in patients with cancer whether they are in the first or the tenth decade of life. They are: activate every important modality of treatment in an attempt at cure; preserve locomotion and continence; protect the ability to think; relieve pain or suffering; and support dignity (Silberman, 1986).

KEY POINTS

- The presentation of cancer in the elderly may be as a urgent problem with either an anatomic or metabolic cause.
- Hypercalcemia may have subtle symptoms in the elderly, and requires a high index of suspicion.
- Weakness may be a result of spinal cord compression, central nervous system metastases, metabolic derangements due to cancer, or be unrelated to a patient's malignancy.
- Cancer is associated with a pronounced tendency towards thrombosis.
- Encourage patients and families to formally make known their wishes regarding end of life care, before an urgent situation arises.

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Breast Cancer in the Elderly

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THE PRESENTATION

Diagnosis of breast cancer in the elderly is made by the discovery of a lump in 60–80% women. Since screening is applied less rigorously to elderly patients, the majority of women present with a palpable lump. Some studies reveal that the stage at presentation is more advanced in the elderly women (Goodwin *et al.*, 1986; Homes and Hearne, 1981). A patient care evaluation survey was conducted by Commission on Cancer of the American College of Surgeons for 1983 and 1990 (Busch *et al.*, 1996). They surveyed all states of United States including Puerto Rico and Canada and studied 17 029 women in 1983 and 24 004 women in 1990. Twenty percent of women in 1983 and 23% in 1990 were 75 years of age or older. The survey included 2000 hospitals (25 patients from each). The percentage of cancers detected by physicians' examination decreased in the younger group from 27% in 1983 to 21% in 1990, whereas in the elderly, the corresponding figures were 41% and 34% respectively.

Veronesi's group from Milan reported various features of presentation and choice of therapy in the elderly (Gennari *et al.*, 2004). They studied 2999 postmenopausal patients referred for surgery at the European Institute of Oncology, Milan, Italy, from 1997 to 2002. The patients were grouped according to age: young postmenopausal (YPM age 50–64 years, $n = 2052$), older postmenopausal (OPM age 65–74, $n = 801$), and elderly postmenopausal (EPM age ≥ 75, $n = 146$). EPM patients had larger tumors compared with YPM patients (pT4: 6.7 vs 2.4%) and more nodal involvement (lymph node positivity: 62.5 vs 51.3%). EPM patients showed a higher degree of estrogen and progesterone receptor expression, less peritumoral vascular invasion and less human epidermal growth factor receptor-2 (HER-2)/*neu* expression than YPM patients. Although, comorbidities were more often recorded for elderly patients (72% EPM vs 45% YPM), it did not influence surgical choices which were similar across groups (breast conservation: 73.9, 76.9, and 72.9%, respectively). No systemic therapy was recommended for 19.1% of the EPM compared with 5.4 and 4.7% of the two other groups.

In women over 70 years, estrogen receptor positive tumors are more common, range 69 to 95% compared with all tumors, range 53 to 72% (Busch *et al.*, 1996).

Pathologically infiltrating ductal carcinoma accounts for 77 to 85% of all tumors in the elderly women as compared to 68% in younger women. There is an increase in the proportion of papillary and mucinous carcinoma with advancing age. Whereas the number of lobular carcinoma *in situ*, comedo, medullary, and inflammatory carcinoma decreases with advancing age, the prevalence of ductal carcinoma *in situ* (DCIS) increases until 75 years, after which it declines (Rosen *et al.*, 1985; Law *et al.*, 1996).

In summary, elderly women generally present with large palpable estrogen receptor positive, infiltrating ductal carcinoma with a positive lymph node (Law *et al.*, 1996).

STAGE OF PRESENTATION

Age and delay – there is generally a delay in the diagnosis of breast cancer in elderly women. In a study by Berg and Robbins (1961), the diagnosis was delayed by more than 6 months in 28% of women under 70 years of age compared to 42% delay in women above the age of 70. Similarly, Devitt (1970) observed a delay of more than 6 months in diagnosis in 35% of women above the age of 70, compared to 28% below the age of 70. The tumor is generally advanced in elderly group as shown in Table 1.

COMORBIDITY: THE MAIN REASON TO JUSTIFY UNDERTREATMENT

Women suffering from heart disease, obstructive airway disease, stroke, or other major incapacitating illnesses receive inadequate diagnostic and therapeutic attention.

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Table 1 TNM Stage with age at presentation

Age(yrs)	I	II	III	IV	Reference
>80	52%	18%	6%	24%	Robin and Lee (1985)
>80	25%	49%	15%	10%	Davis *et al.* (1985)
>75	53%	22%	12%	13%	Host (1986)

TNM, tumor nodes metastases.

Nicolucci *et al.* (1993) analyzed the data on 1724 women treated in 63 general hospitals in Italy. A comorbidity index was computed from individual disease value (IDV) and functional status (FS). IDV summates the severity and presence of specific complications for each disease suffered on a scale of 0–3, with 0 = full recovery and 3 = life-threatening disease. FS from signs and symptoms of 12 system categories evaluated the impact of all conditions, whether diagnosed or not, on patients' health status. The study showed higher proportions of inadequate diagnosis and therapy in the elderly group. The quality of care was assessed by a score based on observed degree of compliance with standard care. The median value of overall diagnostic and staging score was 60%. About one-third of surgical operations were inappropriate; 24% of cases with stage I-II disease had unnecessary Halsted mastectomy, and breast conservation in smaller tumors of $\leq$2 cm was underutilized. The presence of one or more coexistent diseases was associated with failure to undergo axillary dissection and lower utilization of conservative surgery.

Newschaffer *et al.*, 1996 from the Virginia Cancer Centre evaluated 2252 women with breast cancer (without metastasis). In the group of women above 85 years, the odds of being treated surgically were one-third of those women in 66–74 years age-group. The odds of getting breast-conserving surgery with radiotherapy (RT) were 0.55. Even after adjusting for comorbidity, the odds ratio remained the same.

Ganz *et al.* (2003) examined health-related quality of life (QoL) of a cohort of older women with breast cancer. They used standardized QoL measures in a group of 691 women of 65 and above who were interviewed 3 months after surgery and twice in the following year. Physical and mental health scores declined significantly in the follow-up year, independent of age. However, a cancer-specific psychosocial instrument showed improvement in the scores. Better 3-month physical and mental scores and better emotional support predicted more favorable self-perceived health, 15 months after surgery. The authors concluded that significant decline occurs in the physical and mental health of older women in 15 months after surgery, whereas cancer-specific QoL measure improved over time.

Alvan Feinstein, a famous clinical epidemiologist from Yale, has said that the failure to classify and analyze comorbid disease has led to many difficulties in medical statistics (Feinstein, 1970). There are four reasons for measuring comorbidity correctly: (1) to be able to correct for confounding thus improving internal validity of the study, (2) to be able to identify effect modification, (3) the desire to use comorbidity as a predictor of outcome, and (4) to construct a comprehensive single comorbid scale that is valid, to improve the statistical efficiency. de Groot *et al.* (2003) have recently reviewed various comorbidity indices. The following indices have been applied for patients with breast cancer: "Charlson Index" – this is the most extensively studied method and includes 19 diseases which are weighted on the basis of strength of association with mortality. The "disease count index" simply counts the coexisting diseases but lacks a consistent definition and weighting for different diseases. The "Kaplan index" uses the type and severity of comorbid condition, for example, types are classified vascular (hypertension, cardiac disease, peripheral vascular disease) and nonvascular (lung, liver, bone, and renal disease). It has good predictive validity for mortality. It may be worthwhile for all the agencies involved in breast cancer research to adopt one of the above indices and record it prospectively.

SCREENING IN THE ELDERLY

Presently, all women in the United Kingdom between age 50 and 65 are being offered breast cancer screening. Although those above 65 are eligible, they have not been called *routinely*. Till recently, those already on the regular screening were not recalled after they reached the age of 65.

The NHS Breast Cancer screening Programme in the UK, 2005 has screened more than 14 million women and has detected over 80 000 cancers. The NHS Breast Screening Programme is saving at least 300 lives per year. This figure is set to rise to 1250 by 2010. By 2010, the effect of the screening program, combined with improvements in treatment and other factors (including cohort effects), could result in up to a halving of the breast cancer death rate in women aged 55–69 from that seen in 1990. The program has now expanded to invite women between 65 and 70.

Thus, from Table 2 it can be seen that with increasing age the number of cancers detected goes up.

In order to enhance the rate of breast examination by doctors in women above 65 years and to increase compliance with mammography, Herman *et al.* (1995) conducted a randomized clinical trials (RCT) at the Metro Health Medical Center Cleveland, Ohio. All house staff in Internal Medicine were asked to fill a questionnaire about their attitude toward prevention of breast cancer in elderly people after providing some basic information (Monograph and a lecture).

In one arm (controls), no specific interventions were offered. In the next group (education), nurses provided educational leaflets to patients attending the clinics. In the third group (prevention), nurses filled the request forms and

Table 2 Result of UK breast cancer screening – 2004 review NHS Breast Cancer screening Programme in the UK, 2005

Age	Cancer detected per 1000 women screened
50–64	7.6
65–69	20.6

Table 3 Rates of examination and mammography by intervention

Group	Breast exam (%)	Mammography (%)
Control ($n = 192$)	18	18
Education ($n = 183$)	22	31
Prevention ($n = 165$)	32	36

facilitated women to undergo mammography. Their results are given in the Table 3:

The study suggests that encouragement and education of older women by motivated doctors and nurses improves compliance. Chen *et al.* (1995) reported the mortality rate of women aged 65–74 screened in the Swedish 2-county trial – 77 080 women were randomized to undergo screening every 33 months and 55 985 women served as controls. Of the screened group, 21 925 were in the age-group 65–74. In the control arm, 15 344 women belonged to the age-group 65–74 years. The relative breast cancer mortality in the screened group was 0.68, demonstrating a survival advantage in the elderly population.

RISK FACTORS IN ELDERLY

Age: With advancing age, the risk of developing breast cancer rises.

In a cohort of National Surgical Adjuvant Breast and Bowel Project's Breast cancer prevention trial of USA, the presence of nonproliferative lower category benign breast disease (LCBBD) has been found to increase the risk of invasive breast cancer. The overall relative risk (RR) of breast cancer was 1.6 for LCBBD, compared to women without any LCBBD. This risk increased to 1.95 (95% confidence interval (CI) 1.29–2.93) among women aged 50 and over (Wang *et al.*, 2004).

Hormone replacement therapy (HRT) has been identified as a *risk factor for breast cancer*. The impact of HRT on the incidence and death due to breast cancer in the United Kingdom was assessed through a study on 1 million women (Million Women Study Collaborators, 2003). In this prospective cohort of 1 084 110 women aged 50–64, current users of HRT were found to have a higher risk of developing breast cancer than nonusers (RR = 1.66; 95% CI 1.58–1.75). The risk was highest for combined estrogen-progestogen (RR = 2; 95% CI 1.88–2.12) than for estrogen alone (RR = 1.3; 95% CI 1.2–1.4) and for tibolone (RR = 1.45; 95% CI 1.25–1.68) compared to those who never used. There was a dose response relationship of increasing risk of cancer, with increasing duration of HRT usage, the highest being with combined estrogen + progestogen used for 10 years or more (RR = 2.31; 95% CI 2.08–2.56).

The Danish Nurses Cohort study (Stahlberg *et al.*, 2004) provided data on 10 874 nurses (aged 45 years and above). Of these, 244 women developed breast cancer. After adjusting for confounding, increased risk was found with current use of estrogens (RR = 1.96; 95% CI 1.16–3.35), for combined use of estrogen + progesterone (RR = 2.7; 95% CI 1.96–3.73), for current use of Tibolone (RR = 4.27; 95% CI 1.74–10.51), compared to never ever use of HRT. In current users of combined HRT with progestins, continuous combined use has higher risk (RR = 4.16; 95% CI 2.56–6.75) than cyclical combined use (RR = 1.94; 95% CI 1.26–3).

Natural History of Breast Cancer in the Elderly

It has long since been thought that breast cancer in the elderly is rather indolent and a biologically less aggressive disease. Singh *et al.* (2004) studied the *metastatic proclivity* as indicated by the virulence (defined as the rate of appearance of distant metastasis) and *metastagenecity* (defined as the ultimate likelihood of developing distant metastasis). These authors examined 2136 women who underwent mastectomy without systemic adjuvant therapy at the University of Chicago Hospitals between 1927 and 1987. The median follow-up period was 12 years. Distant disease-free survival(DDFS) was determined and virulence (V) and *metastagenecity* (M) were obtained from log linear plots of DDFS. No significant difference was observed between size of primary tumor in age-group <40 years, 40–70 years and >70 years. Significantly, fewer women above 70 years presented with positive nodes. In women with negative nodes, the DDFS was higher among age 40–70 years, compared with those among age over 70. However, no significant difference was observed in the DDFS in the node positive group in any of the age categories. The 10-year DDFS for age 40–70 was 33% and for women >70 it was 38%. Among the node negative women, V was 3% per year for age 40–70 years, as well as for age >70 years and M was 0.2 for age 40–70 years and 0.35 for age >70 years. In women with positive nodes, both V (11% per year vs 10% per year) and M (0.7 vs 0.65) were similar in both age-groups. These authors concluded that there was no evidence that breast cancer was more indolent in the elderly. Therefore, similar diagnostic and therapeutic efforts should be made in the elderly as in the younger women, the only modification made on the basis of comorbidity.

TREATMENT OF OPERABLE DISEASE

The optimum treatment of breast cancer in the elderly is not yet well established. It is reasonable to apply the principles of therapy largely learned from studies in the younger cohort of women, viz. breast-conserving wide tumor excision and axillary dissection for smaller lesions, mastectomy for the larger tumors, tamoxifen for estrogen receptor (ER)-positive lesions and chemotherapy for node positive or >1 cm tumors and radiotherapy for locally advanced lesions. Unlike the treatment of younger women, which is based on sound high-level evidence from meta-analyses of large RCTs, the therapy for the elderly is not evidence based, as there is paucity of large RCTs. The women over 65 years have been excluded from many trials. In order to fill up this lacuna

in knowledge, two European Organization for Research and Treatment of Cancer (EORTC) trials were set up. In Britain, a CRC trial and a trial at Nottingham were conducted to answer the question of what would be the best therapy for the elderly. The results of these trials are summarized below. Moreover, a decision analysis has also been performed by (Punglia *et al.*, 2003). Truong *et al.* (2004) have reported an overview of literature on breast-conserving therapy (BCT) in elderly women with early breast cancer. They found a paucity of prospective data and numerous retrospective series of diverse treatments with conflicting results. Their observation supports BCT + postoperative RT as the standard of care for the elderly.

Crowe *et al.* (1994) reported the outcome of modified radical mastectomy (MRM) in a group of 1353 women (age range 22–75). The hazard ratio for death were similar in all the three age-groups (<45, 46–65and >65). This data demonstrates that older women achieve similar results as younger ones, provided they are treated adequately.

Among cooperative group clinical trials sponsored by the National Cancer Institute for early-stage breast cancer, women of 65 years and above constitute only 18% of participants, although they constitute 49% of eligible pool of all newly diagnosed cases. Physicians have been incriminated as the key barrier to enrolling older women in trials (Kemeny *et al.*, 2003).

The Cancer Research UK Breast Cancer Trial Group (Fennessy *et al.*, 2004) conducted a RCT for women over 70 years of age with operable breast cancer. Of 455 patients, from 27 hospitals in the United Kingdom, 225 were randomized to surgery + tamoxifen and 230 to receive tamoxifen alone. The analysis was based on a median follow-up of 12 years. The local control was better achieved when surgery was combined with tamoxifen. Fifty-seven patients randomized to surgery and 141 to tamoxifen alone progressed. The hazard ratio (HR) for local progression for tamoxifen as compared to mastectomy was 17.24; 95% CI 6.4–47.6 and for tamoxifen compared to BCT, 5.99; 95% CI 4.12–8.7. The risk of local progression was greater in the BCT arm compared to mastectomy (HR = 2.98; 95% CI 1.06–8.39). The 5 year risk of local progression was 8% after mastectomy, 18% after breast conservation and 64% in women who had tamoxifen alone.

The 10 year survival was 37.7% for surgery + tamoxifen and 28.8% for tamoxifen alone. Primary tamoxifen therapy is inferior to mastectomy and breast-conserving surgery in achieving local control. Among patients randomized to surgery + tamoxifen, the risk of local progression was greater in those who had breast conservation than in those who had a mastectomy (Fennessy *et al.*, 2004).

A strong consensus prevails that by the time the breast tumor is palpable, dissemination has already occurred and local treatment can only provide local control. Surgery cannot influence development of metastases. Data from mature randomized trials challenges this belief. Thus, local treatment offers more than local control and may prevent the spread of breast cancer from residual cancer left behind after surgery.

ROLE OF RADIOTHERAPY

In a study of 558 women aged ≥50 years, by the University of Pennsylvania, who had been treated with breast conservation and RT, for stage I and II breast cancer, there were 173 women who were aged ≥65years. Treatment included complete gross excision of tumor, pathological axillary lymph node staging and breast irradiation. Women ≥65 years and those between 50–64 years, were found to have large T2 lesions (43% vs 34%; p = 0.05), ER negativity (9% vs 16%; p = 0.13). The proportion of axillary node positivity (24%) as well as the mortality rates due to breast cancer at 10 years (13%) was similar in elderly patients and those in the 50–64 age-group. The overall survival at 10 years (77% vs 85%; p = 0.14), local failure (13% vs 12%; p = 0.6) and freedom from distant metastasis (83% vs 78%; p = 0.45) were similar. The study revealed that breast cancer in the elderly is not an indolent disease and has many aggressive prognostic factors. Moreover, breast-conserving surgery and RT achieves good local control and a survival comparable to women below 65 years (Solin *et al.*, 1995).

In a decision analysis of a hypothetical cohort, by a Markov model including postmenopausal women with ER-positive T1 tumors (≤2 cm), Punglia *et al.* (2003) from Harvard Medical School, computed the benefits of adding RT to conservative breast surgery and tamoxifen versus BCT + tamoxifen (tam.) alone. The modeled recurrence free survival benefit of radiation was 3.35 years for women of 50 years and 0.61 years for women at 80. A 50 year old was less likely to die from breast cancer when treated with RT + tam. than with tam. alone (relative risk reduction, RRR = 54%). An 80 year old had a RRR = 42% when RT was added to tamoxifen. Compared with the untreated group, the adjusted hazard ratio of breast cancer mortality was 0.4 for tamoxifen alone (95%CI 0.2–0.7), 0.4 for BCT alone (95%CI 0.1–1.4), 0.2 for mastectomy alone (95% CI 0.1–0.7) and 0.1 for BCT + adjuvant therapy (95%CI 0.03–0.4).

It is thought by some that in a selected group of elderly women, radiation could be avoided. Gruenberger *et al.* (1998) from University of Vienna evaluated the need of RT in a retrospective review of 356 women above 60 years, treated by quadrantectomy + axillary dissection followed or not followed by adjuvant radiation. Among node negative, ER-positive cases, there was no benefit of RT as locoregional recurrence rate was 3% with or without radiation. In this subgroup (ER positive, node negative women), adjuvant tamoxifen reduced LR to 2% with or without radiation. These authors suggest that elderly women aged 60 or above with a T1, ER positive, node negative tumor, may be spared the toxicity of RT when treated by conservation surgery, axillary dissection, and tamoxifen.

Milan Trials of Breast conservation: Prof. Veronesi of Milan Institute has been a great proponent of breast conservation. He initially developed the technique of quadrantectomy plus radiotherapy (QUART) and later reduced the extent of resection to only lumpectomy. The results of the Milan trials were published in a meta-analysis of data from 1973

patients treated in three consecutive randomized trials by four different radiosurgical procedures: Halsted mastectomy, QUART, lumpectomy plus RT, and quadrantectomy without RT (Veronesi *et al.*, 1995). Median follow-up for all patients was 82 months. The annual rates of local recurrence was 0.2 for patients treated with Halsted mastectomy and 0.46 for QUART, 2.45 for lumpectomy plus radiotherapy and 3.28 for quadrantectomy without RT. The local recurrences were much higher in patients under 45 years of age as compared to women over 55 years. Overall survival was identical in the four groups of patients. This study indicated that in elderly patients, lumpectomy and RT is a satisfactory option.

ADJUVANT ENDOCRINE THERAPY

Since the majority of tumors in the postmenopausal women are ER positive, hormonal manipulation by antiestrogen molecules or aromatase inhibitors is used with advantage in over 60% of cases.

Crivellari *et al.* (2003) reported the results of International Breast Cancer Study Group Trial IV conducted in many centers from the United States, Australia, Sweden, Switzerland, Italy, and Slovenia. From 1978 to 1981, 349 women 66 to 80 years of age with pathologically involved nodes after total mastectomy and axillary clearance were randomly assigned to receive 12 months of tamoxifen (20 mg daily) plus prednisolone (7.5 mg daily) (T + P) or no adjuvant therapy. At 21 years, median follow-up T + P prolonged the disease-free survival and overall survival – 15-year DFS 10 versus 19% in control; hazard ratio 0.71; 95% CI 0.58–0.86. The therapy was also superior in controlling breast cancer recurrences.

The long-term use of tamoxifen is associated with increased hazard of thrombotic episodes and endometrial proliferation. In an RCT (Rutqvist and Mattsson, 1993) of adjuvant tamoxifen (tamoxifen 40 mg daily for 2–5 years) versus no adjuvant therapy among 2365 postmenopausal women with early breast cancer in Stockholm, there was significantly reduced hospital admission due to cardiac disease. The relative hazard (tam. vs control) was 0.68 (95% CI 0.48–0.97; $p = 0.03$). Comparing 5- versus 2-year therapy, there was grater protection from cardiac disease with longer use of tamoxifen (relative hazard = 0.37, 95% CI 0.15–0.92, $p = 0.03$).

The results from meta-analysis of RCTs on early breast cancer have been published by the (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005).

For ER-positive disease only, allocation to about 5 years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31% (SE 3), largely irrespective of the use of chemotherapy and of age (<50, 50–69, ≥70 years), progesterone receptor status, or other tumor characteristics.

Mastectomy or Tamoxifen?

Professor RW Blamey and his group reported the results of a trial comparing tamoxifen alone with wedge mastectomy for women above age 70. They randomized 135 women with operable, <5 cm tumors −68 to tamoxifen (20 mg b.d.) group and 67 to mastectomy arm. Those women developing local recurrence or progression in the tamoxifen arm underwent wedge mastectomy later. In the wedge mastectomy group, local recurrences were treated with further excision or RT, and if tumor recurred again, patients were given tamoxifen. The mortality from metastatic breast cancer was 10% in the tamoxifen group and 15% in the mastectomy group. In the mastectomy group, 70% remained alive and free of recurrence at 24 months, compared with 47% in the tamoxifen group. Authors concluded that since many patients in the tamoxifen arm eventually required surgery, optimum treatment should include surgery and tamoxifen (Robertson *et al.*, 1988).

This issue was also evaluated by EORTC 10 851 multicenter trial (Fentiman *et al.*, 2003a). Women above 70 years with operable breast cancer were randomized to either MRM (82 cases) or tamoxifen – 20 mg daily (82 cases). The tamoxifen was given till death or relapse. The median follow-up was for 11.7 years for MRM and 10.2 years in the tam. group. Eleven percent of women in the MRM arm and 62% in the tam. group developed locoregional progression, the difference being highly significant ($p < 0.001$). The risk of distant progression was noted in 20% of MRM and 23% of those getting tam. alone ($p = 0.654$). For overall survival, the modified logrank test gave a $p = 0.001$, rejecting the null hypothesis of nonequivalence, thus indicating that the two groups are similar in terms of overall survival.

The GRETA trial: Mustacchi *et al.* (2003) reported the results of a multicenter RCT on tamoxifen alone versus surgery followed by adjuvant tamoxifen in elderly women. Between 1987 and 1992, women above 70 with operable breast cancer were randomized – 239 to surgery + tamoxifen (20 mg/day) and 235 to tamoxifen alone. The tamoxifen was given for 5 years. At a median follow-up of 80 months, 274 patients had died, there was no difference between the two groups as regards the overall and breast cancer survival. Local progression was noted in 27 cases in surgery group and 106 in the tam. alone group. They concluded that minimal surgery followed by tam. appears to be appropriate therapy for older women as compared to tamoxifen alone.

EORTC 10 850 study (Fentiman *et al.*, 2003b): In this multicenter study, 236 women above 70 years with operable breast cancer were randomized to either modified radical mastectomy (MRM; $n = 120$) or wide excision + tamoxifen (WLE + tam.; $n = 116$). No other adjuvant therapy was given. The tamoxifen group received 20 mg daily till death or relapse. The median follow-up period was 10.9 years for the mastectomy and 10.4 years for the WLE + tam. group. Women experienced locoregional recurrences in 16% in MRM arm versus 26% in the WLE + tam. group. Distant relapse was observed in 28% in MRM and only 13% in WLE + tam. group. There was a higher risk of local relapse and a significantly reduced risk of distant relapse in the WLE + tam. arm. The multivariate Cox's modeling revealed no treatment effect according to time to progression (Hazard ratio = 0.89; $p = 0.06$). In terms of overall survival, all

predictors except for age were removed. A model with age showed that the patients in the most elderly group had the highest mortality hazard.

Newer forms of hormone therapy have now been tried in the elderly group. A RCT using exemestane (Coombes *et al.*, 2004) has been reported. After 2–3 years of tamoxifen, 2362 patients were switched to exemestane and 2380 continued on tamoxifen. After a median follow-up of 30 months, the first recurrence (local or systemic) was noted. There were 183 recurrences in the exemestane arm and 266 in the tamoxifen arm. This represents a 32% risk reduction with exemestane. The overall survival was similar – 93 deaths in exemestane and 106 in tamoxifen. Contralateral cancer occurred in nine in exemestane and 20 in tamoxifen group.

The duration and type of hormone therapy in the elderly is a matter of debate. The benefits of tamoxifen for 2 years are not very much different from tamoxifen given for 5 years. In an RCT of 2 versus 5 years of tamoxifen for women above 50 years, no difference in overall survival was observed even in ER-positive patients (hazard ratio = 0.98; 95% CI 0.72–1.32). Prolonging the therapy from 2 to 5 years doubled the risk of thromboembolic events (absolute excess number of thromboembolic events in 5-year arm as opposed to 2-year arm was 2.48 of 1000 women years for age 50–55, 2.96 of 1000 women years for women 56 to 65, and 2.75 of 1000 women years for women 66 to 70 years at diagnosis) and this excess risk was counterbalanced by the benefit derived from protection from contralateral breast cancer (Sacco *et al.*, 2003). Recently, aromatase inhibitors have been recommended in place of tamoxifen as endocrine therapy for ER positive tumors. The aromatase inhibitor anastrozole was compared with tamoxifen for 5 years in 9366 postmenopausal women with localized breast cancer. After a median follow-up of 68 months, anastrozole prolonged disease-free survival with a hazard ratio 0.87, 95% CI 0.78–0.97 and time to recurrence and reduced distant metastases (HR 0.86, 95% CI 0.74–0.99) and contralateral breast cancer (42% reduction, 95% CI 12–62). Anastrozole was associated with fewer side effects than tamoxifen, especially gynecological and vascular events, but fractures were increased (Howell *et al.*, 2005).

Ragaz and Coldman (1998), calculated the relative risk of mortality from thromboembolic events with tamoxifen use at age 50 to be 1.5. At age 80, it rose to 17.5.

The duration of tamoxifen use in women above 70 is an open question as there is no good data about long-term morbidity in this age-group. Newer aromatase inhibitors like anastrozole seem to carry a reduced risk of thrombotic episodes and need further evaluation in the elderly who are more prone to arterial and venous thrombosis.

CHEMOTHERAPY

Owing to concerns of excessive toxicity, there is a defeatist attitude toward chemotherapy in the elderly. Hence, women above 65 are not included in chemotherapy trials. In the National Institute of Health (NIH) consensus, chemotherapy is recommended only for women below 70 years of age.

Allocation to about 6 months of anthracycline-based polychemotherapy (e.g. with 5 flourouracil, adiamycin and cytoxan (FAC) or 5 flourouracil, epirubicin and cyclophosphamide (FEC)) reduces the annual breast cancer death rate by about 38% (SE 5) for women younger than 50 years of age when diagnosed and by about 20% (SE 4) for those of age 50–69 years when diagnosed, largely irrespective of the use of tamoxifen and of ER status, nodal status, or other tumor characteristics. Such regimens are significantly ($2p = 0.0001$ for recurrence, $2p < 0.00001$ for breast cancer mortality) more effective than cyclophosphamide, methotraxate and 5 flourouracil (CMF) chemotherapy. Few women of age 70 years or older entered these chemotherapy trials (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005).

Recently, Taxanes have been tried in older women with good tolerance. Taxanes are considered a most effective drug in breast cancer, and have been tried on weekly regimens. The toxicity of weekly therapy is much lower than 3 weekly courses. Since there is decreased clearance of both paclitaxel and docetaxel in elderly, it seems safer to use lower doses of weekly regimens. A dose of paclitaxel $80\,mg\,m^{-2}$ per week and docetaxel $36\,mg\,m^{-2}$ per week is usually well tolerated with impressive response. Severe neutropenia, the dose limiting toxicity of 3 weekly regimen, is rare in weekly therapy (Wildiers and Paridaens, 2004).

In a phase II study of weekly docetaxel $36\,mg\,m^{-2}$ among 47 frail or elderly patients with metastatic breast cancer, a response rate of 30% with low toxicity was achieved (D'hondt *et al.*, 2004).

TREATMENT OF ADVANCED DISEASE

Patients with locally advanced disease need evaluation by a combined breast care team and should be offered good local control by limited surgery and radiation followed by tamoxifen and chemotherapy (preferably Taxanes). Women presenting with a fungating or bleeding ulcer should not be denied the benefit of limited surgical ablation and coverage of the defect with a myocutaneous flap. Palliative hemostatic fractions of radiation may help arrest bleeding. Women with dissemination of cancer need systemic chemoendocrine administration till the level of tolerance and, later, tender loving care for the debility.

PROGNOSTIC FACTORS IN ELDERLY BREAST CANCER

Ian Fentimen, in an editorial in a recent issue of British Journal of Surgery (1), pointed out that 60% of deaths from breast cancer occurred in women of age 65 and above because of late diagnosis and treatment.

The outcome of the elderly patients and the posttreatment QoL has been studied by a number of authors.

Age has been considered an important determinant of the type of treatment and hence the outcome. In the CRUK, trial age and tumor size were found to predict mortality independently (Fennessy *et al.*, 2004).

Data from six regional National Cancer Institute Surveillance Epidemiology End Result Cancer registries evaluated a population-based random sample of 1800 patients in the age-group of 55 and above. Seventy-three percent of the women presented with stage I and II breast cancer, 10% with III and IV, and 17% did not have stage assignment. Of the 1017 cases with stage I and II, node negative disease, 95% of women received therapy in agreement with NIH consensus. Patients in older age-group were less likely to receive therapy according to the consensus statement. Women aged 70 years and above were significantly less likely to receive axillary lymph node dissection. Diabetes, renal failure, stroke, liver disease, and history of smoking were significant predictors of early mortality in a statistical logistic regression model that included age and disease stage. These authors concluded that patient care decision making occurs in the context of age and other comorbid conditions. Comorbidity in older patients results in less number of axillary dissections. As a result, information on axillary node is not available in many elderly patients. Breast cancer was the underlying cause of death in 51% and heart disease in 17%. The number of women getting breast conservation therapy is also reduced and comorbidity also increases the risk of death from breast cancer (Yancik *et al.*, 2001).

QUALITY-OF-LIFE ISSUES

The impact of the diagnosis of breast cancer and the effect of different therapeutic modalities has been addressed by a number of authors. Kroenke *et al.* (2004) from Harvard School of Medicine and Harvard school of Public Health reported changes in physical and psychological functions before and after breast cancer by age at diagnosis. From 122 969 women from the Nurses' Health Study (NHS) and NHS2 of age 29 to 71 years, who responded to a pre- and postfunctional status assessment, who were included, 1082 women were diagnosed with breast cancer between 1992 and 1997. FS was assessed using Short form SF-36. Mean changes in health-related quality of life (HRQoL) scores was computed. Compared with women $\leq$40 years without breast cancer, women with breast cancer experienced a functional decline. Young women who developed breast cancer experienced the largest decline in HRQoL as compared with older women in multiple domains such as physical roles, bodily pain, social functioning, and mental health. Much of the decline in HRQoL was age related (age $\geq$65 years).

A telephone survey was conducted from a random cross-sectional sample of 1812 medicare beneficiaries of 67 years and above treated for breast cancer 3–5 years earlier. The QoL and satisfaction with treatment were evaluated. The use of axillary dissection was the only surgical treatment that affected outcome, increasing the risk of arm problems fourfold (95% confidence interval 1.56–10.51). Having arm problems exerted a negative independent effect on all outcomes. Processes of care were also associated with QoL and satisfaction. Women who perceived high levels of agism or felt that they had no choice of treatment reported more bodily pain, lower mental health scores and less general satisfaction. These same factors as well as high perceived racism were significantly associated with diminished satisfaction with the medical care system. The authors concluded that with the exception of axillary dissection, the process of care and not the therapy itself are the most important determinants of long-term QoL in older women (Mandelblatt *et al.*, 2003).

VARIATION IN CARE OF ELDERLY

Monica Morrow in a review on treatment in the elderly noted that screening by physical exam and mammography is underutilized for the older women. Since mastectomy offers excellent local control and has only less than 1% operative mortality in women above 65, it should be offered to more (suitable) patients. She further points that failure to use adjuvant therapy when indicated is one of the most frequent problems in management of elderly (Morrow, 1994).

Pattern of care of elderly women is different from that offered to younger patients. In the study by Commission on Cancer of the American College of Surgeons for 1983 and 1990 (Busch *et al.*, 1996) in 1983, 23% of older women received total or partial mastectomy without axillary dissection compared with 8% of younger females. In 1990, the rate of total or partial mastectomy without nodal dissection was 20.6% in older women and 10% in younger women. The use of reconstruction was limited in the older women. The percentage of elderly females receiving reconstruction was 1.2% in 1983 and 1.3% in 1990. The operative mortality rates were higher in the older age-group (2.9% in 1983 and 1.5% in 1990). RT was used less frequently in the older group in both study years.

Gold and Dick (2004) reported the variation in the care of women with DCIS across the registries of the Surveillance, Epidemiology, and End Result (SEER) program in the United States. They studied 2701 women from SEER database from 1991 to 1996 aged 65 or over, diagnosed with unilateral DCIS. The results indicated significant geographic and temporal variations in treatment with increasing use of breast conservation alone. The treatment choice is explained by the particular SEER registry, diagnosis year, marital status, race, age, urban/rural status, educational attainment, and number of radiation oncologists. Increasing variability in treatment implies continued uncertainty about optimal therapy of DCIS.

In another retrospective review study from Italy on 1724 cases (median age 61, range 17–89) treated in 63 hospitals, 541 (38%) were inappropriately treated. More than two-thirds of these inappropriate surgical procedures were unnecessary Halsted Mastectomy. There was considerable geographical

variation in the rate of appropriateness (range 52–88%). The authors suggested an urgent need of technology transfer to promote more appropriate surgical care and increased patient participation (Scorpiglione *et al.*, 1995). The same authors in another report on the same subjects (1724 cases) showed that elderly patients were less likely to have intensive diagnostic work-up, greater use of radical surgery and less use of limited surgery, independently of their overall health status. The presence of one or more coexistent diseases was associated with a failure to undergo axillary clearance and a lower utilization of conservative surgery, independent of age. The authors recommend the development of practice guidelines and their implementation to improve the quality of care (Nicolucci *et al.*, 1993).

In an editorial in Journal of Clinical Oncology, Rebecca A. Silliman (2003) chided clinicians for not offering definitive treatment to elderly women with breast cancer. Although breast cancer-specific mortality has declined among women younger than 70 years, they are either stable in 70–79 years or increased in women above 65 years of age. This proportion is likely to grow as older age is the most important risk factor for breast cancer and gains in life expectancy will result in more women being at risk for longer periods. Currently, the average life expectancy of a 75 year old is 12 years (17 years if she is healthy) and that of 85 years is 6 years (9 years if she is healthy). Owing to paucity of good evidence-based data, there is considerable controversy about what constitutes appropriate care for older women. More than one-fourth (27%) of breast cancer deaths in 2001 in the United States were in the age-group of 80 years and older. Although the patient's health status, patient and family preferences and support, and patient–physician interactions explain in part, age-related treatment variations, age alone remains an independent risk factor for less than definitive breast cancer care.

In a cohort of 407 octogenarian women from Canton province of Geneva, Switzerland, Bouchardy *et al.* (2003) addressed the relationship between undertreatment and breast cancer mortality. They used tumor registry data including sociodemographic data, comorbidity, tumor, and treatment characteristics, and the cause of death. The main problem they noted in analyzing this data was the issue of missing information – 20% for comorbidity, 49% for tumor grade, 74% for ER status. Because of loss of data on these important prognostic factors, there was a problem in multivariate analysis and incomplete control of confounding, decreasing the statistical power and precision. Both mastectomy plus adjuvant therapy and breast-conserving surgery plus adjuvant therapy appear to protect against death from causes other than breast cancer, suggesting residual confounding either because comorbidity was not well measured or because undertreatment of breast cancer is associated with undertreatment of other medical conditions. This cohort of Swiss women differed from women presenting elsewhere. The average tumor size in this group was 30 mm, only 22% presented in stage I, 22% received no therapy, 32% got tamoxifen alone. Despite the limitations of this study, it highlights the link between undertreatment and high rate of breast cancer recurrence and mortality.

A similar study from Quebec, Canada, assessed the variation in care with age. Herbert-Croteau *et al.* (1999) selected a stratified random sample of 1174 women from new cases of node negative breast cancer of age 50 and above. Women over 70 were less likely to receive definitive locoregional treatment than younger women (48 vs 83%; $p < 0.0001$). Older women were less likely to receive breast-conserving surgery (76 vs 86%; $p < 0.0001$) and RT (54 vs 90%; $p < 0.0001$), axillary dissection (55 vs 86%; $p < 0.0001$), or receive chemotherapy (1.2 vs 13%; $p < 0.0001$). Tamoxifen was given equally to both the groups (66 vs 64%; $p = 0.41$). Adjusting for comorbidity and other disease characteristics, age remained the strong determinant of definitive therapy (odds ratio 0.14; 95% CI 0.12–0.18 for age $\geq$70 vs age 50–69 years). The authors lamented that elderly women receive less aggressive therapy independent of comorbidity.

CONCLUSIONS

Breast Cancer in the elderly is inadequately diagnosed with a significant delay. Many women are improperly treated, as there is a lack of practice guidelines for women above 65 years of age. Screening and prevention strategies need to be applied more rigorously to older women. The same therapeutic principles and selection criteria should be utilized as established for the younger women. Breast care providers need to be cognizant of the associated illnesses and tailor therapy to suit the tolerance of the individual case.

GUIDELINES FOR THERAPY

The present knowledge base supports the following general guideline for the elderly:

<4 cm tumor, ER+ve → BCT + axillary dissection + RT + Tamoxifen

<4 cm tumor, ER+ve on warfarin/ Stroke /Deep vein thrombosis

→ BCT + axillary dissection + RT + Anastrozole

<4 cm tumor, ER−ve → BCT + axillary dissection + RT + Chemotherapy with weekly Taxanes if patient is rich, otherwise CMF; Consider Herceptin

>4 cm tumor, ER+ve → MRM + RT + Tamoxifen

>4 cm tumor, ER−ve → MRM + RT + Chemotherapy; Consider Herceptin. Consider downstaging for large tumors by neoadjuvant Anastrozole/Tamoxifen with or without chemotherapy prior to operation.

More elderly patients should be recruited in trials to expand the evidence base not confounded by ageist bias. Oncologists ought to explore newer modes of delivering less toxic chemotherapy, intraoperative radiotherapy and biological response modifiers. Interventions to address the

physical and emotional needs of older women with breast cancer should be developed.

KEY POINTS

- Improve awareness among the geriatric care providers for early diagnosis.
- Apply screening and prevention strategies similar to younger women to reduce the burden of disease and morbidity of therapy.
- Apply same therapeutic principles as in younger women.
- Recruit more elder women in therapeutic trials and develop practice guidelines.
- Be cognizant of comorbidity and tailor therapy accordingly.

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PART III

Medicine in Old Age

Section 13

Functional Disorders and Rehabilitation

Multidimensional Geriatric Assessment

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INTRODUCTION

The essence of a good geriatric practice is the expert management of the medical, psychological, and social needs of elderly patients and their family caregivers. In order to accomplish this, the members of the interdisciplinary geriatric team – whether based in a hospital geriatric unit, an outpatient clinic, a nursing home, or a home-care program – must work closely together to carefully assess the patient's risks and problems and translate the knowledge into care plans that will have far-reaching effects on both the patient's and the caregiver's lives.

Such multidimensional assessment implies the detailed investigation of the elderly individual's total situation in terms of physical and mental state, functional status, formal and informal social support and network, and physical environment. This requires the clinician to become involved in collecting, interpreting, synthesizing, and weighing a formidable amount of patient-specific information. Much of this differs in kind from the physical symptoms and signs, laboratory values, radiology results, and other data that are traditionally combined to reach a medical diagnosis.

Definition

Multidimensional geriatric assessment is a diagnostic process, usually interdisciplinary, intended to determine an elderly person's medical, psychosocial, functional, and environmental resources and problems, with the objective of developing an overall plan for treatment and long-term follow-up. The process differs from the standard medical evaluation in its concentration on elderly people with their often complex problems, its emphasis on functional status and quality of life, and its frequent use of interdisciplinary teams and quantitative assessment scales.

As described in this chapter, multidimensional geriatric assessment can vary in its level of detail, its purpose, and other aspects depending on the clinical circumstances. Therefore, multidimensional assessment denotes both the relatively brief multidimensional screening assessment for preventive purpose in a patient's home as well as the interdisciplinary work-up of a newly hospitalized patient. Despite this broad definition, the term must meet the primary criteria above. For example, a multidimensional evaluation of an elderly person without any link to the overall plan for treatment and follow-up does not meet these criteria. Similarly, a home visit emphasizing psychosocial and environmental factors, but not including a medical evaluation of the elderly person, is not a multidimensional assessment, since one of the key components of the multidimensionality is not included.

Rationale

While the principles of geriatric assessment may be valid in the treatment of younger persons as well, since biopsychosocial factors play an important role in medicine for patients of all age-groups, there is additional justification for using this multidimensional approach in elderly people for various reasons:

- *Multimorbidity and complexity*: Many elderly people suffer from multiple conditions, and multidimensional assessment helps to deal with these complex situations through its systematic approaches and its setting of priorities.
- *Unrecognized problems*: Many elderly people suffer from problems that have not been reported to the physician or may not even be known to the elderly person. One of the reasons problems may go undetected is that they may be falsely considered as nonmodifiable consequences of aging. Multidimensional geriatric assessment is a method for identifying previously unknown problems.
- *Chronic conditions*: Many elderly people suffer from chronic conditions. Diagnostic information without information on functional relevance of the underlying condition

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is often of limited value for therapeutic decisions or for monitoring follow-up.

- *Interaction with social and environmental factors*: Once functional impairments or dependencies arise, the elderly person's condition is strongly influenced by his or her social and physical environment. For example, the arrangement of the elderly person's in-home environment and the availability of his or her social network might determine whether a person can continue to live in his or her home.
- *Functional status*: One of the main objectives of medicine for elderly people is to prevent or delay the onset of functional status decline. Epidemiological research has shown that functional status decline is related to medical, functional, psychological, social, and environmental risk factors. Therefore, for both rehabilitation as well as prevention, the approach of multidimensional assessment helps to take into account potentially modifiable factors in all relevant domains.
- *Intervention studies*: Multiple intervention studies that compared the effects of programs on the basis of the concept of multidimensional geriatric assessment with usual care did show benefits of geriatric assessment, including better patient outcomes and more efficient health-care use.

Brief History of Geriatric Assessment

The basic concepts of geriatric assessment have evolved over the past 70 years by combining elements of the traditional medical history and physical examination, the social worker assessment, functional evaluation and treatment methods derived from rehabilitation medicine, and psychometric methods derived from the social sciences.

The first published reports of geriatric assessment programs (GAPs) came from the British geriatrician Marjory Warren, who initiated the concept of specialized geriatric assessment units during the late 1930s while in charge of a large London infirmary. This infirmary was filled primarily with chronically ill, bedfast, and largely neglected elderly patients who had not received proper medical diagnosis or rehabilitation and who were thought to be in need of lifelong institutionalization. Good nursing care kept the patients alive, but the lack of diagnostic assessment and rehabilitation kept them disabled. Through evaluation, mobilization, and rehabilitation, Warren was able to get most of the long bedfast patients out of bed and often discharged home. As a result of her experiences, Warren advocated that every elderly patient receive comprehensive assessment and an attempt at rehabilitation before being admitted to a long-term care hospital or nursing home (Matthews, 1984).

Since Warren's work, geriatric assessment has evolved. As geriatric care systems have been developed throughout the world, GAPs have been assigned central roles, usually as focal points for entry into the care systems (Brocklehurst, 1975). Geared to differing local needs and populations, GAPs vary in intensity, structure, and function. They can be located in different settings, including acute hospital inpatient units and consultation teams, chronic and rehabilitation hospital units, outpatient and office-based programs, and home-visit outreach programs. Despite diversity, they share many characteristics. Virtually all programs provide multidimensional assessment, utilizing specific measurement instruments to quantify functional, psychological, and social parameters. Most use interdisciplinary teams to pool expertise and enthusiasm in working toward common goals. Additionally, most programs attempt to couple their assessments with an intervention, such as rehabilitation, counseling, or placement.

Today, geriatric assessment continues to evolve in response to increased pressures for cost containment, avoidance of institutional stays, and consumer demands for better care. Geriatric assessment can help achieve improved quality of care and plan cost-effective care. This has generally meant more emphasis on noninstitutional programs and shorter hospital stays. Geriatric assessment teams are well positioned to deliver effective care for elderly persons with limited resources. Geriatricians have long emphasized judicious use of technology, systematic preventive medicine activities, and less institutionalization and hospitalization.

COMPONENTS OF GERIATRIC ASSESSMENT

A typical geriatric assessment begins with a functional status "review of systems" that inventories the major domains of functioning. The major elements of this review of systems are captured in two commonly used functional status measures – basic activities of daily living (ADL) and instrumental activities of daily living (IADL). Several reliable and valid versions of these measures have been developed (Rubenstein *et al.*, 1987a; Rubenstein *et al.*, 1995a; Kane and Kane, 2000; Osterweil *et al.*, 2000; Gallo *et al.*, 2000), perhaps the most widely used being those by Katz *et al.* (1963), Lawton and Brody (1969), and Barthel (Mahoney and Barthel, 1965; Wade and Colin, 1988). These scales are used by clinicians to detect whether the patient has problems performing activities that people must be able to accomplish to survive without help in the community. Basic ADL include self-care activities such as eating, dressing, bathing, transferring, and toileting. Patients unable to perform these activities will generally require 12–24-hour support by caregivers. Instrumental activities of daily living include heavier housework, going on errands, managing finances, and telephoning – activities that are required if the individual is to remain independent in a house or an apartment.

In order to interpret the results of impairments in ADL and IADL, physicians will usually need additional information about the patient's environment and social situation. For example, the amount and type of caregiver support available, the strength of the patient's social network, and the level of social activities in which the patient participates will all influence the clinical approach taken in managing the detected deficits. This information could be obtained by an experienced nurse or a social worker. A screen for mobility and fall risk is also extremely helpful in quantifying

function and disability, and several observational scales are available (Tinetti, 1986; Mathias *et al.*, 1986). An assessment of nutritional status and risk for undernutrition is also important in understanding the extent of impairment and for planning care (Vellas and Guigoz, 1995). Likewise, a screening assessment of vision and hearing will often detect crucial deficits that need to be treated or compensated for.

There are two other key pieces of information that must always be gathered in the face of functional disability in an elderly person. These are a screen for mental status (cognitive) impairment and a screen for depression (Rubenstein *et al.*, 1987a; Rubenstein *et al.*, 1995a; Gallo *et al.*, 2000). Among the several validated screening tests for cognitive function, the Folstein Mini-mental State is one of the best tests because of its efficiency to test the major aspects of cognitive functioning (Folstein *et al.*, 1975). Among the various screening tests for geriatric depression, the Yesavage Geriatric Depression Scale (Yesavage *et al.*, 1983), and the Zung Self-rating Depression Scale (Zung, 1965) are in wide use, and even shorter screening versions are available without significant loss of accuracy (Hoyl *et al.*, 1999).

The major measurable dimensions of geriatric assessment, together with examples of commonly used health status screening scales, are listed in Table 1 (Rubenstein *et al.*, 1987a; Rubenstein *et al.*, 1995a; Kane and Kane, 2000; Osterweil *et al.*, 2000; Gallo *et al.*, 2000; Katz *et al.*, 1963; Lawton and Brody, 1969; Mahoney and Barthel, 1965; Wade and Colin, 1988; Tinetti, 1986; Mathias *et al.*, 1986; Vellas and Guigoz, 1995; Folstein *et al.*, 1975; Yesavage *et al.*, 1983; Zung, 1965; Hoyl *et al.*, 1999; Rubenstein, 1996; Hedrick, 1995; Kane, 1995; Rubenstein *et al.*, 2001; Gurland and Wilder, 1995; Duke University Center for the Study of Aging and Human Development, 1978; Lubben, 1988; Kahn *et al.*, 1960; Chambers *et al.*, 1982; Reisberg *et al.*, 1982; Hoehn and Yahr, 1967; Stewart *et al.*, 1988; Nelson *et al.*, 1987; Bergner *et al.*, 1981; Jette *et al.*, 1986). The instruments listed are short, have been carefully tested for reliability and validity, and can be easily administered by virtually any staff person involved with the assessment process. Both observational instruments (e.g. physical examination) and self-report (completed by patient or proxy) are available. Components of them – such as watching a patient walk, turn around, and sit down – are routine parts of the geriatric physical examination. Many other kinds of assessment measures exist and can be useful in certain situations. For example, there are several disease-specific measures for stages and levels of dysfunction for patients with specific diseases such as arthritis (Chambers *et al.*, 1982), dementia (Reisberg *et al.*, 1982), and parkinsonism (Hoehn and Yahr, 1967). There are also several brief global assessment instruments that attempt to quantify all dimensions of the assessment in a single form (Stewart *et al.*, 1988; Nelson *et al.*, 1987; Bergner *et al.*, 1981; Jette *et al.*, 1986). These latter instruments can be useful in community surveys and some research settings but are not detailed enough to be useful in most clinical settings. More comprehensive lists of available instruments can be found by consulting published reviews of health status assessment (Rubenstein *et al.*, 1987a; Rubenstein *et al.*, 1995a; Kane and Kane, 2000; Osterweil *et al.*, 2000; VanSwearington and Brach, 2001).

SETTINGS OF GERIATRIC ASSESSMENT

A number of factors must be taken into account in deciding where an assessment should take place – whether it should be done in the hospital, in an outpatient setting, or in

Table 1 Measurable dimensions of geriatric assessment with examples of specific measures

Dimension	Basic context	Specific examples
Basic ADL (Hoyl *et al.*, 1999; Hedrick, 1995)	Strengths and limitations in self-care, basic mobility, and incontinence	Katz (ADL) (Katz *et al.*, 1963), Lawton personal self-maintenance scale (Lawton and Brody, 1969) Barthel index (Mahoney and Barthel, 1965; Wade and Colin, 1988)
IADL (Hedrick, 1995)	Strengths and limitations in shopping, cooking, household activities, and finances	Lawton (IADL) (Lawton and Brody, 1969) OARS, IADL section (Duke University Center for the Study of Aging and Human Development, 1978)
Social activities and supports (Kane, 1995)	Strengths and limitations in social network and community activities	Lubben social network scale (Lubben, 1988) OARS, Social resources section (Duke University Center for the Study of Aging and Human Development, 1978)
Mental health Affective (Gurland and Wilder, 1995)	Degree of anxiety, depression, and happiness	Geriatric depression scale (Yesavage *et al.*, 1983; Hoyl *et al.*, 1999) Zung depression scale (Zung, 1965)
Mental health Cognitive (Gurland and Wilder, 1995) Questionnaire (Kahn *et al.*, 1960)	Degree of alertness, orientation, concentration, and mental task capacity	Folstein mini-mental state (Folstein *et al.*, 1975) Kahn mental status
Mobility, gait, and balance (Lawton and Brody, 1969; Wade and Colin, 1988)	Quantification of gait, balance, and risk of falls	Tinetti mobility assessment (Tinetti, 1986) Get-up-and-go test (Mathias *et al.*, 1986)
Nutritional checklist (Vellas and Guigoz, 1995) Adequacy (Vellas and Guigoz, 1995)	Current nutritional status and risk of malnutrition	Nutritional screening Mini-nutritional assessment (Rubenstein *et al.*, 2001)

ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living.

the patient's home. Mental and physical impairment make it difficult for patients to comply with recommendations and to navigate multiple appointments in multiple locations. Functionally impaired elders must depend on families and friends, who risk losing their jobs because of chronic and relentless demands on time and energy and in their roles as caregivers, and who may be elderly themselves. Each separate medical appointment or intervention has a high time-cost to these caregivers. Patient fatigue during periods of increased illness may require the availability of a bed during the assessment process. Finally, enough physician time and expertise must be available to complete the assessment within the constraints of the setting.

Most geriatric assessments neither require the full range of technology nor the intense monitoring found in the acute-care inpatient setting. Yet, hospitalization becomes unavoidable if no outpatient setting provides sufficient resources to accomplish the assessment fast enough. A specialized geriatric setting outside an acute hospital ward, such as a day hospital or subacute inpatient geriatric evaluation unit, will provide the easy availability of an interdisciplinary team with the time and expertise to provide needed services efficiently, an adequate level of monitoring, and beds for patients unable to sit or stand for prolonged periods. Inpatient and day hospital assessment programs have the advantages of intensity, rapidity, and ability to care for particularly frail or acutely ill patients. Outpatient programs are generally cheaper and avoid the necessity of an inpatient stay.

Assessment in the Office Practice Setting

A streamlined approach is usually necessary in the office setting. An important first step is setting priorities among problems for initial evaluation and treatment. The "best" problem to work on primarily might be the problem that most bothers a patient or, alternatively, the problem upon which resolution of other problems depends (alcoholism or depression often fall into this category).

The second step in performing a geriatric assessment is to understand the exact nature of the disability by performing a task or a symptom analysis. In a nonspecialized setting, or when the disability is mild or clear cut, this may involve taking only a careful history. When the disability is more severe, more detailed assessments by a multidisciplinary or interdisciplinary team may be necessary. For example, a patient may present with difficulty in dressing. There are multiple tasks associated with dressing, any one of which might be the stumbling block (e.g. buying clothes, choosing appropriate clothes to put on, remembering to complete the task, buttoning, stretching to put on shirts, or reaching downward to put on shoes). By identifying the exact areas of difficulty, further evaluation can be targeted toward solving the problem.

Once the history reveals the nature of the disability, a systematic physical examination and ancillary laboratory tests are needed to clarify the cause of the problem. For example, difficulty in dressing could be caused by mental status impairment, poor finger mobility, or dysfunction of shoulders, back, or hips. An evaluation by a physical or occupational therapist may be necessary to pinpoint the problem adequately, and evaluation by a social worker may be required to determine the extent of family dysfunction engendered by or contributing to the dependency. Radiologic and other laboratory tests may also be necessary.

Each abnormality that could cause difficulty in dressing suggests different treatments. By understanding the abnormalities that contribute the most to the functional disability, the best treatment strategy can be undertaken. Often one disability leads to another – impaired gait may lead to depression or decreased social functioning; and immobility of any cause, even after the cause has been removed, can lead to secondary impairments in performance of daily activities due to deconditioning and loss of musculoskeletal flexibility.

Almost any acute or chronic disease can reduce functioning. Some common but easily overlooked causes of dysfunction in elderly people include impaired cognition, impaired special senses (vision, hearing, balance), unstable gait and mobility, poor health habits (alcohol, smoking, lack of exercise), poor nutrition, polypharmacy, incontinence, psychosocial stress, and depression. In order to identify the contributing causes of the disability, the physician must look for worsening of the patient's chronic diseases, occurrence of a new acute disease, or appearance of one of the common occult diseases listed above. The physician does this through a refocused history guided by the functional disabilities detected and their differential diagnoses, and a focused physical examination. The physical examination always includes, in addition to usual evaluations of the heart, lungs, extremities, and neurologic function, postural blood pressure, vision and hearing screening, and a careful observation of the patient's gait. The mini-mental state examination, already recommended as part of the initial functional status screen, may also determine the parts of the physical examination that require particular attention as part of the evaluation of dementia or acute confusion. Finally, basic laboratory testing including a complete blood count and a blood chemistry panel, as well as tests indicated on the basis of specific findings from the history and physical examination, will generally be necessary.

Once the disability and its causes are understood, the best treatments or management strategies for it are often clear. When a reversible cause for the impairment is found, a simple treatment may eliminate or ameliorate the functional disability. When the disability is complex, the physician may need the support of a variety of community or hospital-based resources. In most cases, a strategy for long-term follow-up and often, formal case management should be developed to ensure that needs and services are appropriately matched up and followed through.

Preventive Home Visits

Preventive home visitation programs in elderly people are part of a national policy in several countries. The

rationale is to delay or prevent functional impairment and subsequent nursing home admissions by primary prevention (e.g. immunization and exercise), secondary prevention (e.g. detection of untreated problems), and tertiary prevention (e.g. improvement of medication use).

This is a typical description of a preventive home visitation program (Stuck *et al.*, 1995a). "The assessment included a medical history taking, a physical examination, hematocrit and glucose measurements in blood samples obtained by finger stick, a dipstick urinalysis, and a mail-in fecal occult-blood test. The subjects were also evaluated for functional status, oral health, mental status (presence or absence of depression and cognitive status), gait and balance, medications, percentage of ideal body weight, vision, hearing, extensiveness of social network, quality of social support, and safety in the home and ease of access to the external environment. The nurse practitioners discussed each case with the project geriatricians, developed rank-ordered recommendations, and conducted in-home follow-up visits every three months to monitor the implementation of the recommendations, make additional recommendations if new problems were detected, and facilitate compliance. If additional contact was considered necessary, the nurse practitioner telephoned the participant or was available by telephone. All the participants were encouraged to take an active role in their care and to improve their ability to discuss problems with their physicians. Only in complex situations did the nurse practitioners or study physicians contact the patients' physicians directly".

A variety of studies have shown the advantage of the home environment in conducting a multidimensional assessment. The yield of a home visit does not seem to be limited to the preventive application; home visits can also play an important role as part of outpatient or inpatient programs.

Inpatient Geriatric Assessment

If a referral to a specialized geriatric setting has been chosen, the process of assessment will probably be similar to that described above, except that the greater intensity of resources and the special training of all the members of the multidisciplinary team in dealing with geriatric patients and their problems will facilitate carrying out the proposed assessment and the plan more quickly, and in greater breadth and detail. In the usual geriatric assessment setting, the key disciplines involved include, at a minimum, physicians, social workers, nurses, and physical and occupational therapists, and optimally may also include other disciplines such as dieticians, pharmacists, ethicists, and home-care specialists. A special geriatric expertise among the interdisciplinary team members is crucial.

The interdisciplinary team conference, which takes place after most team members have completed their individual assessments, is critical. Most of the successful trials of geriatric assessment have included such a team conference. By bringing the perspectives of all disciplines together, the team conference generates new ideas, sets priorities, disseminates the full results of the assessment to all those involved in treating the patient, and avoids duplication or incongruity. The development of fully effective teams requires commitment, skill, and time as the interdisciplinary team evolves through the "forming, storming, and norming" phases to reach the fully developed "performing" stage (Campbell and Cole, 1987). The involvement of the patient (and carer if appropriate) at some stage is important in maintaining the principle of choice (Campbell and Cole, 1987; Wieland *et al.*, 1996).

Hospital-home Assessment Programs

A number of additional published reports have described another multidimensional assessment model in which hospitalized elderly patients in need of comprehensive assessment are referred to an in-home assessment program that occurs in their homes following the hospital discharge. The advantages of this approach include shortening the hospital stay, providing the assessment in the home environment that allows evaluation of the home itself and how the patient functions therein, and allowing careful targeting of the in-home assessment to individuals who can derive maximal benefit.

A special approach has been tested in elderly patients with cardiac risk. In these patients, geriatric assessment in the hospital was combined with a systematic ambulatory follow-up. An early detection of heart failure and optimizing patient adherence with medication prescriptions were the key ingredients of these programs (Gwadry-Sridhar *et al.*, 2004). Several studies have confirmed that geriatric assessment also reduces unnecessary or inappropriate medications use.

EFFECTIVENESS OF GERIATRIC ASSESSMENT PROGRAMS

A large and still growing literature supports the effectiveness of GAPs in a variety of settings. Early descriptive studies indicated a number of benefits from GAPs such as improved diagnostic accuracy, reduced discharges to nursing homes, increased functional status, and more appropriate medication prescribing. Since they were descriptive studies, without concurrent control patients, they were neither able to distinguish the effects of the programs from simple improvement over time nor did these studies look at long-term, or many short-term outcome benefits. Nonetheless, many of these early studies provided promising results (William *et al.*, 1964; Lowther *et al.*, 1970; Brocklehurst *et al.*, 1978; Applegate *et al.*, 1983; Rubenstein *et al.*, 1987b).

Improved diagnostic accuracy was the most widely described effect of geriatric assessment, most often indicated by substantial numbers of important problems that were uncovered. Frequencies of the new diagnoses that were found ranged from almost 1 to more than 4 per patient. The factors contributing to the improvement of diagnosis in GAPs include the validity of the assessment itself (the capability

of a structured search for "geriatric problems" to find them), the extra measure of time and care taken in the evaluation of the patient (independent of the formal elements of "the assessment"), and a probable lack of diagnostic attention on the part of referring professionals.

Improved living location on discharge from health-care setting was demonstrated in several early studies, beginning with T. F. Williams' classic descriptive prepost study of an outpatient assessment program in New York (Williams *et al.*, 1973). Among the patients referred for nursing home placement in the county, the assessment program found that only 38% actually needed skilled nursing care, while 23% could return home, and 39% were appropriate for board and care or retirement facilities. Numerous subsequent studies have shown similar improvements in living locations (Rubenstein *et al.*, 1984; Hendriksen *et al.*, 1984; Thomas *et al.*, 1993; Vetter *et al.*, 1984; Vetter *et al.*, 1992; Winograd *et al.*, 1993; Collard *et al.*, 1985; Allen *et al.*, 1986; Hogan *et al.*, 1987; Hogan and Fox, 1990; Williams *et al.*, 1987; Gilchrist *et al.*, 1988; Reid and Kennie, 1989; Pathy *et al.*, 1992; Hansen *et al.*, 1992; Gayton *et al.*, 1987). Several studies that examined mental or physical functional status of patients before and after comprehensive geriatric assessment coupled with treatment and rehabilitation showed patient improvement on measures of function (Rubenstein *et al.*, 1984; Hendriksen *et al.*, 1984; Thomas *et al.*, 1993; Vetter *et al.*, 1984; Vetter *et al.*, 1992; Hogan *et al.*, 1987; Reid and Kennie, 1989).

The Pioneering Studies of Geriatric Assessment

Beginning in the 1980s, controlled studies appeared that corroborated some of the earlier studies and documented additional benefits such as improved survival, reduced hospital and nursing home utilization, and in some cases, reduced costs (Rubenstein *et al.*, 1984; Hendriksen *et al.*, 1984; Thomas *et al.*, 1993; Vetter *et al.*, 1984; Vetter *et al.*, 1992; Winograd *et al.*, 1993; Collard *et al.*, 1985; Allen *et al.*, 1986; Hogan *et al.*, 1987; Hogan and Fox, 1990; Williams *et al.*, 1987; Gilchrist *et al.*, 1988; Reid and Kennie, 1989; Pathy *et al.*, 1992; Hansen *et al.*, 1992; Gayton *et al.*, 1987; Rubenstein *et al.*, 1995b; Rubenstein *et al.*, 1988; Schuman *et al.*, 1978; Lefton *et al.*, 1983; Berkman *et al.*, 1983; Lichtenstein and Winogard, 1984; Burley *et al.*, 1979; Tulloch and Moore, 1979; Rubenstein *et al.*, 1995c). These studies were by no means uniform in their results. Some showed a whole series of dramatic positive effects on function, survival, living location, and costs, while others showed relatively few, if any, benefits. However, the GAPs being studied were also very different from each other in terms of the process of care offered and patient populations accepted. To this day, controlled trials of GAPs continue, and as results accumulate, we are able to understand the aspects that contribute to their effectiveness and the ones that do not.

One striking effect confirmed for many GAPs has been a positive impact on survival. Several controlled studies of different basic GAP models demonstrated significantly increased survival, reported in different ways and with varying periods of follow-up. Mortality was reduced for Sepulveda geriatric evaluation unit patients by 50% at 1 year, and the survival curves of the experimental and control groups still significantly favored the assessed group at 2 years (Rubenstein *et al.*, 1984; Rubenstein *et al.*, 1995b; Rubenstein *et al.*, 1988). Survival was improved by 21% at 1 year in a Scottish trial of geriatric rehabilitation consultation (Reid and Kennie, 1989). Two Canadian consultation trials demonstrated a significantly improved 6-month survival (Hogan *et al.*, 1987; Hogan and Fox, 1990). Two Danish community-based trials of in-home geriatric assessment and follow-up demonstrated reduction in mortality (Hendriksen *et al.*, 1984; Hansen *et al.*, 1992), and 2 Welsh studies of in-home GAPs had beneficial survival effects among patients assessed at home and followed for 2 years (Vetter *et al.*, 1984; Vetter *et al.*, 1992). On the other hand, several other studies of geriatric assessment found no statistically significant survival benefits (Winograd *et al.*, 1993; Allen *et al.*, 1986; Gilchrist *et al.*, 1988; Reid and Kennie, 1989).

Multiple studies followed patients longitudinally after the initial assessment and thus were able to examine the longer-term utilization and cost impacts of assessment and treatment. Some studies found an overall reduction in nursing home days (Rubenstein *et al.*, 1984; Reid and Kennie, 1989; Schuman *et al.*, 1978; Lefton *et al.*, 1983). Hospital utilization was examined in several reports. For hospital-based GAPs, the length of hospitalization was obviously affected by the length of the assessment itself. Thus, some programs appear to prolong the initial length of stay (Rubenstein *et al.*, 1987b; Berkman *et al.*, 1983; Lichtenstein and Winogard, 1984), while others reduce initial stay (Collard *et al.*, 1985; Reid and Kennie, 1989; Pathy *et al.*, 1992; Hansen *et al.*, 1992; Burley *et al.*, 1979). However, studies following patients for at least 1 year have usually shown a reduction in use of acute-care hospital services, even in those programs with initially prolonged hospital stays (William *et al.*, 1964; Hendriksen *et al.*, 1984; Williams *et al.*, 1987).

Compensatory increases in use of community-based services or home-care agencies might be expected with declines in nursing home placements and use of other institutional services. These increases have been detected in several studies (Hendriksen *et al.*, 1984; Vetter *et al.*, 1984; Hogan *et al.*, 1987; Tulloch and Moore, 1979) but not in others (Rubenstein *et al.*, 1984; Williams *et al.*, 1987; Gayton *et al.*, 1987). Although increased use of formal community services may not always be indicated, it usually is a desirable goal. The fact that several studies did not detect increases in use of home and community services probably reflects the unavailability of community service or referral networks rather than that more of such services were not needed.

The effects of these programs on costs and utilization parameters have only seldom been examined comprehensively, because of methodologic difficulties in gathering comprehensive utilization and cost data, as well as statistical limitations in comparing highly skewed distributions. The Sepulveda study found that the total first-year direct health-care costs had been reduced because of overall reductions in

nursing home and rehospitalization days, despite significantly longer initial hospital stays in the geriatric unit (Rubenstein *et al.*, 1984). These savings continued through 3 years of follow-up (Rubenstein *et al.*, 1995b). Hendriksen's in-home program (Hendriksen *et al.*, 1984) reduced the costs of medical care, apparently through successful early case-finding and referral for preventive intervention. Williams' outpatient GAPs (Williams *et al.*, 1987) detected reductions in medical care costs primarily because of the reductions in hospitalization. Although it would be reasonable to worry that prolonged survival of frail patients would lead to increased service use and charges, or, of perhaps greater concern, to worry about the quality of the prolonged life, these concerns may be without substance. Indeed, the Sepulveda study demonstrated that GAPs could improve not only survival but can also prolong high-function survival (Rubenstein *et al.*, 1984; Rubenstein *et al.*, 1995b) while at the same time reduce the use of institutional services and costs.

Meta-analyses of Controlled Studies

A 1993 meta-analysis attempted to resolve some of the discrepancies between study results, and tried to identify whether particular program elements were associated with particular benefits (Stuck *et al.*, 1993; Stuck *et al.*, 1995b). This meta-analysis included published data from the 28 controlled trials completed as of that date, involving nearly 10 000 patients, and was also able to include substantial amounts of unpublished data systematically retrieved from many of the studies. The meta-analysis identified five GAP types: hospital units (six studies), hospital consultation teams (eight studies), in-home assessment services (seven studies), outpatient assessment services (4 studies), and hospital-home assessment programs (three studies). The meta-analysis confirmed many of the major reported benefits for many of the individual program types. These statistically and clinically significant benefits included reduced risk of mortality (by 22% for hospital-based programs at 12 months, and by 14% for all programs combined at 12 months), improved likelihood of living at home (by 47% for hospital-based programs and by 26% for all programs combined at 12 months), reduced risk of hospital (re)admissions (by 12% for all programs at study end), greater chance of cognitive improvement (by 47% for all programs at study end), and greater chance of physical function improvement for patients in hospital units (by 72% for hospital units).

Clearly, not all studies showed equivalent effects, and the meta-analysis was able to indicate a number of variables at both the program and patient levels that tended to distinguish trials with large effects from ones with more limited ones. When examined on the program level, hospital units and home-visit assessment teams produced the most dramatic benefits, while no major significant benefits in office-based programs could be confirmed. Programs that provided hands-on clinical care and/or long-term follow-up were generally able to produce greater positive effects than purely consultative programs or ones that lacked follow-up. Another factor associated with greater demonstrated benefits, at least in hospital-based programs, was patient targeting; programs that selected patients who were at high risk for deterioration yet still had "rehabilitation potential" generally had stronger results than less selective programs.

The 1993 meta-analysis confirmed the importance of targeting criteria in producing beneficial outcomes. In particular, when use of explicit targeting criteria for patient selection was included as a covariate, increases in some program benefits were often found. For example, among the hospital-based GAPs studies, positive effects on physical function and likelihood of living at home at 12 months were associated with studies that excluded patients who were relatively "too healthy". A similar effect on physical function was seen in the institutional studies that excluded persons with relatively poor prognoses. The reason for this effect of targeting on effect size no doubt lies in the ability of careful targeting to concentrate the intervention on patients who can benefit, without diluting the effect with persons too ill or too well to show a measurable improvement.

Recent Studies of Geriatric Assessment

Studies performed after the 1993 meta-analysis have been largely corroborative. A recent meta-analysis confirmed that inpatient comprehensive assessment programs for elderly hospital patients may reduce mortality, increase the chances of living at home at 1 year, and improve physical and cognitive function (Ellis and Langhorne, 2005). However, with principles of geriatric medicine becoming more diffused into usual care, particularly at places where controlled trials are being undertaken, differences between GAPs and control groups seem to be narrowing (Reuben *et al.*, 1995; Burns *et al.*, 2000; Stuck *et al.*, 2000; Boult *et al.*, 2001; Elkan *et al.*, 2000; Rubenstein and Stuck, 2001). For example, a recent study of inpatient and outpatient geriatric assessment and management has failed to demonstrate substantial benefits in elderly patients (Cohen *et al.*, 2002). Other studies however continue to reveal major benefits of inpatient programs (Saltvedt *et al.*, 2004). Effects of outpatient GAPs have been less impressive, with a recent meta-analysis showing no favorable effects on mortality outcome (Kuo *et al.*, 2004). For cost reasons, growth of inpatient units has been slow, despite their proven effectiveness, while outpatient programs have increased, despite their less impressive effect size in controlled trials. However, some newer trials of outpatient programs have shown significant benefits in areas not found in earlier outpatient studies, such as functional status, psychological parameters, and wellbeing, which may indicate improvement in the outpatient care models being tested (Burns *et al.*, 2000; Stuck *et al.*, 2000; Boult *et al.*, 2001; Elkan *et al.*, 2000; Rubenstein and Stuck, 2001).

A recent meta-analysis of preventive home visits revealed that home visitation programs are effective if based on multidimensional geriatric assessments with extended follow-up, and if offered to elderly persons with relatively good function at baseline (Stuck *et al.*, 2002). On the

basis of a large number of trials, the findings from this meta-analysis indicate that preventive home visitation programs are effective only if interventions are based on multidimensional geriatric assessment, include multiple follow-up home visits, and target persons with relatively good function at baseline. The NNV (number needed to visit) to prevent one admission in programs with frequent follow-up visits is around 40. Recently, it has been confirmed that a key component of successful programs is a systematic approach for teaching primary care professionals. These results have important policy implications. In countries with existing national programs of preventive home visits, the process and organization of these visits should be reconsidered on the basis of the criteria identified in this meta-analysis. In the United States, a system for functional impairment risk identification and appropriate intervention to prevent or delay functional impairment seems promising. There are a variety of chronic disease management programs specifically addressing the care needs of the elderly (Vass *et al.*, 2005). Engrafting the key concepts of home-based preventive care programs into these programs should be feasible, as they continue to evolve, and are cost-effective. Identifying risks and dealing with them as an essential component of the care of elderly persons is central to reducing the emerging burden of disability and improving the quality of life in the elderly.

CONCLUSION

Published studies of multidimensional geriatric assessment have confirmed its efficacy in many settings. A continuing challenge has been obtaining adequate financing to support adding geriatric assessment services to existing medical care. Despite GAPs' many proven benefits, and their ability to reduce costs documented in controlled trials, health-care financers have been reluctant to fund GAPs – presumably out of concern that the programs might be expanded too fast and that costs for extra diagnostic and therapeutic services might increase out of control. Many practitioners have found ways to "unbundle" the geriatric assessment process into component services and receive adequate support to fund the entire process. In this continuing time of fiscal restraint, geriatric practitioners must remain constantly creative in order to reach the goal of optimal patient care.

While there is no single optimal blueprint for geriatric assessment, the participation of the multidisciplinary team and the focus on functional status and quality of life as major clinical goals are common to all settings. Although the greatest benefits have been found in programs targeted to the frail subgroup of elderly persons, a strong case can be made for a continuum of GAPs – screening assessments performed periodically for all elderly persons and comprehensive assessment targeted to frail and high-risk patients. Clinicians interested in developing these services will do well to heed the experiences of the programs reviewed here in adapting the principles of geriatric assessment to local resources. Future research is still needed to determine the most effective and efficient methods for performing geriatric assessment and on developing strategies for best matching needs with services.

KEY POINTS

- Multidimensional geriatric assessment is an efficient and effective way for evaluating complex elderly patients and planning improved care.
- The process of multidimensional geriatric assessment usually involves the systematic evaluation of function, medical conditions, psychological parameters, and social networks through use of an interdisciplinary team and validated assessment measures.
- Multidimensional geriatric assessment has been shown to improve function and survival while reducing health-care utilization and costs.

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Function Assessment Scales

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THEORETICAL FRAMEWORK

The functional assessment literature may be somewhat crudely characterized by two statements. On the one hand, functional assessment is critically important in gerontology and geriatrics. On the other hand, there is little agreement on how to do it right. How can there be so much confusion about such an important area? Jette *et al.* suggest that the confusion stems from:

"... similar terms used to describe outcomes that are operationalized in myriad ways. Lack of sensitivity of existing outcome instruments to detect important changes in disability status hinders the evaluation of interventions. Use of disability or health status measures not designed for evaluative purposes frequently results in ceiling or floor effects, if the content of the measures lacks sufficient breadth or if the increments in the ratings are too global."

(Jette *et al.*, 2002:M209)

Therefore, in order to understand functional assessment, it would seem most helpful to start with a conceptual framework. The model that is most appropriate to functional assessment was first proposed by Nagi (1965, 1969, 1976, 1991). A simplistic rendering of Nagi's conceptual model is shown in Figure 1. The four core components of the disablement process are: *active pathology, impairment, functional limitations*, and *disability*. The arrows reflect the principal pathway: a progressive stream in which active pathology may result in impairment, impairment may result in functional limitation, and functional limitation may result in disability.

To fully understand Nagi's model, it is essential to know exactly how he defined each of the four core components, and the best way to do this is to rely on the definitions provided in his reflective chapter included in the 1991 IOM report. In Nagi's own words, the four concepts are defined as follows:

"1. The state of *active pathology* may result from infection, trauma, metabolic imbalance, degenerative disease processes, or other etiology. Such a condition involves (a) interruption of or interference with normal processes and (b) the simultaneous efforts of the organism to regain a normal state." (pp. 313–314)

"2. The concept of *impairment* indicates a loss or abnormality of an anatomical, physiological, mental, or emotional nature. The concept comprises three distinct categories: (1) all conditions of pathology, which are by definition impairments because such conditions involve anatomical, physiological, mental, or emotional deviation; (2) residual losses or abnormalities that remain after the active state of pathology has been controlled or eliminated (e.g. healed amputations, residual paralysis); and (3) abnormalities not associated with pathology (e.g. congenital formations)." (p. 314)

"3. *Functional limitations* and impairments both involve function. The difference, however, is in the level at which the limitations are manifested. Functional limitation refers to manifestations at the level of the organism as a whole.... Although limitations at a lower level of organization may not be reflected at higher levels, the reverse is not true.... Functional limitations are the most direct way through which impairments contribute to disability." (pp. 314–315)

"4. *Disability* refers to social rather than to organismic functioning. It is an inability or limitation in performing socially defined roles and tasks.... Not all impairments or functional limitations precipitate disability, and similar patterns of disability may result from different types of impairments and limitations in function. Furthermore, identical types of impairments and similar functional limitations may result in different patterns of disability." (p. 315).

Disease histories are the principal measure of *active pathology*. Although clinical examination and laboratory testing represent the gold standard, self-reported disease histories are generally used to minimize the costs of data collection. Study subjects are typically asked to report whether a physician has ever told them that they have a particular disease, such as angina, arthritis, asthma, cancer, coronary artery disease (CAD), congestive heart failure, chronic obstructive pulmonary disease, diabetes, a heart attack, hypertension, kidney disease, or a stroke. Either a series of individual binary markers are then used for each disease, or a simple summary score is calculated.

Essentially, *impairments* are decrements to normal functional abilities that have not progressed far enough to affect

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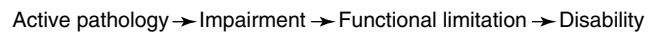

Figure 1 A simplistic representation of the main pathway in Nagi's (1965, 1969, 1976, 1991) conceptual scheme for the epidemiology of disability

an individual's ability to perform a given task, even though she/he may recognize that the deficit exists. That is, study subjects may have statistically significantly less balance, quadriceps strength, and digital dexterity than extant age and sex norms would suggest, but these impairments do not yet pose difficulties in terms of her/his ability to perform routine functions such as bending over to pull on socks and tie one's shoes. As with disease histories, impairments can be assessed in multiple ways, including self-reported symptoms (e.g. dizziness or shortness of breath), examinations by a physician or other clinician, or epidemiologic field testing (e.g. gait speed, balance, or strength evaluations).

When impairments progress to the point where they inhibit the individual's ability to perform routine sensory motor or cognitive functions, such as walking, stair-climbing, reaching out to grab an object, vision, hearing, memory or processing speed, they are considered to have become *functional limitations*. The measurement of functional limitations can involve either self-report or observed performance. Self-report measures ask study subjects if they have no, some, or great difficulty in standing for long periods, lifting or carrying weights of approximately ten pounds, going up and down stairs, walking, stooping-bending-kneeling, using hands and fingers, and reaching out with either or both arms. Alternatively, performance evaluations involve observation of the study subject as she/he simulates the sensory motor functions involved in such tasks.

Disability involves difficulties in the performance of work and independent living. The work dimension has received relatively little attention in gerontology and geriatrics given the thorny problems of status determination among older adults, many of whom are either fully or partially retired. Independent living, however, has received considerable attention, and has given rise to variously named measures of activities of daily living (ADLs). The more basic ADLs involve personal care activities and are typically measured by asking study subjects if they have difficulty (yes/no), *due to health reasons*, in performing activities such as bathing or showering, dressing, eating, getting in or out of a bed or a chair, walking across a room, getting outside, or using the toilet. When study subjects indicate difficulty with a particular task, the follow-on question is how much – some difficulty, a lot of difficulty, or are they unable to perform the task at all. Higher level or instrumental ADLs (IADLs) involve activities like meal preparation, shopping for groceries or personal items, keeping track of expenses and paying bills, using the telephone, doing light housework, doing heavy housework, or managing medications. As with ADLs, study subjects expressing difficulty with IADL tasks are asked about the degree of difficulty. Performance-based (observed) measures have been developed for both ADLs and IADLs, although their associated time and prop demands have limited their practicality.

What sets disability apart, conceptually, is that it is essentially a social (i.e. relational) phenomenon involving the performance of task and role assignments. That is, it goes beyond the individual and involves the social role and task expectations that society places on the individual in the context of her/his environment. In contrast, active pathology, impairment, and functional limitations can be measured within the individual, inasmuch as these concepts are all attributes or properties of the individual.

Although Figure 1 implies that the disablement process is linear, fixed, and unrecoverable, this is not so. To underscore this point, Figure 2 contains Verbrugge and Jette's (1994) clarification and elaboration of the model. It contains the four core components: active pathology, impairment, functional limitation, and disability. What makes Figure 2 different is that risk factors, extra-individual factors, and intra-individual factors have been added because these moderate the rate of progression and flow through the main pathway.

Risk factors include long-term or permanent behaviors and attributes of the study subjects and the places where they live, which increase the incidence of functional limitations and/or disabilities. The position of risk factors on the far left side of the model indicates that they exist prior to or at the onset of the disablement process. In contrast, the extra-individual and intra-individual factors appear where functional limitations are manifest, and are shown as moderators whose function is to buffer progression along the main disablement pathway. Buffering interventions involve avoiding disability onset, slowing down its progression, or returning the study subject to the prior functional ability. Such interventions can reside within the study subject (e.g. personal activity accommodation), or come from extra-individual sources (e.g. standby assistance/help or environmental modifications). To be sure, some intra- and extra-individual factors have negative effects, and exacerbate the disablement process. This happens when therapeutic side effects do more harm than good, when the atrophic response of study subjects initiates downward spirals, or when inflexible role obligations are faced.

Figure 2 provides further clarifications. One involves the distinction between "intrinsic" versus "actual" disability. The former taps the study subject's abilities without the use of aids (devices) or aides (people), whereas the latter taps abilities when assistive devices or personnel are available. In this sense, actual disability reflects person-environmental-fit failure, and can be seen as an indicator of unmet need. Feedback loops resulting in secondary conditions or dysfunctions are also explicitly recognized. Finally, it is clear that disability has important consequences, such as reduced quality of life and increased odds of depression, hospitalization, nursing home placement, and death. These outcomes would be placed after an arrow flowing out of disability.

PRINCIPLES OF PSYCHOMETRIC ASSESSMENT

Psychometrics is another word for measurement science. When constructing scales to measure functional assessment,

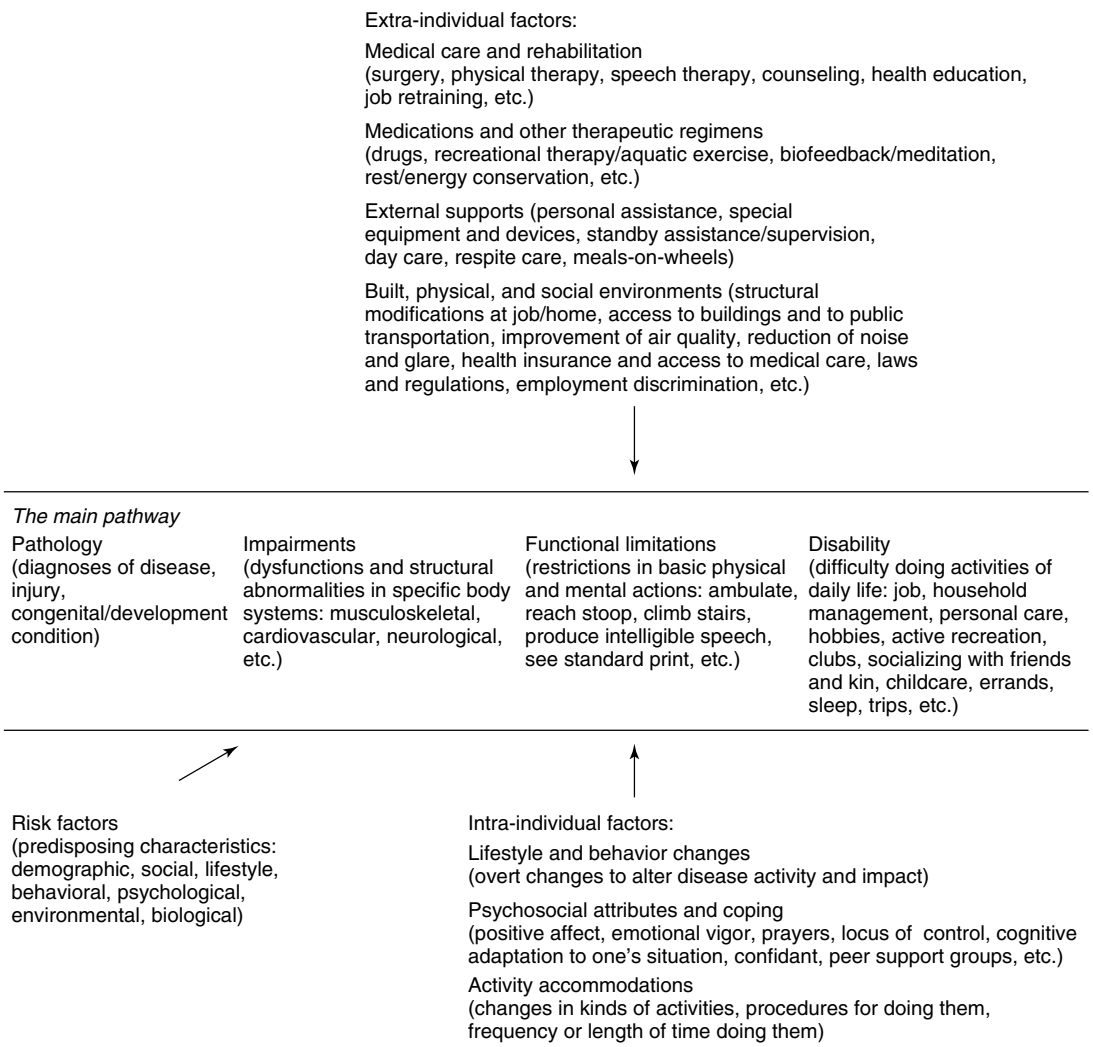

Figure 2 Verbrugge and Jette's (1994) conceptual scheme for the disablement process

or any other construct, there are four key principles to consider: reliability, validity, responsiveness, and clinically important change (DeVellis, 2003; Trochim, 2004). These principles can be intuitively understood by considering a repeated target shooting scenario. The target consists of a series of concentric circles, with the innermost being the bull's-eye. When shooting at the target, the marksperson is trying to do two things. One is to hit the bull's-eye. The other is to have a tight cluster of shots in the target. After the marksperson fires all of his/her bullets, the target is repositioned (usually further away) and the process is repeated. Hitting the bull's-eye is analogous to validity. Having a tight cluster is analogous to reliability. Proper adjustment (resighting) after the target has been moved is analogous to responsiveness. Clinically important change is analogous to whether the target has been repositioned in a trivial (i.e. lateral movement that maintains the same distance from the marksperson), or a meaningful (i.e. greater distance) manner.

The bullet holes from each round represent the scale items. As with sampling principles, the larger the sample, the more representative and stable the obtained estimate. The best estimate of the actual value is the centroid (average) from that round of bullets. Reliability coefficients essentially gauge the magnitude of the average distance from each bullet hole to the centroid. Classical test theory dictates that:

$$X = t + e$$

where X represents the bullet holes (items), t represents the bull's-eye (true score), and e represents the distance to the centroid (amount of error). Because t is a latent value (never observed), the average of the Xs is considered the best estimate when five assumptions hold: (1) the expected value of the error score is zero (random error distribution); (2) the true score and error score are uncorrelated (homoscedasticity), (3) the true score for one marksperson is uncorrelated with the error score of another (independent observations); (4) the error scores for different marksperson are uncorrelated (no omitted confounders); and, (5) the amount of error for each bullet hole is equal (common factor loadings). Reliability problems involve random error, whereas validity problems

involve systematic error. That is, reliability gauges the dispersal around the centroid (size of the cluster), whereas validity indicates whether the centroid is properly positioned in the bull's-eye. Thus, it is possible for a scale to be very reliable but invalid because it is consistently missing the mark.

There are four major ways to assess reliability: (1) test–retest; (2) alternative forms; (3) split halves; and (4) internal consistency. Test–retest reliability involves the correlation between scores on the same scale administered at two different points in time, and makes two strong assumptions. The first assumption is that the construct being measured does not change between the two administrations (i.e. the bull's-eye is not moved), and the second is that the two observations are independent. An issue here is the length of the interval between administrations – if it is too short, reproducibility will be biased upwards because subjects may try to remember their prior answers or interviewers try to remember their prior readings. If the interval between administrations is too long, reliability is attenuated because there is greater opportunity for change in the true score. To some extent, alternative forms reliability overcomes the memory and reactivity problems that limit test–retest reliability by using two different forms of the same test. The new problem here, however, is how do you construct alternative forms of the same test that are truly equivalent?

These difficulties give rise to assessing reliability at a single point in time. Split half reliability accomplishes this by dividing the set of scale items into two subscales and then using the correlation between those subscales as the reliability estimate. Although this resolves the assumption that the true score has not changed over time (because both subscales are administered at the same time), it poses a new problem – how do you separate the items into the two subscales? This is not a trivial issue, inasmuch as there are 125 unique ways to divide 10 items into two five-item subscales. Internal consistency reliability overcomes this problem by focusing on the average interitem correlation among items in the scale, where the reliability estimate is defined as:

$$r_{tt} = \frac{k^* \bar{r}_{ij}}{[1 + (k-1)\bar{r}_{ij}]}$$

where r_{tt} is coefficient alpha (the t subscripts represent the true score), k is the number of items in the scale, and $\bar{r}_{ij}$ is the average interitem correlation coefficient. Coefficient alpha ranges between zero (unreliability, or when the variance in the errors is equal to the variance in X) and one (perfect reliability), and is a lower bound estimate or conservative measure of the scale's reliability. Current reliability standards require a minimum reliability coefficient of 0.70 for basic science and a minimum reliability coefficient of 0.90 when diagnostic and treatment decisions are being made.

Compared to evaluating the reliability of a scale, assessing its validity is more difficult. After all, reliability assessments involve correlations between observed scores at two different points in time (test–retest or alternative forms), or between components of the same score at the same time (split halves or internal consistency). In contrast, validity assessments involve a greater leap of faith inasmuch as the correlations between observables must be linked to the latent constructs. There are three main methods for evaluating validity: (1) content; (2) criterion; and (3) construct. Content validity is the most primitive approach, and is basically concerned with face and sampling validity. Face validity is simply whether items look like they are measuring what they are supposed to be, a rather subjective process. Some objectivity can be had by having an expert panel review the items and reach consensus about their face validity. The problems here lie in the picking of the experts, and whether these experts really know what the items will mean to the intended population. Sampling validity involves conceptually identifying all of the domains of the construct, and then developing multiple measures of each domain. It is akin to assuming that the population pool of potential items is known, and that stratified sampling of items within domains has occurred. Even when used in combination, face and sampling validity approaches cannot be said to make a strong case for the validity of the scale.

Criterion-related validity is reasonably straightforward, and assumes that some criterion or gold standard is available. It involves correlating the scale score with the known criterion (gold standard). The criterion value can be ascertained retrospectively (postdictive), at the same time (concurrent), or in the future (predictive). Thus, neither the timing of the criterion assessment nor the theoretical relationship between the gold standard and the latent construct is important. All that matters is that there is a known gold standard (criterion) with which to correlate the scale score.

Construct validity is a theory-driven approach that involves embedding the latent construct in a conceptual model that includes other latent constructs that are also measurable. Expected relationships between the construct measured by the scale score and the other constructs in the model are specified (positive or negative, strong or weak, null), and then these latent construct level correlations are estimated using the observable data (scale scores). The closer that the observed correlations conform to the theoretical expectations, then the greater the degree of construct validity. The main limitation here involves knowing how strong or weak the various correlations should be. The multitrait, multimethod matrix approach is the underlying framework for such determinations, and a good grasp of its principles leads directly to both exploratory and confirmatory factor analyses, which are the common approaches to construct validation.

Determining the responsiveness of a scale score generally involves known-group comparisons. Sometimes known-group comparisons are used in criterion validity, such as when a depression scale is administered to patients who have been diagnosed with depression, and to the general public. It is assumed that the diagnosed patients will register more depressive symptoms on the scale score than the community sample. Similarly, if study subjects are being followed over the course of a year to evaluate the responsiveness of an ADL scale, one would expect the change in the ADL scale score to be greatest among those who reported having an acute event like a heart attack, stroke, or hip fracture

than among those not reporting having had such events. That is, the assumption would be made that those suffering such an acute event would have diminished ADL abilities (their bull's-eye should have moved, because this is a known effect of such acute events), and that this should be reflected in greater baseline-to-follow-up differences in their scale scores. A more subjective approach is to ask the study subjects at the posttest assessment whether their ability to perform ADLs has diminished since the pretest. If the ADL scale is responsive, then the change in scores among those who answered in the affirmative should be greater than those who did not.

Determining whether the difference between pretest and posttest scale score assessments is clinically meaningful is less straightforward. The issue is whether the observed change in scale scores represents movement of the bull's-eye versus random measurement error. The most widely used approach relies on Cohen's (1969) effect-size measures. Cohen suggested that the magnitude of group-level differences (as in intervention versus control) could best be gauged by (1) obtaining the average change from baseline to the end of the study in each group, (2) subtracting the average change in the control group from the average change in the intervention group, and (3) dividing the result by the pooled standard deviation obtained from both groups at baseline. The result (effect size) is a measure of the average change attributable to the intervention expressed relative to the amount of variation in the population.

Cohen (1969) further suggested that effect sizes $\geq$0.20 were small, effect sizes $\geq$0.50 were medium, and effect sizes $\geq$0.80 were large. The main problem with Cohen's effect-size approach is that the categorization of levels is arbitrary and atheoretical. Nonetheless, a recent meta-analysis (Norman *et al.*, 2003) of 38 studies containing 68 effect-size estimates found that the mean estimated meaningfully important difference was equivalent to an effect size of 0.50. Furthermore, if seven response options exist for each question in the scale, an effect size of 0.50 is remarkably close to estimates of human abilities to discriminate between two feeling states (Miller, 1956). Thus, in the absence of known-groups or criterion guidelines for how much change in scale scores is clinically relevant, an effect-size difference of 0.50 is a plausible rule of thumb.

IMPAIRMENTS

It is well established that the assessment of physical impairments in older adults is crucial, and there is growing con*sensu*s that performance-based estimates in this area have distinct advantages over self-reports, especially with respect to sensitivity and responsiveness (Avlund, 1997; Berg and Norman, 1996; Gross, 2004; Guralnik, 1997; Ostir *et al.*, 2002; Reuben and Siu, 1990; Reuben *et al.*, 1995). Building upon initial work conducted as part of the EPESE (Established Populations for the Epidemiologic Study of the Elderly; Guralnik *et al.*, 1994, 1995), Guralnik and colleagues have developed, refined, and provided considerable psychometric evidence for a standardized physical performance measure of lower body function using data from the 1002 moderately to severely disabled women participating in the Women's Health and Aging Study (WHAS), a 3-year prospective community-based cohort study. The focus on lower body function derives from the substantial evidence that mobility-related dysfunction is the most detrimental, and that such limitations drive the disablement process.

The standardized, lower body physical performance measure was designed to be administered by a single lay interviewer within the spatial limitations typically encountered in the study subject's home. It consists of a hierarchical balance test, a 4-m walk, and repetitive chair stands. A summary score (0–5) is determined for each component, with those unable to perform the task scored as a zero. The hierarchical balance test involves tandem, semi-tandem, and side-by-side stands:

> "For each stand, the interviewer first demonstrated the task, then supported one arm while participants positioned their feet, asked if they were ready, then released the support and began timing. The timing was stopped when participants moved their feet or grasped the interviewer for support, or when 10 seconds had elapsed. Each participant began with the semi-tandem stand, in which the heel of one foot was placed to the side of the first toe of the other foot, with the participant choosing which foot to place forward. Those unable to hold the semi-tandem position for 10 seconds were evaluated with the feet in the side-by-side position [for a maximum of 10 seconds]. Those able to maintain the semi-tandem position for 10 seconds were further evaluated with the feet in full-tandem position, with the heel of one foot directly in front of the toes of the other foot [for a maximum of 10 seconds]."
>
> (Guralnik *et al.*, 1994, p. M86)

The summary balance scale score was determined as follows. Subjects who could not hold the side-by-side stand for a full 10 seconds, who tried but were unable to hold this stand at all, or who did not attempt any of the three stands either based on their concerns or those of the interviewer (for safety reasons) were scored as a zero. Subjects who were able to hold the side-by-side stand for a full 10 seconds, but who could not hold the semi-tandem stand for a full 10 seconds were scored as a one. Subjects who held the semi-tandem stand for a full 10 seconds but could not hold the tandem stand for at least two seconds were scored as a two. Subjects who were able to hold the tandem stand for 3 to 9 seconds were scored as a three, and subjects who could hold the tandem stand for the full 10 seconds were scored as a four.

The 4-m walk was performed at the study subject's normal pace, with a 3-m course substituted when necessary given unobstructed spatial constraints in the home (which occurred 9% of the time; Ostir *et al.*, 2002). A premeasured flat cord was used to layout the walking course, with the starting line, end of course line (for the interviewer's benefit), and stopping line (for the study subject's benefit) appropriately indicated. Subjects were instructed to "...walk to the other end of the course at your usual speed, just as if you were walking down the street to go to the store" (Guralnik *et al.*, 1994, p. M86). Each study subject was asked to perform this gait speed test twice, with the faster timing of their

two trials (expressed in meters/second to adjust for two course lengths) used in the analyses. Scores were categorized into approximate quartiles with cut-points at ≤0.43, ≤0.60, ≤0.77, and ≥0.78 m second, with these quartiles assigned scores of one to four, respectively, and those unable to perform the test scored as a zero.

The repetitive chair stand test was performed as follows. Interviewers demonstrated the chair stand protocol using a straight-backed chair without arms, and having the arms folded across their chests. After the study subject demonstrated that she/he could perform a single chair stand safely, interviewers then asked them to perform five repetitive chair stands as quickly as possible. Timings from the start of the test to the peak of the fifth rise were categorized into approximate quartiles, with cut-points at ≥16.7, ≥13.7, ≥11.2, and ≤11.1 seconds assigned scores of one to four, respectively, with those unable to perform the test scored as a zero.

The overall score for the standardized lower body functional performance measure is the simple sum of the three categorical component scores, and thus ranges from 0 to 12. In general, the distribution of WHAS study subjects across the overall score range approximates the intended uniform function, with the notable exception of relatively few subjects in the best performing category (Guralnik *et al.*, 1995; Onder *et al.*, 2002). The short-term (weekly) test–retest reliability of the overall score has been shown to be excellent in multiple comparisons (≥0.88), and the long-term (six-month) test–retest reliability is very good (0.72 to 0.79; Ostir *et al.*, 2002). Furthermore, the overall score has been shown to be highly predictive of subsequent disability (ADL limitations) over both 2- and 4-year follow-ups (Guralnik *et al.*, 1995; Ostir *et al.*, 1998), and lower values on the overall score have been highly associated with increased risk of nursing home admission, health services use, and death (Ferrucci *et al.*, 2000; Guralnik *et al.*, 1994; Penninx *et al.*, 2000). Finally, the responsiveness of the overall score has been well established in that study subjects experiencing any of four incident medical events (heart attack, stroke, hip fracture, or congestive heart failure) had substantially poorer lower body function performance scores at their follow-up assessment (Ostir *et al.*, 2002). Thus, the standardized lower body functional performance measure has excellent psychometric properties and should be considered the test of choice for future epidemiologic and/or office-based clinical assessments.

FUNCTIONAL LIMITATIONS

Functional capacity refers to the ability to perform specific tasks that require fine and/or gross motor skills and actions (Nagi, 1991; Verbrugge and Jette, 1994). As indicated earlier, the items originally used by Nagi (1976) to measure functional limitations included standing for long periods, lifting or carrying weights of approximately ten pounds, going up and down stairs, walking, stooping-bending-kneeling, using hands and fingers, and reaching out with either or both arms. Subjects were simply asked whether they had no, some, or great difficulty in performing these tasks. Because functional limitations affect the organism as a whole, self-reports can provide reliable and valid measures (Avlund *et al.*, 1996; Siu *et al.*, 1990; Wolinsky and Miller, 2005). The problems with extant functional limitation scales, however, are that they have seldom covered the full spectrum of gross and fine motor scales, and their reproducibility and responsiveness have been inadequate (Linn and Linn, 1980; Reuben, 1995).

Recently, Jette and colleagues (Jette *et al.*, 2002; Haley *et al.*, 2002) have developed the Late-Life Function and Disability Instrument (Late-Life FDI) to overcome these problems. Building on Nagi's (1976, 1991) conceptual framework for the epidemiology of disability, the Late-Life FDI focuses on discrete activities and expands the range of actions under study beyond basic physical skills, which have been shown to be rather ineffective measures for capturing the variation in functional abilities found in the general population of community-dwelling older adults. After an extensive review of the literature, focus groups with older adults, and consultation with measurement experts, 54 items were initially developed to tap the full range of functional limitations, and after initial pilot testing, 48 of these were retained. A convenience sample of 150 older community-dwelling adults aged 60 years old and older from central and eastern Massachusetts was empanelled for further development and evaluation purposes.

Exploratory factor analyses were used to identify the 32 items that formed the most reliable and valid scales tapping three domains – basic lower extremity functions, advanced lower extremity functions, and upper extremity functions – that satisfied established criteria for simple structure (unidimensional scales, unipolar principal factor loadings ≥0.40, and no factorial complexity; DeVellis, 2003). Table 1 contains the final items for each scale and lists the items in ascending order of the degree of item difficulty. That is, the items are ordered from the easiest to accomplish functions to the most difficult to accomplish functions. Item difficulty calibrations were determined using Item Response Theory (IRT; Wright and Masters, 1982) methods. Scale scores are transformed to range between 0 (worst function) and 100 (best function).

Cronbach's alphas were 0.96 for the basic lower extremity scale, 0.96 for the advanced lower extremity scale, and 0.86 for the upper extremity scale. Test–retest reliability coefficients obtained on a small subset at approximately 2 weeks were ≥0.91. Responsiveness was evaluated using known-groups comparisons, with four groups (no functional limitations, slight, moderate, or severe functional limitations) determined based on scores from the SF-36 physical function scale. For each of the functional limitations domains, a monotonic and statistically significant decline in scale scores was observed progressing from the no functional limitations group to the severe functional limitations group. Although further research is needed on a nationally representative sample in order to establish population-based norms, the Late-Life FDI functional limitations scales are extremely promising and their use is epidemiologic and office-based clinical settings is strongly encouraged.

Table 1 The functional status items of the late-life function and disability instrument, by domain and in ascending order of difficulty (Haley *et al.*, 2002)

How much difficulty do you have . . .without the help of someone else and without the use of assistive devices? (Responses: none, a little, some, quite a lot, or cannot do)

The 14 basic lower extremity items
Wash dishes while standing
Put on and take off coat
Walk around one floor of home
Pick up a kitchen chair
Get in and out of a car
Make bed
Reach overhead while standing
Go up and down a flight of stairs
Bend over from standing position
Up and down from a curb
Open heavy outside door
On and off a step stool
On and off bus
Stand up from a low soft couch

The 11 advanced lower extremity items
Walk several blocks
Walk 1 mile with rests
Get up from floor
Go up and down 1 flight, no rails
Go up and down 3 flights, inside
Carry while climb stairs
Run to catch bus
Walk a brisk mile
Walk on slippery surface
Hike a few miles including hills
Run one-half mile

The 7 upper extremity items
Hold full glass of water in one hand
Put on and take of pants
Use common utensils
Reach behind back
Pour from a large pitcher
Remove wrapping with hands only
Unscrew lid without assistive device

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DISABILITY

Disability refers to the ability to perform ADLs and IADLs (Nagi, 1991; Verbrugge and Jette, 1994). Despite considerable work on the development and evaluation of ADL and IADL scales, however, a number of problems remain (Avlund *et al.*, 1993; Fitzgerald *et al.*, 1993; Katz *et al.*, 1963; Kempen and Suurmeijer, 1990; Thomas *et al.*, 1998; Wolinsky and Johnson, 1991; Wolinsky and Miller, 2005). As with functional limitations, the principal problems with disability scales involve the lack of conceptual clarity, the limited spectrum of activities that are tapped, and limited responsiveness for the detection of change (Jette, 1994, 2003; Jette and Keysor, 2003). Thus, Jette and colleagues (2002) set out to develop a more comprehensive, reliable, valid, and responsive disability measure.

Using the same approach and sample as in the development of the Late-Life FDI, functional limitations scales (Haley *et al.*, 2002), Jette *et al.* (2002) developed the Late-Life FDI disability scales. A refined list of 25 life tasks were administered to the 150 community-dwelling adults aged 60 years old or older in central and eastern Massachusetts. Unlike the functional limitations items, the disability questions are asked twice, once to determine how often the study subject does the life task, and once to determine the extent of their limitations in performing the life task.

Exploratory factor analyses were used to identify the 16 items that formed the most reliable and valid scales tapping the two domains – frequency of performance, and limitation in capability – that satisfied established criteria for simple structure (unidimensional scales, unipolar principal factors loadings $\geq$0.40, and no factorial complexity; DeVellis, 2003). Table 2 contains the final items and lists the items in ascending order of the degree of item difficulty, with item difficulty calibrations again determined using IRT methods (Wright and Masters, 1982). Scale scores are transformed to range between 0 (worst function) and 100 (best function).

Table 2 The 16 disability items of the late-life function and disability instrument, by domain and in ascending order of difficulty (Jette *et al.*, 2002)

Frequency items
How often do you
(Responses: very often, often, once in a while, almost never, never)
take care of your own personal care needs?
take care of your own health?
keep in touch with others?
provide meals for yourself and family?
take care of household business and finances?
take care of local errands?
take care of inside of home?
go out with others in public places?
visit friends in their homes?
provide care or assistance to others?
take part in regular exercise program?
invite people into your home?
take part in organized social activities?
travel out of town?
work at a volunteer job?
take part in active recreation?

Limitation items
To what extent do you feel limited in
(Responses: not at all, a little, somewhat, a lot, completely)
taking care of your own health?
taking care of your own personal care needs?
taking care of household business and finances?
providing meals for yourself and family?
keeping in touch with others?
taking care of local errands?
taking part in organized social activities?
going out with others in public places?
inviting people into your home?
providing care or assistance to others?
visiting friends in their homes?
taking care of inside of home?
taking part in regular exercise program?
working at a volunteer job?
traveling out of town?
taking part in active recreation?

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Cronbach's alphas were 0.82 for the frequency of performance scale and 0.92 for the limitation in capability scale, and test–retest reliability coefficients were 0.68 and 0.82, respectively. Responsiveness was evaluated using known-groups comparisons, again with four groups (no functional limitations, slight, moderate, or severe functional limitations) based on scores from the SF-36 physical function scale. For each of the disability domains, a monotonic and statistically significant decline in scale scores was observed progressing from the no functional limitations group to the severe functional limitations group. Thus, the Late-Life FDI disability scales are also extremely promising and their use is strongly encouraged in epidemiologic and office-based settings. Taken together, it takes less than 25 minutes to administer all of the Late-Life FDI scales.

HEALTH-RELATED QUALITY OF LIFE

Health-related quality of life (HRQoL) is an important consequence of the disablement process for older adults. The most widely used HRQoL instrument in the world, regardless of study subject age, is the SF-36, which comprehensively addresses all facets of the classic WHO (1947) definition. A detailed description of the SF-36 developmental process and procedures is readily available elsewhere (Ware, 1996), and the exact wording of the items for both the original version and the second version (SF-36 V2) can be found in the SF-36 web page (www.sf-36.org). Thirty-five of the 36 items make up eight scales: physical functioning (10 items), role limitations due to physical functioning (4 items), bodily pain (2 items), general health perceptions (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items), and mental health (5 items). The remaining item asks respondents about any health changes over the past year, but is not used in any of the scales. Within scales, a proration imputation method is used for missing data. That is, as long as the subject answers at least half of the items within a scale, the average of those items is imputed for any items not answered in that scale. Because of the different number of items and response options in each scale, raw scores are transformed to range from 0 (worst health) to 100 (best health).

The original version of the SF-36 was selected in 1998 by the Centers for Medicare and Medicaid Services (CMS) as the core instrument for monitoring the quality of care proved by managed care organizations (MCOs). To evaluate MCOs, CMS requires each Medicare + Choice plan, Social HMO (SHMOs), and Section 1876 risk and cost contract plan to participate in the Health Outcomes Survey (HOS). Each HOS-participating plan annually identifies a random sample of 1000 beneficiaries for the National Center for Quality Assurance (NCQA). NCQA and its approved subcontractors then mail out the HOS protocol to the samples during the baseline line year and during the follow-up survey 2 years later. Plans are evaluated based on a trichotomous classification of the obtained change scores as better, the same, or worse HRQoL. The HOS calls for five successive cohorts (samples) starting in 1998 and 2000 for cohort one, and finishing in 2002 and 2004 for cohort five. Baseline response rates have been in the upper 60% range, and retention rates among survivors who remained in the health plans have been in the lower 80% range.

Deidentified data files from the HOS are now available (www.ncqa.org) for public use. The 1998 baseline data are used here to demonstrate the reliability, validity, and responsiveness of the SF-36 for older adults. As reported by Gandek *et al.* (2004), the reliability and validity of the SF-36 based on these data is good. Item analyses indicated that 95% or more of the respondents completed all of the items within any given scale. Floor and ceiling effects were modest for physical function and pain scales, low for the general health, vitality and mental health scales, substantial for the role physical and role emotional scales, and notable for the social function scale. Internal consistency reliability coefficients (Cronbach's alpha) for the eight SF-36 scales exceeded 0.80 and were greater than 0.90 for the physical and mental component summary scales. Indeed, the only unexpected results involved the exploratory factor analyses. In contrast to the hypothesized model of separate physical and mental composites, a unidimensional second-order factor structure was identified based on eigenvalue and scree criteria. When a two-factor solution was forced, however, the role emotional and mental health scales did load principally on the second factor, with near zero loadings on the first factor. Thus, overall, the 1998 HOS baseline data provide considerable support for the SF-36's underlying conceptual model.

To address the responsiveness of the SF-36, additional analyses were conducted for this chapter using the 1998 baseline HOS data for subjects aged 65 years old or older. Table 3

Table 3 Mean scores for each of the eight SF-36 scales by the number of diseases for subjects 65 years old or older in the baseline (1998) Center for Medicaid and Medicare Services (CMS) Health Outcomes Study (HOS)[a]

Number of diseases (N)	Physical function	Role-physical	Bodily pain	General health	Vitality	Social function	Role-emotional	Mental health
None (47 345)	74.2	71.8	71.2	73.5	64.7	86.9	84.5	81.5
1 (51 193)	67.6	63.1	65.9	67.3	59.5	83.0	80.0	79.0
2 (25 650)	59.6	51.6	60.4	59.7	53.4	77.2	73.4	76.4
3 (10 755)	53.1	42.3	56.2	53.3	48.7	72.2	68.9	74.3
4 (4744)	47.6	35.3	51.9	47.8	44.1	67.5	63.7	72.1
≥5 (2128)	38.6	25.0	45.7	40.2	36.1	58.4	55.2	67.3

[a]Where 0 = worst possible health, and 100 = best possible health. p-values obtained from global analysis of variance tests within columns were all <0.001. Shaded cells reflect deviations from expected monotonic decline within columns.

Table 4 Mean scores for each of the eight SF-36 scales by the number of activities of daily living (ADLs) for which subjects 65 years old or older in the baseline (1998) Center for Medicaid and Medicare Services (CMS) Health Outcomes Study (HOS) Reported Difficulty[a]

Number of six ADLs(*N*)	Physical function	Role-physical	Bodily pain	General health	Vitality	Social function	Role-emotional	Mental health
None (88 171)	79.8	78.3	75.7	73.8	66.9	90.3	87.5	82.6
1(20 253)	54.2	43.6	55.3	59.1	50.7	76.8	72.5	76.0
2(15 207)	41.4	27.6	45.5	52.5	42.9	67.7	64.4	72.7
3(5643)	31.7	17.3	40.0	45.4	37.4	56.7	54.1	68.0
4(3906)	25.0	11.8	34.6	41.2	33.2	48.9	47.5	65.0
5(2636)	20.2	9.33	1.03	7.13	0.84	1.54	0.86	1.0
6(1841)	33.7	25.5	42.0	42.5	38.0	48.9	44.2	60.0

[a]Where 0 = worst possible health, and 100 = best possible health. *P*-values obtained from global analysis of variance tests within columns were all <0.001. Shaded cells reflect deviations from expected monotonic decline within columns.

Table 5 Unstandardized partial regression coefficients obtained from multivariable linear regression of the eight SF-36 scales on demographics, ADLs, and diseases for subjects 65-years old or older in the baseline (1998) Center for Medicaid and Medicare Services (CMS) Health Outcomes Study (HOS)[a]

Independent variables	Physical function	Role-physical	Bodily pain	General health	Vitality	Social function	Role-emotional	Mental health
Demographics								
Age ≥ 75	−5.36	−8.02	−0.05	−0.50	−1.67	−1.37	− 5.61	− 0.57
Male	4.94	2.18	3.35	−0.38	2.08	1.55	2.32	2.18
Black	−1.89	0.08	0.99	−2.72	3.36	−1.48	− 4.09	0.91
Other race	−0.55*	0.31	1.02	−1.51	1.89	−2.79	− 2.43	− 0.78
Education	2.85	3.35	1.52	2.73	1.67	1.44	4.87	2.49
ADLs								
Bathing	−12.59	−11.18	−4.93	−7.78	−6.51	−12.28	− 11.06	− 5.18
Dressing	−5.44	−5.65	−4.67	−3.58	−3.22	−6.80	− 4.34	− 2.28
Eating	1.82	−2.58	−0.76*	−5.29	−3.72	−6.64	− 10.26	− 7.43
Chair/bed transfer	−9.03	−15.33	−12.15	−5.21	−7.91	−6.82	− 7.17	− 3.26
Walking	−26.91	−31.22	−18.36	−12.48	−13.91	−13.02	− 11.31	− 4.70
Toileting	0.33	1.29*	− 1.14	−0.43	0.42	−3.26	− 3.36	− 2.00
Diseases								
Hypertension	−2.27	−2.65	−2.07	−3.19	−2.31	−1.06	− 1.19	− 1.43
Angina/CAD	−3.48	−7.65	−5.07	−6.03	−4.31	−3.39	− 3.49	− 2.23
CHF	−7.43	−8.20	−1.85	−7.69	−5.09	−5.36	− 4.74	− 1.67
AMI	−1.48	−2.50	−0.51*	−2.50	−1.58	−1.09	− 0.83*	− 0.54**
Stroke	−3.60	−5.31	0.27	−3.25	−3.03	−3.27	− 4.31	− 1.90
Diabetes	−2.56	−2.81	−1.22	−4.93	−2.64	−1.84	− 3.66	− 0.98
Cancer	−2.86	−5.77	−2.28	−4.65	−3.46	−3.10	− 2.44	− 1.01
Intercept	86.36	91.71	72.50	73.01	68.32	91.66	91.25	76.08
R-Squared	0.52	0.34	0.33	0.35	0.31	0.31	0.16	0.15
Number of cases	126,102	123,242	124,655	125,044	124,595	124,753	122,821	124,552

[a]Where 0 = worst possible health, and 100 = best possible health. Shaded cells reflect p-values > 0.05; p-values < 0.05 indicated by one asterisk (*), p-values < 0.01 indicated by two asterisks (**), with all other p-values < 0.001.

contains the mean scores for each of the eight SF-36 scales by the number of self-reported diseases (hypertension, angina or CAD, congestive heart failure, heart attack, stroke, diabetes, and cancer). As shown, the progressive decline in scale scores with increasing comorbidity holds for each scale. As expected, the extent of the decline is greatest for those scales tapping the physical health components of HRQoL than for those tapping the mental health components. Table 4 contains similar data based on the number of ADL limitations (bathing, dressing, eating, getting out of a chair, walking across a room, and toileting). In general, the same pattern holds, with the exception of those who were limited in all six ADLs, which is likely an artifact of the relatively small sample in that group.

Although the data shown in Tables 3 and 4 provide rather convincing known-groups evidence of the responsiveness of the SF-36 scales, those differences are crude (one-way analyses of variance) and aggregated. To estimate the net effects of each ADL and disease on the eight SF-36 scales, multiple linear regression analyses were conducted, adjusting for age, gender, race, and education. Table 5 contains the intercepts, unstandardized regression coefficients, and R-squared values obtained from these analyses. The unstandardized regression coefficients can be interpreted as the attributable change in the SF-36 scale score for older adults having that ADL limitation or disease, adjusted for the other ADLs and diseases, as well as the sociodemographic factors. As shown, although nearly all effects are statistically

significant given the very large sample sizes, the dominant effect for all scales is associated with the walking ADL item, followed by the bathing ADL item. This is as expected and is consistent with the remarkable predictive power of lower body impairments on subsequent health outcomes. Somewhat less expected is the more modest effect of the individual diseases on HRQoL, although this may be reflective of their mediation through the ADLs. It is also worth noting that the R-squared value is greatest (0.52) for the physical function scale and smallest for the role emotional and mental health scales. This is consistent with the results of the exploratory factor analysis and supports the general notion that the mental health component of the SF-36 is not as responsive to disease and disability as the physical health component.

Acknowledgment

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KEY POINTS

- Despite the clinical and pragmatic importance of functional assessment, this area of geriatrics suffers from conceptual confusion and methodological limitations.
- Functional assessment scales should be based on established theoretical models of the disablement process and traditional psychometric principles.
- On the basis of the theoretical and methodological considerations, the following state-of-the-art measures were selected and are recommended for each of the principal components of the disablement process:
  - for *impairments*: the standardized lower body physical performance measure
  - for *functional limitations*: the functional component of the Late-Life Functional Disability Instrument (Late-Life FDI)
  - for *disability*: the disability component of the Late-Life Functional Disability Instrument (Late-Life FDI)
  - for *health-related quality of life*: the SF-36.

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Frailty

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INTRODUCTION

Frailty can be defined as that condition when a person loses the ability to carry out important, practiced social activities of daily living when exposed to either psychological or stressful conditions (Morley *et al.*, 2005). It should be distinguished from disability. Frailty represents a form of predisability.

Frailty has been objectively defined by Linda Fried and her colleagues at John's Hopkins University (Table 1) (Fried *et al.*, 2004, 2001). Their definition includes weight loss, exhaustion, weakness, walking speed, and low physical activity. By this definition, approximately 6.9% of the older population are frail. Females are more often classified as frail than are males of the same age. Frailty is the beginning of a cascade that leads to functional deterioration, hospitalization, institutionalization, and death (Figure 1). Over our lifetime, there is a peak in vitality between 20 and 30 years of age, after which there is a gradual physiological decline in performance (Figure 2). This decline can be delayed by positive behaviors, such as exercise, or accelerated by negative factors such as disease. However, eventually all individuals, if they live long enough, will cross the frailty threshold. This chapter will discuss the factors involved in the acceleration of the life slope toward the frailty threshold.

PATHOPHYSIOLOGY OF FRAILTY

The causes of frailty are multifactorial. The backdrop for the development of frailty is the physiological changes of aging. The interaction of normal physiology with genes, lifestyle, environment, and disease determines which individuals will become frail. In most individuals, frailty is caused by the failure to generate adequate muscle power and/or the failure to have sufficient executive function to appropriately utilize the available executive function. The major causes of frailty are illustrated in Figure 3.

Disease

Numerous disease processes can directly or indirectly result in frailty. Many diseases produce an excess of cytokines that can lead to a decrease in muscle mass, food intake, and cognitive function. Diseases also lead to a decline in levels of the anabolic hormone, testosterone.

Congestive heart failure (CHF) is a condition that is classically associated with frailty. Persons with CHF have a marked decline in their VO_{2max}, leading to an inability to perform endurance or resistance tasks. Left-sided heart failure leads to intestinal wall edema. This results in bacterial translocation into the lymphatic and systemic circulation. The bacterial endotoxins (lipopolysaccharides) result in the activation of the immune system and release of cytokines, such as TNFα. This results in anorexia, loss of muscle mass, weight loss, hypoalbuminemia, and hypocholesterolemia (Figure 4). In CHF, the best predictors of poor outcome are weight loss and hypocholesterolemia (Von Haehling *et al.*, 2004). Activation of the angiotensin II system that leads to cleaving of actomyosin and subsequent clearance of muscle protein by the ubiquitin-proteasome system may also play a role. Angiotensin-converting enzyme inhibitors reverse weight loss and frailty in some persons with CHF.

Persons with chronic obstructive pulmonary disease have a decrease in endurance, weight loss due to poor food intake, and increased resting metabolic rate and thermic energy of eating. They lose muscle because of low testosterone levels and increased circulating cytokine levels.

Diabetes mellitus is classically associated with an increase in frailty, injurious falls, disability, and premature death (Figure 5). Again, the causes are multifactorial, and include low testosterone, increased angiotensin II, increased cytokines, peripheral neuropathy, reduced executive function, and accelerated atherosclerosis (Maty *et al.*, 2004; Rodriguez-Saldana *et al.*, 2002; Miller *et al.*, 1999; Sinclair, 1999).

Persons with anemia have reduced endurance, decreased muscle strength, orthostasis, increased falls, increased frailty,

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Table 1 Objective definition of frailty

- Weight loss (10 lbs in 1 year)
- Exhaustion (self-report)
- Weakness (grip strength: lowest 20%)
- Walking speed (15 feet; slowest 20%)
- Low physical activity (Kcals/week: lowest 20%)

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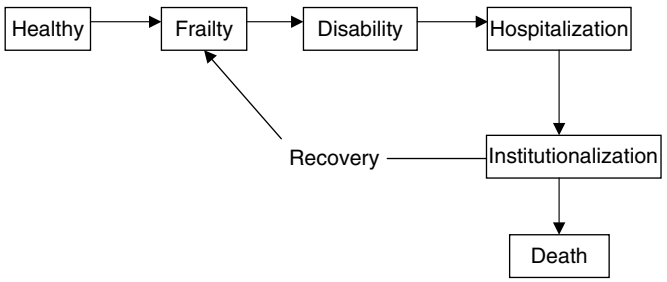

Figure 1 The pathway from frailty to death

decreased mobility, increased disability, and increased mortality (Figure 6). Both erythropoietin and darbopoetin-α can reverse the anemia and many of these changes (Cesari *et al.*, 2004a; Thomas, 2004). The use of these agents has led to a marked increase in the quality of life of patients with chronic kidney failure, anemia of chronic disease, and myelofibrosis.

Polymalgia rheumatica results in painful muscles with proximal myopathy. The diagnosis is confirmed by finding an elevated erythrocyte sedimentation rate. Treatment of this condition with corticosteroids reverses the frailty it produces. Unfortunately, this totally reversible condition is often misdiagnosed by clinicians.

Endocrine disorders, such as hyperthyroidism, hypothyroidism, and hypoadrenalism, can have insidious onset in older persons. When this occurs, they are the classical causes of the frailty syndrome.

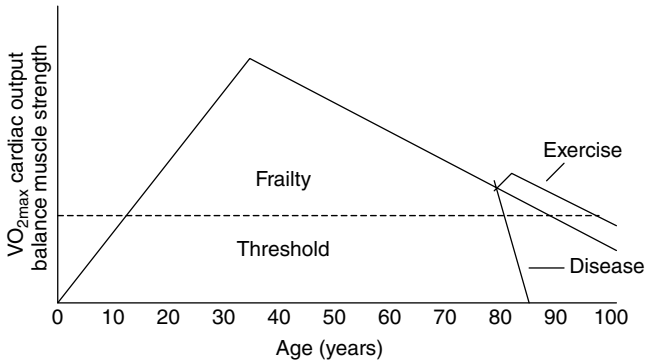

Figure 2 The frailty threshold

Pain

Joint pain, that is, the arthritides, is classically associated with immobility. Immobility, over time, leads to loss of muscle mass and power and to a decline in endurance, the hallmarks of frailty. Pain can further induce frailty secondarily to increasing depression in older persons.

Decreased Food Intake

Older persons develop a physiological anorexia of aging that is associated with a loss of weight. The causes of the anorexia of aging are multifactorial (Morley, 1997). Social causes, such as isolation and dysphoria, and the decline in smell and increase in taste threshold are obvious causes. Recently, there have been a number of studies that demonstrated

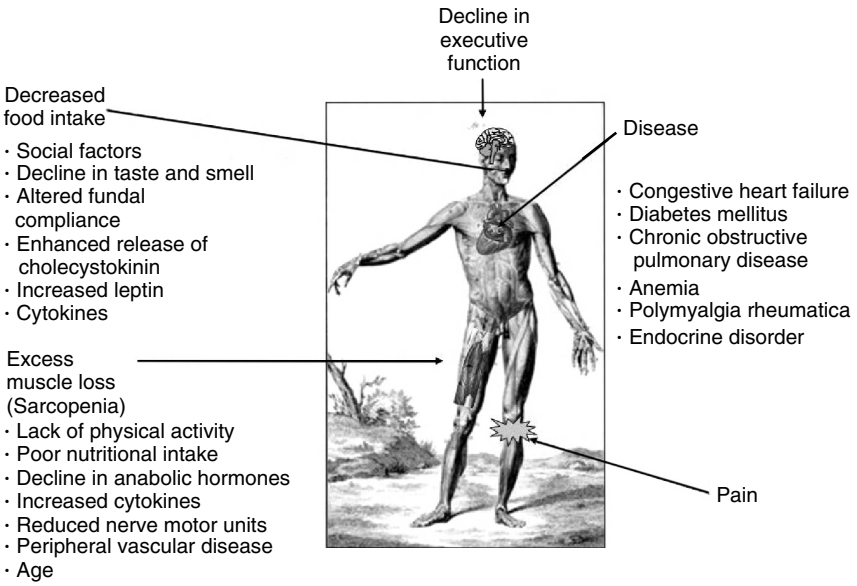

Figure 3 The major causes of frailty

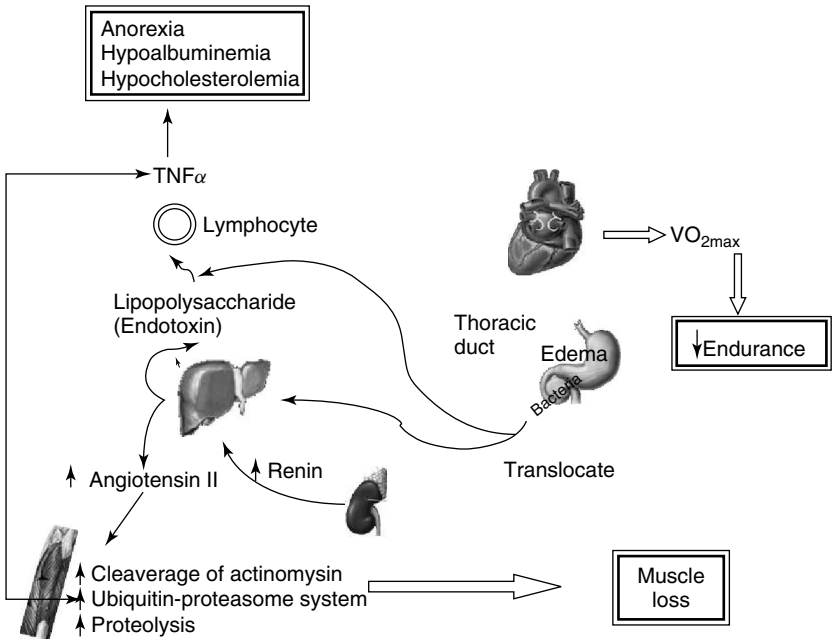

Figure 4 The pathogenesis of frailty in congestive heart failure

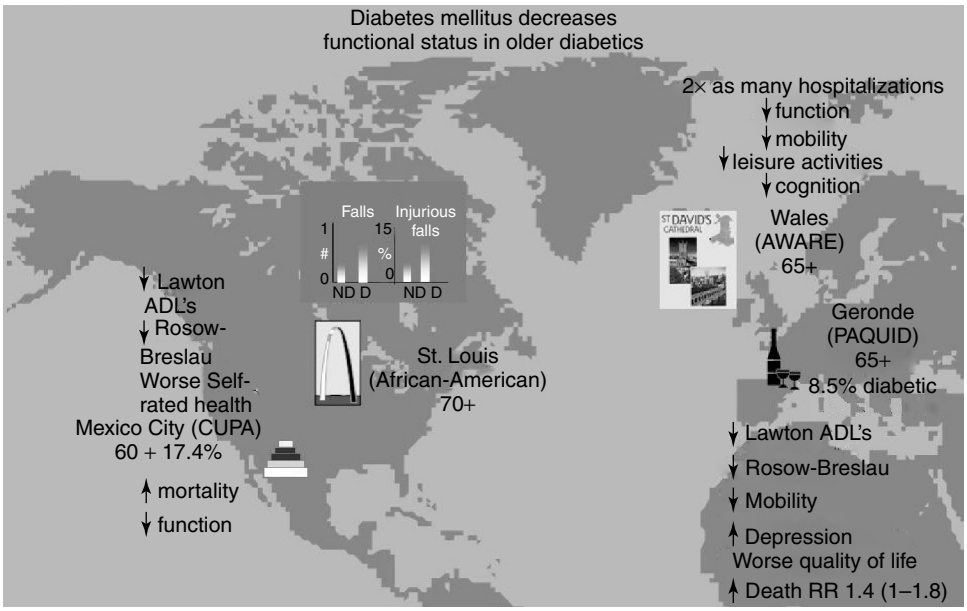

Figure 5 Frailty and diabetes mellitus

that decreased compliance and adaptive relaxation of the stomach results in a more rapid antral filling and early satiety. Excess production of cholecystokinen from the duodenum in response to a fatty meal is another cause of anorexia in older persons. High circulating cytokine levels in older persons have been associated with anorexia. Males have a greater decrease in both absolute and relative amounts of food intake over the life span. This appears to be due to the fall in testosterone, which results in an increase in leptin levels and, therefore, a greater anorexia.

In addition to the physiological anorexia of aging, many reversible causes of anorexia occur in older persons. These are easily remembered by the mnemonic, MEALS-ON-WHEELS (Table 2).

Sarcopenia

Sarcopenia is the excessive loss of muscle mass that occurs in older persons (Morley *et al.*, 2001; Roubenoff, 2003). It

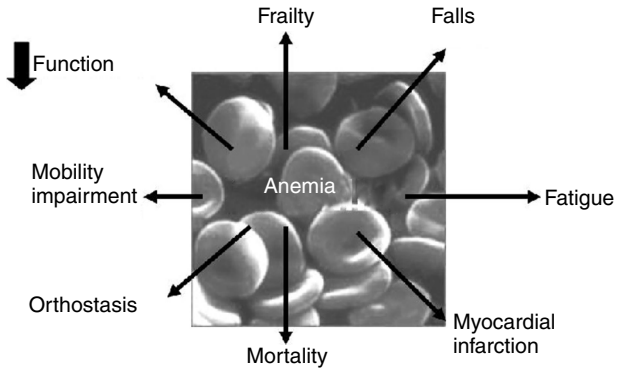

Figure 6 Frailty and anemia

Table 2 MEALS-ON-WHEELS mnemonic for treatable causes of weight loss

Medications (e.g. digoxin, theophylline, cimetidine)
Emotional (e.g. depression)
Alcoholism, elder abuse, anorexia tardive
Late-life paranoia
Swallowing problems
Oral factors
Nosocomial infections (e.g. tuberculosis)
Wandering and other dementia related factors
Hyperthyroidism, hypercalcemia, hypoadrenalism
Enteral problems (e.g. gluten enteropathy)
Eating problems
Low salt, low cholesterol, and other therapeutic diets
Stones (cholecystitis)

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is usually defined as a greater than two standard deviations amount of lean tissue compared to that of younger persons. It occurs in 13–24% of persons aged 60–70 years and in about 50% over 80 years of age. The best measure of sarcopenia is based on the appendicular skeletal mass as measured by DEXA, divided by the height in meters squared. It can also be calculated using magnetic resonance imaging (MRI), computed tomography, or bioelectrical impedance. DEXA and MRI measures are highly correlated. Sarcopenia is strongly correlated with disability. Most sarcopenic individuals have lost fat as well. However, a subset of individuals remain fat while losing muscle mass. These individuals have been characterized as the "sarcopenic obese" or the "fat frail". Longitudinally, those with obese sarcopenia have been found to be the most likely to develop future disability and mortality (Baumgartner *et al.*, 2004). Myosteatosis – the infiltration of fat into muscle – appears to be a separate condition related to insulin resistance. Mitochondrial failure or elevated circulating triglycerides lead to accumulation of triglycerides within the cell. This alters the function of the insulin receptor substrate and, therefore, the GLUT transporter, leading to insulin resistance.

The development of sarcopenia and its effect on frailty have been characterized in the worm *Caenorhabditis elegans*. In *C. elegans*, muscle deterioration (sarcopenia) with aging leads to a decline in body movement. The muscle deterioration also correlates with behavior deficits (a frailty equivalent). These changes rarely correlated with a decreased life span. Mutations in daf-2 (the worm's IGF-1) delay these changes.

There is evidence that sarcopenia originates at birth. In the Hertfordshire cohort study, it has been shown that grip strength correlates with birth weight. Genetic studies have shown that persons with a single I or double I allele for angiotensin-converting enzyme appear to be able to generate more power when exercising regularly than those with D allele. Epidemiological studies have suggested that the best predictors of muscle mass and strength in older persons are age, energy intake, physical activity, IGF-1, testosterone, and cytokines (Baumgartner *et al.*, 1999).

Testosterone levels decline at the rate of 1% per year from the age of 30 years in men and rapidly between 20 and 40 years in women (Morley, 1997; Harman *et al.*, 2001). Testosterone inhibits the movement of pluripotential stem cells into the fat cell lineage and stimulates the muscle cell lineage to result in the production of satellite cells. Satellite cells are essential for the repair of skeletal muscle (Bhasin, 2003). Testosterone also stimulates muscle protein synthesis and inhibits the ubiquitin-proteasome pathway, resulting in a decrease in muscle protein turnover. Testosterone replacement, even in nonhypogonadal males, increases muscle mass (Wittert *et al.*, 2003). Pharmacological doses of testosterone or testosterone replacement in hypogonadal males lead to an increase in muscle strength and muscle power (Matsumoto, 2002). These changes have now been shown to lead to functional improvement. However, there is a small amount of evidence that testosterone has similar effects in older women.

A number of selective androgen receptor molecules (SARMs) are being developed, in an attempt to find androgenic compounds that have a specific effect on muscle but are less likely to produce side effects (Table 3). Dehydroepiandrosterone (DHEA), a weak androgen, failed to produce an effect on muscle strength or muscle mass when given at 50 mg daily for a year to 288 men and women.

Another anabolic hormone, growth hormone, increases muscle mass but not strength in older persons (Harman and Blackman, 2004). The effect of growth hormone is predominantly on type-II muscle fibers. Ghrelin, a growth hormone secretagogue produced in the fundus of the stomach, also appears to increase muscle mass.

Insulin growth factor (IGF) is produced in three alternative forms in muscle. One of these forms, a mechanogrowth

Table 3 Selective androgen receptor molecules

Steroids
Nandrolone
Oxymethalone
Oxandrolone
Nonsteroidal
2-Quinoline
Coumarin
Phthalimide
Bicalcutamide
Acetothiolutamide

factor (MGF) is produced in response to mechanical overload (McKoy *et al.*, 1999). The ability of MGF to be produced in response to mechanical overload declines with aging. Resistance exercise increases MGF in human quadriceps, and this increase is greater when growth hormone is also given. IGF enhances satellite cell production. Localized IGF transgene expression sustains hypertrophy and regeneration of senescent skeletal muscle (Musaro *et al.*, 2001).

Myostatin D inhibits muscle growth. A double deletion of myostatin D in mice leads to muscle hypertrophy, a veritable "mighty mouse". Double deletions of myostatin D in cows and in a single human result in marked muscle hypertrophy (Schuelke *et al.*, 2004).

Motor unit functioning is essential for the maintenance of muscle function. Motor unit firing rate is significantly decreased in the old-old, that is, those over 80 years of age. Ciliary neurotrophic factor (CNTF) levels decline with age and this decline correlates with the decrease in muscle strength with aging. Administration of CNTF leads to twofold increase in soleus muscle size.

Cytokines are soluble peptide messengers that are synthesized by white cells, neuronal cells, and adipocytes. Excess of tumor necrosis-α and interleukin-6 leads to loss of muscle strength. High levels of C-reactive protein and interleukin-6 are associated with a decrease in handgrip strength and in physical performance (Cesari *et al.*, 2004b).

Elevated homocysteine levels and peripheral vascular disease lead to poor blood flow to muscles, with muscle atrophy and decreased function. Creatine is an essential amino acid for muscle. Creatine, together with exercise, may improve muscle performance in older persons.

In the end, the development of sarcopenia depends on an imbalance of the normal everyday renewal cycle of muscle. There is either an excess of atrophy and apoptosis or a diminution of hypertrophy and satellite cell production. Figure 7 provides a schematic view of the biochemistry of sarcopenia.

CONCLUSION

Frailty is a predisability state. It is best defined objectively by the criteria developed by Linda Fried and her colleagues at John's Hopkins University. The causes of frailty are multifactorial. Frailty can have a single cause, such as anemia. Reversal of the anemia with iron, folate, vitamin B12 or erythopoetin will, in this case, reverse frailty. In

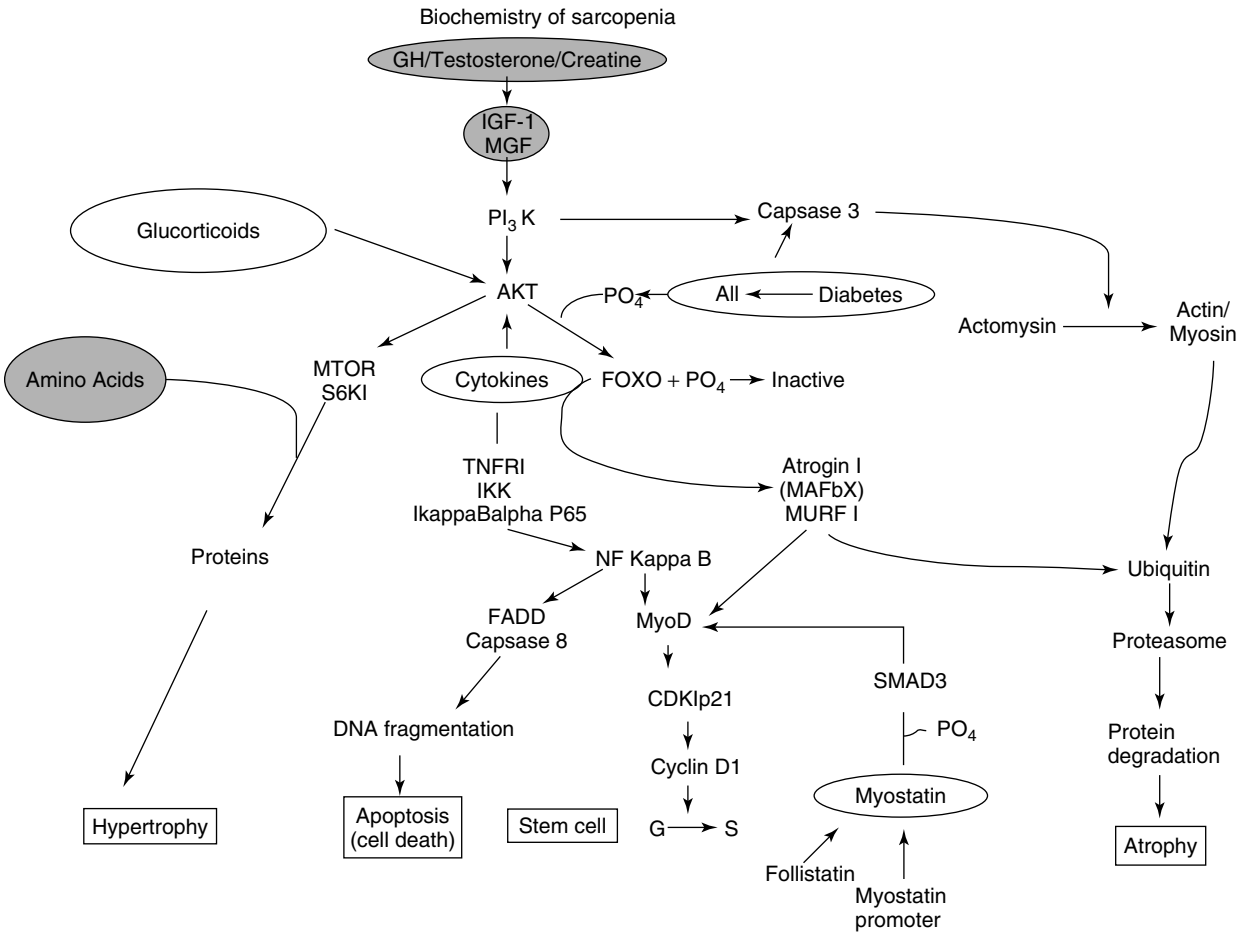

Figure 7 Schematic view of the biochemistry of sarcopenia

Table 4 Preventive strategies to slow the onset of frailty

Food intake maintained
Resistance exercises
Atherosclerosis prevention
Isolation avoidance
Limit pain
Tai Chi or other balance exercises
Yearly check for testosterone deficiency

other cases, frailty is due to the interplay of hormones and cytokines with disease processes and poor-quality nutritional intake. In these cases, the management of frailty requires a careful assessment of the causative factors and a multifaceted treatment regimen. One approach to the preventive strategies necessary to slow the onset of frailty is given in Table 4.

KEY POINTS

- Frailty is predisability and can be objectively defined by the Fried criteria.
- Frail persons are precipitated into disability by experiencing a stressful event.
- Causes of frailty include chronic diseases, pain, poor-quality nutritional intake, impaired executive function, and sarcopenia.
- The interplay of hormones and cytokines is an important determinant of frailty.

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Rehabilitation

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INTRODUCTION

The human and economic consequences of avoidable dependency in older people are indeed great. Sixty years ago, Marjorie Warren identified this reality in her short but powerful paper describing the "proper care and rehabilitation of older persons" (Warren, 1946). She emphasized the need to help elderly people regain their best possible functional independence, the primary elements of which are mobility and self-care without assistance.

Older people who typically benefit from rehabilitation will have had a disabling event of recent onset. This is commonly an age-related event such as a stroke, hip fracture, other fall-related injury or deconditioning, following a major medical or surgical illness. Many elderly people will have ongoing limitations from other diseases such as osteoarthritis or Parkinson's disease.

Rehabilitation of older persons differs from that in the young. There is less physiological reserve with which to combat a disabling insult, so that recovery is typically prolonged and, at its conclusion, the previous state of function and health is often not fully regained. The specific diseases to which elderly people are susceptible are extensively described throughout this textbook. This chapter focuses on the process of optimizing recovery from the major disabling diseases of old age and on strategies for adaptation to their long-term sequelae.

TERMINOLOGY AND CLASSIFICATIONS

For many years, the World Health Organization (WHO) has sought to apply various classification systems to aspects of health and disease, most notably through its International Classification of Disease, now in its tenth revision (ICD-10) (World Health Organization, 1992–1994). Such systems provide a unified and standard language and framework for the description of health and health-related states across geographical boundaries, disciplines, and sciences.

To complement the ICD, WHO introduced its International Classification of Impairments, Disabilities, and Handicaps (ICIDH) in 1980 (World Health Organization, 1980). This stated that any illness could be considered at three levels: impairment, disability, and handicap. In simple terms, *impairment* refers to the pathological process affecting the person, *disability* to the resulting loss of function, and *handicap* to any consequent reduction in that individual's role in society.

The ICIDH had significant limitations, including the use of pejorative terms that emphasized the negative consequences of ill health and also insufficiently recognized its social and societal dimensions. Consequently, in 2001, WHO produced a revised classification known as the *International Classification of Functioning, Disability and Health* (ICF), which challenged traditional views on health and disability and allowed positive experiences to be described (World Health Organization, 2001). The ICF provides a mechanism to document the impact of the social and physical environment on a person's functioning.

The International Classification of Functioning, Disability and Health has the following two *parts*, each with two *components*:

Part 1. Functioning and Disability
- (a) Body Functions and Structures
- (b) Activities and Participation

Part 2. Contextual Factors
- (c) Environmental Factors
- (d) Personal Factors

The classification structure further divides each component into various *domains* and each domain into a number of *categories*, which form the units of classification.

The ICF provides the following definitions:

Impairment: problems in body function or structure such as a significant deviation or loss.

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Activity: the execution of a task or action by an individual.

Activity limitations: difficulties an individual might have in executing activities.

Participation: involvement in a life situation.

Participation restrictions: problems an individual may experience in involvement in life situations.

Environmental factors: the physical, social, and attitudinal environment in which people live and conduct their lives.

Components of the ICF can be expressed in both positive and negative terms. Thus, *functioning* is an umbrella term for all body functions, activities, and participation, while *disability* is a collective term for impairments, activity limitations, or participation restrictions.

As illustrated by Figure 1, an individual's functioning is a result of a complex interaction between the health condition and contextual factors (i.e. environmental and personal factors). The interaction between these is highly dynamic such that any intervention in one area is likely to impact the other, perhaps in ways that are not easily predictable.

As an example, consider an individual with Parkinson's disease. The impairment (problems in body function or structure) is described elsewhere in this text. As a consequence, the person may have a number of activity limitations such as difficulty with personal care and mobility. In turn, the person cannot pursue former hobbies and interests (participation restriction). These restrictions are exacerbated by the fact that the person is widowed and lives alone in a first floor apartment. Now, suppose that she falls on the stairs and fractures her hip. This new impairment causes her to lose confidence and further restrictions in activity and participation result. She becomes even more isolated, withdrawn, and depressed; the feedback loops illustrated in Figure 1 indicate how vicious circles can develop with the person's level of activity and participation continuously deteriorating.

Simply stated, rehabilitation is a process that seeks to minimize activity and participation restrictions resulting from impairment. Many and more comprehensive definitions exist; perhaps the most widely accepted is the UN definition (United Nations, 2003):

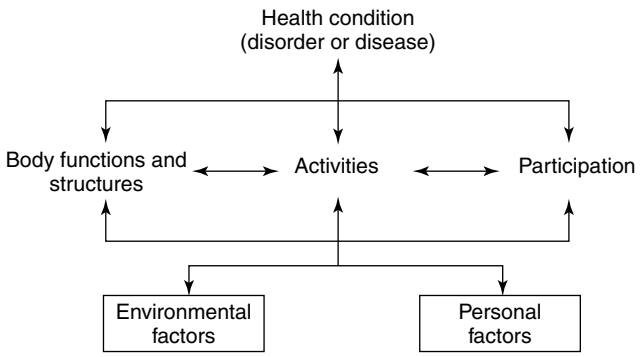

Figure 1 The complex interaction between health status, activity, and participation

> Rehabilitation means a goal-orientated and time-limited process aimed at enabling an impaired person to reach an optimum mental, physical and/or social functional level, thus providing him or her with the tools to change his or her own life. It can involve measures intended to compensate for a loss of function or a functional limitation (for example the use of technical aids) and other measures intended to facilitate social adjustment or readjustment.

Figure 1 also illustrates how rehabilitation programs can impact at various points in the impairment-activity-participation cycle. Not only can they prevent the progression of impairment to activity restriction and of activity restriction to participation restriction, they can also prevent further impairments and the development of vicious circles.

The Determinants of Activity and Participation Restrictions

As summarized in Table 1, a number of factors determine the extent to which activity and participation restrictions result from a given impairment. The type of impairment is clearly of paramount importance, with some diseases being inherently more likely to cause restrictions than others. The site of the lesion is also important as is well illustrated by stroke disease, where relatively large lesions in some parts of the brain may be relatively asymptomatic while much smaller lesions in strategic areas may cause major problems.

Elderly patients often have a number of coexisting impairments contributing to activity and participation restrictions (Figure 2). The rehabilitation program can be influenced as much by the existing as by the new impairments.

Elderly people have less physiological reserves. The aging process is characterized by a gradual functional decline in most bodily systems – a phenomenon that is relatively unimportant when organs and physiological systems are "at rest" but is most relevant when they are placed under stress by a disabling illness or event.

It must be emphasized that even very old people have the capacity to recover from such major events, and failure to make progress at rehabilitation can seldom be attributed to a lack of physiological reserve alone. Of far greater

Table 1 Determinants of activity and participation restrictions

Determinants of activity restriction
Type of impairment (nature and severity of the disease process)
Presence of associated impairments
Degree of physiological reserve
Level of physical fitness
Determinants of participation restriction
Intrinsic factors
Attitude
Personality
Ability to adjust
Cultural issues
Extrinsic factors
Financial resources
Housing
Other resources
Social supports (spouse, family, neighbors, friends, pets)

Figure 2 A 76-year old man with osteoarthritis who is undergoing rehabilitation following a right total knee replacement. He had a left above-knee amputation some years previously because of peripheral vascular disease, and this greatly impacts on the rehabilitation process

importance is the lack of activity and physical fitness that typifies elderly people in modern societies (Finucane *et al.*, 1997). Many of today's older people grew up in an era when exercise was not encouraged and sports and recreation facilities were relatively inaccessible. An age-related decline in muscle mass (sarcopenia) and strength is aggravated by physical inactivity (Castille *et al.*, 2003), and numerous studies have shown an association between sarcopenia and activity restriction (Janssen *et al.*, 2002). Weight training increases muscle strength in older people and has a positive effect on some functional limitations (Lathan *et al.*, 2004). Although little research has been done on the relationship between physical fitness and the ability to overcome impairment, it is probable that those who are unfit have a worse outcome from rehabilitation.

The degree of participation restriction resulting from activity restriction is influenced by a variety of intrinsic and extrinsic factors (Table 1). Intrinsic factors include the person's attitude in adjusting to activity restriction. A person who suffers a functional loss typically goes through a grief reaction similar to that seen following bereavement. Some people demonstrate better coping strategies than others. They are more positive in their approach, assume greater control of their situation, and find adaptive solutions to problems more readily. The psychological aspects of rehabilitation are discussed in more detail later in this chapter.

Extrinsic factors that impact participation include the resources and supports at one's disposal in dealing with activity restriction. In societies where public health care and welfare systems are poorly developed, personal finance is required for the many components of a rehabilitation program. These include the provision of physical therapy, prosthetic devices, home modification, and ongoing care. Of even greater importance are the social supports on which the person can rely on at all stages of the rehabilitation program, and particularly upon returning to their usual environment. In this regard, elderly people are often disadvantaged, with many females in particular, being widowed and living alone. In Australia, for example, 20% of people aged 65 years and over and 27% of elderly people with activity restriction live alone (Australian Bureau of Statistics, 1998). In recent decades, other demographic trends, such as the disappearance of the nuclear family and recruitment of the traditional informal carers, especially women, into paid employment have increased the social isolation and reduced the supports available to elderly people.

Psychological Aspects of Rehabilitation

The onset of impairment, particularly if unexpected or catastrophic, is generally associated with some emotional disturbance. Expected feelings include a sense of loss with regard to one's physical or mental faculties, to relationships with others or to inanimate objects such as one's home or other possessions. Normally, a grief reaction occurs with phases of denial, anger, and depression leading to a degree of acceptance sufficient to allow a relatively normal life to be resumed. However, adjustment to impairment is sometimes abnormal. For example, over 40% of older people with acute myocardial infarction have depressive symptoms, and this adversely affects the prognosis (Shiotani *et al.*, 2002). High levels of depression have also been found following stroke (Burvill *et al.*, 1995; Mast *et al.*, 2004), despite participation in a rehabilitation program (Young and Forster, 1992).

The manner in which people adapt to impairment greatly influences the development of activity and participation restriction. Some people appear inherently more adaptable and optimistic than others when faced with a potentially adverse situation. At one end of the spectrum are "highly motivated" people who set ambitious goals and work hard at achieving them. At the other end are those who appear to submit to their impairment, disengage, surrender power and autonomy, and adopt a "sick role".

Psychological theories exist to explain such different responses. An excellent model based on behaviorist concepts

has been proposed by Kemp (1988), who contends that motivation is a dynamic process driven by four elements: the individual's wants; beliefs; the rewards to achievement; and the cost to the patient. The first three elements drive motivation in one direction, and this is counteracted by the cost of the behavior in terms of pain and effort. Thus, if a person really wants something, believes it to be attainable and potentially rewarding, he will strive to achieve it, provided the cost is acceptable. On the other hand, a goal is unlikely to be achieved if it is not strongly desired, if the person believes that it cannot be attained, if there is little reward for achieving it or if the actual or perceived cost of striving for the goal is too great. Using this framework, the rehabilitation specialist can help individuals in a number of ways, including setting goals, challenging incorrect beliefs, establishing rewards, and minimizing the physical and mental cost of the rehabilitation process (cf. section on Psychosocial Support).

THE PRINCIPLES OF REHABILITATION

The principles of rehabilitation are broadly similar irrespective of the problem with which one is dealing and the environment in which one is working. *Early intervention* is crucial, as much avoidable activity and participation restriction can occur soon after the onset of impairment. Certain problems should be anticipated and avoided, as once they have occurred, they may be irremediable. For example, a person with a flaccid hemiplegia is at risk of shoulder subluxation and its long-term sequelae. Proper handling and limb positioning in the immediate post-stroke period can minimize this risk.

Another key principle is the need for a *team approach*. A properly resourced team will include input from medical and nursing staff, physiotherapists, occupational therapists, speech pathologists, clinical psychologists, dietitians, and social workers. The particular expertise of different team members is complementary. Medical staff are primarily concerned with the assessment and management of impairment. Remedial therapists have particular skills in dealing with activity restriction. Social workers are best equipped to deal with participation restriction. Nursing staff in particular have a holistic brief with areas of expertise capable of influencing both activity and participation restriction.

To function effectively, team members need to communicate. When they are colocated (e.g. in a designated rehabilitation unit), exchange of information tends to occur regularly and informally. Most teams also have regular formal meetings to discuss the progress of individual patients, to revise goals, plan discharge, and organize follow-up in the community.

THE REHABILITATION PROCESS

A number of steps (see Table 2) are identifiable. While these steps are presented in chronological sequence, in practice, there is considerable overlap between the elements, many of which take place concurrently and some of which need to be regularly revisited. For example, while the assessment of a patient's impairment, activity, and participation restriction is an important initial step, this needs to be repeated frequently (at least weekly) as the rehabilitation program proceeds.

Table 2 Steps in the rehabilitation process

1. Assessment
2. Setting goals
3. Physical therapy
4. Aids and adaptations
5. Education
6. Psychological support
7. Evaluation
8. Follow-up

Assessment

It is essential that patients be assessed before entry into a rehabilitation program to ensure that their problems are remediable and to determine the optimal way of managing them. The selection of patients for rehabilitation is sometimes difficult. On the one hand, it is unfair to subject a person who will not benefit from a demanding rehabilitation program and, in the process, raise false expectations and waste resources. On the other hand, those who can benefit even to a limited extent should not be denied access to rehabilitation.

Assessment should focus on both the problem in the individual as well as the individual with the problem. The nature and severity of all impairments, whether new or long-standing, should be determined. It is essential to obtain a baseline measure of the person's performance status, so that subsequent progress can be monitored and the efficacy of rehabilitation reviewed. A variety of assessment tools are available, ranging from simple subjective measures to objective measures that tend to be more complex and time consuming. The choice of the measure to use will depend on the clinical context. Busy clinicians can usually acquire a reasonable understanding of the extent of activity and participation restriction by asking a few simple questions and by making some equally simple observations. Detailed assessment of activity restriction using standardized scales is generally left to remedial therapists, while social workers have the necessary knowledge and expertise to optimally assess participation restriction.

Assessment of Activity and Activity Restriction

Assessment begins with the clinical history. For the person who has suffered a recent impairment, it is important to determine the premorbid as well as the current functional status. A common approach is to focus on activities of daily living (ADLs). These are classified as items of personal care (e.g. washing, grooming, dressing, using toilet, eating, etc.) and those involving the use of "instruments" – hence

known as *instrumental ADLs* (IADLs). The latter include such tasks as preparing meals, using the telephone, doing laundry and other housework, gardening, shopping, and using public transport. If difficulty is reported with any of these tasks, it is important to determine how the person manages. Are these tasks neglected or do others provide help?

A more formal, objective, and standardized assessment of activity restriction is generally required, particularly when patients are entering a rehabilitation program. A plethora of assessment scales and measures exist and the strengths and weaknesses of the major ones have been described (Barer, 1993). As yet, there is no consensus on the best assessment scales to use, and this lack of uniformity inhibits comparative research. A model drawn from the education literature explains the difficulty in reaching such a consensus (van der Vluten, 1996).

The model in question contends that the utility (U) of any assessment tool is governed by the formula:

$$U = V \times R \times A \times C$$

where V = validity; R = reliability; A = acceptability; and C = cost. While the ideal tool will score highly in the first three areas and be low on cost, in practice, assessment tools with high validity and reliability tend to be costly (i.e. resource intensive) and to have low acceptability (e.g. due to their intrusive nature). The converse is equally true; tools that are acceptable and easy to administer tend to have low validity and reliability. The multiplication factor in the equation is important, because if any one element of the equation measures zero or close to zero, then the overall utility of the assessment tool will also be zero or close to it. As a rule, therefore, the utility of any assessment tool is a trade-off between these elements.

Despite these considerations, the United Kingdom's Royal College of Physicians and British Geriatrics Society jointly endorse a number of standardized functional assessment scales for elderly patients, all of which have stood the test of time (Table 3). Collectively, these assess the following domains: ADLs, vision, hearing, communication, cognitive function and memory, depression, and quality of life (Royal College of Physicians and British Geriatrics Society Joint Workshops, 1992).

The use of assessment scales such as these facilitates the exchange of information between acute-care facilities, rehabilitation units, and community-based health-care teams. Standardized functional assessments also allow the effectiveness of rehabilitation to be measured. This is an essential preliminary step in allowing comparisons of different approaches to treatment in large randomized multicenter trials. Standardized assessment can also help to minimize the repeated questioning and examination that tends to characterize the multidisciplinary approach to rehabilitation.

Other assessment scales deserve special consideration. Neurodegenerative disorders are common in older patients, and Wade has provided a valuable reference for commonly used assessment measures in neurological rehabilitation (Wade, 1992). The drive toward output-driven health funding in many countries has stimulated the development of outcome measures in medical rehabilitation. The Functional Independence Measure (FIM) is used in many countries, most notably the United States, to rate patient progress in a rehabilitation setting against 18 common functions concerning self-care, sphincter control, mobility, locomotion, communication, and social cognition (Keith *et al.*, 1987). The Uniform Data System for Medical Rehabilitation (UDSMR) was established to implement the FIM and to evaluate those centers that use it. Attempts have been made to use the aggregated data to identify the most effective and efficient aspects of rehabilitation programs (Johnston *et al.*, 2003). A useful review of the value of output-based research in medical rehabilitation is available (Wilkerson and Johnston, 1997).

Table 3 Standardized functional assessment scales for elderly patients

Domain assessed	Recommended scale	Comments
Basic ADL	Barthel Index (Mahoney and Barthel, 1965; Collin *et al.*, 1988)	Observation of what the patient *does*. Maximum of 20 points (Royal College of Physicians and British Geriatrics Society Joint Workshops, 1992). Ceiling effect in ambulatory patients.
Vision, hearing, communication	Lambeth Disability Screening Questionnaire (Peach *et al.*, 1980)	Postal questionnaire
Memory and cognitive function	AMT (Hodkinson, 1972)	10 questions from longer Roth-Hopkins test. Can be shortened by dropping some time-related questions (Jitapunkul *et al.*, 1991)
Depression	Geriatric Depression Scale (Yesavage *et al.*, 1983)	Screening test with 30 questions; 15 questions in short form (Yesavage, 1988)
Subjective morale	Philadelphia Geriatric Center Morale Scale (Davies and Challis, 1986)	Distinct from depression, although some overlap

ADL, activities of daily living; AMT, Abbreviated Mental Test.
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Assessment of Participation and Participation Restriction

As individuals uniquely interact with their environment, any reduced role in society (participation restriction) that results from activity restriction will be unique to the individual. Furthermore, it is possible for somebody to develop major participation restriction in one area and have little or no restriction in another. Thus, the person who loses mobility following a lower limb amputation may have to give up playing golf but can continue to drive a car. As explained earlier, the level of participation restriction is mainly determined by one's ability to adapt to activity restriction. Some people largely fail to adapt, while in others the onset of activity restriction prompts a redefinition rather than loss of their

social role. Potential losses in one area may be offset by gains elsewhere and, thereby, participation restriction may be minimal. Some people even claim that their lives have been enriched as a consequence of impairment and activity restriction.

It follows that an assessment of participation restriction can only be obtained from gaining an in-depth understanding of the individual and the manner in which he or she has come to terms with activity restriction. Such measurements are always subjective. They are also unstable over time and can be influenced by psychobehavioral variables such as mood. For these reasons, the assessment of participation restriction is largely neglected in both clinical and research settings.

Goal Setting

Assessment should culminate in the setting of rehabilitation goals. To avoid frustration and disappointment, goals should be realistic and take account of the individual's impairment and premorbid functional status. It is sometimes appropriate to set modest goals, such as helping an amputee patient to become wheelchair-independent rather than to walk. It is essential that all multidisciplinary team members, and particularly the patient, are involved in setting goals and that there is general agreement on the targets set (Wade, 1998). A rehabilitation program can be doomed from the outset if key people differ on what each is trying to achieve. Significant areas of conflict should therefore be identified, analyzed, and resolved at this early stage. In our experience, conflict in this situation usually arises when the patient's targets are considered to be unrealistically high by health professionals. However, there is some evidence to suggest that patients with ambitious goals make greater progress than those with more modest targets (Guthrie and Harvey, 1994). The pragmatic approach therefore is to set goals that are ambitious but achievable.

Short-term (intermediate) as well as long-term (final) goals should be identified. In the context of rehabilitation, as elsewhere in life, achieving a succession of intermediate goals is often the best way to arrive at the final goal. Setting realistic time frames within which to achieve goals is part of the process. The rate of progress at rehabilitation is often difficult to predict, particularly at the time of entry to a program. The goals to be achieved and the time frame within which to achieve them should therefore be flexible, regularly reviewed, and modified if necessary. Again, it is essential that all concerned be involved in the revision of goals and that consensus be reached.

Physical Therapy

A detailed description of the role of the various multidisciplinary rehabilitation team members is outside the scope of this chapter. In brief, medical staff concentrate on the identification and management of the presenting problem and any coexisting impairments. Underlying risk factors should be identified and minimized; potential complications should be anticipated and prevented. Thus, in an arteriopath who has had an embolic stroke, doctors have a role in monitoring anticoagulation, controlling hypertension, and managing coexisting angina pectoris and diabetes mellitus. Occupational therapists assess ability to manage ADLs and to devise strategies to overcome any identified problems. Physiotherapists plan and implement therapies that target specific problems and enhance cardiorespiratory, neuromuscular, and locomotor functions. Speech pathologists have skills in dealing with communication problems and swallowing disorders. In specific situations, input from other health professionals (e.g. podiatrists, dietitians) may be invaluable.

Aids and Adaptations

The use of aids has the potential to reduce activity and participation restriction for many impaired people. Devices range from the simple and inexpensive to the technologically advanced. They help people in diverse ways, from carrying out ADLs to the maintenance of mobility and the management of incontinence. The appropriate use of the most commonly used aids has been well described by Mulley (1989). It should be emphasized that the provision of an aid is not always the correct option for a restricted elderly person as its inappropriate use can cause dependence rather than promote independence. However, those in genuine need often do not avail of even basic and relatively inexpensive aids and appliances (Edwards and Jones, 1998).

Advice on the suitability of aids is best left to occupational therapists or others with particular expertise. Physiotherapists can advise on the selection of mobility aids, speech therapists on communication aids, audiologists on hearing aids, and continence advisors on continence aids. Such people can also provide follow-up and ensure that aids are properly used and maintained and continue to serve their purpose.

Special mention should be made of prostheses (devices that replace body parts) and orthoses (devices applied to the external surface of the body to provide support, improve function, or restrict or promote movement). Their design and construction require particular skill and access to increasingly sophisticated technology. Well-resourced rehabilitation centers will either employ or have access to prosthetists and orthotists who form part of the multidisciplinary team.

Adapting to the environment in which the person normally functions also promotes activity and participation. Home modifications include the installation of simple handrails or ramps, or improving access to shower and toilet areas. Early input from an occupational therapist, often including a home visit, ensures that modifications are appropriate and available at the time of discharge from hospital.

Education and Secondary Prevention

Education is a vital component of rehabilitation, as through it the patient acquires the knowledge, skills, and attitudes

to minimize the activity and participation restrictions that can result from impairment. Modern concepts of adult learning emphasize the central role of the student in any learning situation and the need for active (rather than passive) participation. When applying such principles to the rehabilitation setting, the unique educational needs (in terms of knowledge, skills, and attitudes) of the individual must first be determined. The central role of the patient in setting the educational agenda needs to be acknowledged. If there is a discrepancy between the person's perceived needs and his or her actual needs as determined by health professionals, a compromise needs to be reached.

Generally, patients will require knowledge about their impairment, its etiology, underlying risk factors, management strategies, and prognosis. Such knowledge helps to foster compliance with treatment regimens and has a beneficial effect on attitudes. The skills that people require will also be highly specific and can range from cognitive skills to the more practical. Educated patients are empowered to take charge of their health and to institute life changes to maintain it and thus facilitate secondary prevention.

Education should be integrated into all stages of the rehabilitation program. Ideally, it occurs informally and each and every contact with a health professional affords an opportunity for education. It is important that rehabilitation team members acknowledge their role as educators, even to the extent of acquiring formal educational skills. Formal educational activities can complement the more informal. These can occur on a one-to-one basis or in a group setting. The format can vary from the distribution of educational literature to didactic presentations and small group discussions. Small group discussions have the added advantage of allowing patients to learn from one another and provide mutual support and encouragement so that the rehabilitation unit functions as a "therapeutic community".

Psychosocial Support

It is important that rehabilitation team members have at least a basic understanding of those common psychological issues that impact the rehabilitation process. These include the physiology of grief and loss and the psychology of motivation. Practical skills are also required in helping patients adjust to their loss, mentally as well as physically. The first step is to get to know and understand the patient, and especially his or her beliefs, goals, and fears. This calls for good communication skills and particularly good listening skills. Many people fear the unknown, and informing them about their condition and the rehabilitation process helps to reduce anxiety. Some people will be as concerned about potential future problems (e.g. the risk of a further stroke) as about the immediate one. If such concerns do not surface spontaneously, they should be sought and dealt with.

Psychological support can be provided simply and effectively through reassurance and positive feedback. Patients may need reassurance regularly and from different team members. There is also a need to maintain a consistently positive approach both to patients and to their progress at rehabilitation; there is much anecdotal evidence on the way in which a careless negative remark from a health professional can profoundly demoralize a patient. Demonstrating respect for a patient as an individual fosters feelings of self-worth and enhances motivation. However, attempts at providing positive feedback should never lead to dishonesty or insincerity and care must be taken not to generate false expectations.

The need for psychological support in the patient's spouse and other relatives should not be forgotten. Usually, such people will also be powerful providers of support. In a hospital-based rehabilitation setting, patients can offer each other support and encouragement – the so-called "therapeutic community". The formation of self-help groups is particularly useful in providing ongoing psychological and practical support once the patient is discharged from the rehabilitation program.

Discharge Planning and Follow-up

Discharge from an in-hospital rehabilitation program should signal a transition in the process rather than its conclusion. Many patients will benefit from continuing outpatient rehabilitation aimed at either achieving further gains or preventing the loss of those gains already made. Arrangements for aftercare will vary according to the needs of the individual and the availability of services. At the very least, it is important that the patient be followed up so that any exacerbation of activity or participation restriction can be evaluated and, if possible, remedied.

Evaluation

Rehabilitation programs are costly in terms of both money and manpower resources. Efforts should therefore be made to demonstrate their effectiveness. This involves the collection of data that compares people on entry to and discharge from the program. Data collection is becoming increasingly standardized and this allows comparison to be made between facilities and between different treatment strategies. Such research, which has formerly been relatively neglected, is now coming of age. It holds promise that we will not only be able to prove the overall efficacy of rehabilitation programs but also to demonstrate the elements of programs that contribute to their success (Johnston *et al.*, 2003).

THE REHABILITATION SETTING

Rehabilitation can be provided in various settings, including stand-alone rehabilitation hospitals, designated rehabilitation units in general hospitals, undifferentiated hospital wards, nursing homes, and residential care center, day hospitals,

community day centers, outpatient rehabilitation centers, and the patient's own home. Each of these settings has specific advantages and disadvantages, detailed discussion of which is outside the scope of this chapter. Ideally, a range of options should be available to meet the specific needs of the individual patient at a given time.

In larger hospitals, it is usual to colocate patients with similar rehabilitation needs, often resulting from a specific impairment. Thus, for example, Stroke Units and Ortho-geriatric Units have long been in fashion. Such units foster staff expertise and facilitate research, education, and training. Though Stroke Units have been shown to improve survival and functional outcomes (Stroke Unit Trialists' Collaboration, 2001), evidence on the efficacy of Ortho-geriatric Units is less convincing (Cameron *et al.*, 2001).

Community-based rehabilitation has come of age in recent decades as a complement to hospital-based rehabilitation. In practice, community-based rehabilitation only suits a narrow range of patients, generally those from the least disabled end of the spectrum and who are otherwise well supported in the community. "Intermediate care" is a term to describe intensive, short-term, community or home-based rehabilitation that aims to prevent hospitalization, to facilitate early discharge from hospital and/or to maximize independent living (Stevenson and Spencer, 2002).

SPECIFIC REHABILITATION PROBLEMS

Cardiac Rehabilitation

Cardiac rehabilitation is defined as:

> The process by which patients with cardiac disease, in partnership with a multidisciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychological health.
>
> (Scottish Intercollegiate Guidelines Network, 2002)

It has evolved over the past 50 years, since Levine and Lown first recommended early mobilization rather than prolonged bed-rest following myocardial infarction (Levine and Lown, 1952). Initial cardiac rehabilitation programs were exercise-based and aimed at reducing morbidity and mortality following myocardial infarction. Such programs are effective, resulting in a 27% reduction in all-cause mortality (Jolliffe *et al.*, 2001).

Since its inception, the scope of cardiac rehabilitation has expanded to include such problems as ischemic heart disease, cardiac failure, coronary revascularization, and valve replacement surgery. The nature of the intervention has also expanded to include education, psychological support, lifestyle advice, risk factor reduction, and drug therapy (Dalal *et al.*, 2004). Home-based programs now complement those that are hospital-based, and these may particularly suit some elderly people. Outcomes increasingly focus on improved exercise tolerance and quality of life in addition to reduced mortality (Marchionni *et al.*, 2003).

The Scottish Intercollegiate Guidelines Network (SIGN) have produced comprehensive guidelines on cardiac rehabilitation (Scottish Intercollegiate Guidelines Network, 2002), which have been endorsed by the British Association for Cardiac Rehabilitation. These recognize the four phases of rehabilitation outlined in Table 4.

In Phase 1, early mobilization reduces the risk of thromboembolic disease and other problems associated with immobility. Low-level self-care activities can begin shortly after the acute event and then gradually accelerate. Thus, people with an uncomplicated infarct might feed themselves from the outset, sit out of bed within 24 hours and walk to the toilet within 48 hours. Spouses, partners, and other family members are ideally involved from this initial stage and should also be offered reassurance and information.

The early post-discharge period (Phase 2) is a time when many patients and their families are apprehensive and require particular support. Relevant written information and a telephone "help line" are among the strategies used to provide this.

Though Phase 3 revolves around a structured exercise program, this is just one of its elements (Table 4). This phase is increasingly offered in the community rather than in the traditional hospital setting. As described later, the exercise regimen must be adapted to the individual.

Physical activity and lifestyle changes need to be maintained (Phase 4) if the initial benefits of cardiac rehabilitation are to be sustained. In this regard, many people find that involvement in a local cardiac support group and participation in group activities to be invaluable.

A detailed description of the exercise programs suitable for people with cardiac disease is outside the scope of this chapter and is available elsewhere (Scottish Intercollegiate Guidelines Network, 2002). An initial assessment is essential to identify high-risk patients who either need a modified exercise program and/or who need to be carefully monitored. Ideally, this will include a simple test of functional capacity such as a shuttle walking test (Tobin and Thow, 1999) or a six-minute walking test (Demers *et al.*, 2001). Those identified as high-risk need more careful evaluation, perhaps including a comprehensive exercise stress test.

Aerobic, low to moderate intensity exercise is likely to suit the majority of elderly patients in a cardiac rehabilitation program. This is generally undertaken in a group setting and at least twice weekly for a minimum of eight weeks.

Table 4 The four phases of cardiac rehabilitation

1.	The inpatient stage, following an acute cardiac event, includes medical evaluation, reassurance, education and correction of misconceptions, risk factor assessment, mobilization, and discharge planning.
2.	Following hospital discharge, when patients may need physical and psychological support.
3.	Structured exercise training, together with continuing educational and psychological support and advice on risk factor reduction.
4.	Long-term maintenance of physical activity and lifestyle change.

However, weekly hospital-based group exercise, together with a home-based exercise program, can be just as effective.

The intensity of exercise can be monitored either by perceived exertion or by heart rate, as measured with a simple pulse monitor. With the former, the aim is to achieve "comfortable breathlessness". The target heart rate is derived from the maximal heart rate, which, in turn, can be estimated at 220 minus age (in years). A training effect is best seen at 65–80% of maximal heart rate (Kavanagh, 1995). Thus, an 80-year old person would have a target heart rate of 90–110 b.p.m when exercising.

Patients with unstable angina, cardiac valve stenosis or cardiac failure, or with a history of cardiac arrhythmia, are most at risk of an exercise-induced cardiac event. Such patients require a particularly careful evaluation prior to entry into a rehabilitation program and close medical supervision is then essential. For all who exercise, warm-up and cool-down exercises minimize the risk of musculoskeletal injury and cardiac arrhythmia. Extremes of temperature and overexertion should be avoided and exercise should cease immediately if the person feels unwell. All symptoms should be reported and medically assessed.

Access to a formal cardiac rehabilitation program is not always possible and these are particularly unsuited to elderly people with coincidental respiratory, neurological, or musculoskeletal disorders. However, even chair-bound elderly people can benefit from some form of low-intensity exercise following a cardiac event.

As psychosocial factors predispose to heart disease (Hemingway and Marmont, 1999), it is not surprising that they are particularly prevalent following an acute cardiac event. Thus, over 40% of elderly patients have some depressive symptoms following acute myocardial infarction (Shiotani *et al.*, 2002). Psychological distress in the early post-infarction period predicts a subsequent reduction in quality of life (Mayou *et al.*, 2000). Though psychological rehabilitation aims to reduce such distress, evidence of its efficacy is conflicting (Jones and West, 1996; Milani and Lavie, 1998). The key components of psychological rehabilitation are relaxation, stress management, and counseling. The formats for delivery range from individual to group therapy sessions.

The final important element of cardiac rehabilitation is patient education. This should span the entire program and activities can range from the highly structured and formal to the informal and opportunistic. Patients need to understand their disease, its implications, and the prospect of recovery. They also need to know about underlying risk factors and how these can be minimized in the future – that is, secondary prevention. Lifestyle modification should be recommended for those who smoke, are obese, hypertensive, or with lipid abnormalities. As such modifications impact the spouse and other family members, they should be involved in educational activities. The range of educational material and its manner of delivery (e.g. written material, audiotapes, videotapes, Internet material) continue to expand.

Pulmonary Rehabilitation

Pulmonary rehabilitation is defined as:

> An art of medical practice wherein an individually tailored, multidisciplinary program is formulated which through accurate diagnosis, therapy, emotional support and education, stabilizes or reverses both the physio- and psycho pathology of pulmonary disease and attempts to return the patient to the highest possible functional capacity allowed by his pulmonary handicap and overall life situation.
>
> (American College of Chest Physicians and American Association of Cardiovascular and Pulmonary Rehabilitation Guidelines Panel, 1997)

For people with chronic obstructive pulmonary disease (COPD), there is now good evidence that pulmonary rehabilitation substantially reduces dyspnoea and fatigue, enhances patient control of the disease, and modestly increases exercise capacity (Lacasse *et al.*, 2001). Pulmonary rehabilitation also improves health-related quality of life (American College of Chest Physicians and American Association of Cardiovascular and Pulmonary Rehabilitation Guidelines Panel, 1997) and may reduce hospital admissions (Calverley and Walker, 2003). Similar levels of benefit are seen in all adults, including the "old-old" (Katsura *et al.*, 2004), who should therefore be considered for pulmonary rehabilitation (Couser *et al.*, 1995). People with significant chronic lung disease other than COPD (e.g. asthma, interstitial/restrictive lung disease) also benefit from rehabilitation (Foster and Thomas, 1990).

The key elements of pulmonary rehabilitation are summarized in Table 5. An initial assessment allows the rehabilitation program to be tailored to the individual. While clinical and laboratory tests (e.g. radiology, pulmonary function tests) help to define the nature and severity of lung disease, these are unlikely to improve with rehabilitation. Formal exercise testing, together with blood gas analysis (or oximetry)

Table 5 Elements of pulmonary rehabilitation

Assessment
Define the nature and severity of lung disease
Identify continuing risk factors
Identify comorbidities
Assess nutritional status
Check immunization status (especially against *Pneumococcus* and influenza)
Assess lifestyle factors contributing to activity and participation restriction
Exercise test ± blood gas analysis/oximetry ± ECG monitoring
Intervention
Optimize medical management
Exercise program
Breathing exercises
Patient education
Lifestyle and dietary modification
Psychosocial support
Follow-up
Establish benefits of rehabilitation
Assess need for continued rehabilitation

and cardiac monitoring, should be performed at this stage to determine exercise tolerance, the tendency to hypoxia, and the risk of cardiac dysrhythmia. For those who are hypoxic at rest or who desaturate with exertion, a modified exercise program with supplementary oxygen and appropriate monitoring might still be feasible (Roig *et al.*, 2004).

Exercise training is the cornerstone of the rehabilitation process, and both upper and lower limb exercise improve limb strength and exercise tolerance (American College of Chest Physicians and American Association of Cardiovascular and Pulmonary Rehabilitation Guidelines Panel, 1997). Ventilatory muscle training only benefits a minority of patients with COPD. Ideally, exercise should be undertaken three times weekly, should last a minimum of 20 minutes, should induce a heart rate of not less than two-thirds of the maximum expected in the absence of lung disease, and should last at least 6 weeks and preferably 3 months (Clark, 1994).

In most centers, group exercise programs are conducted in outpatient settings. On the basis of the initial assessment already described, a program of graded exercises is provided for each individual, leading to a gradual increase in exercise capacity and tolerance. Exercise protocols for people with mild, moderate, and severe chest disease are available (American Association of Cardiovascular and Pulmonary Rehabilitation, 2004).

Pulmonary rehabilitation includes education to help patients reach a greater understanding of their disease and the factors that may contribute to its progression and retardation (American Association of Cardiovascular and Pulmonary Rehabilitation, 2004). Lifestyle and dietary modifications may be appropriate and people may need practical help to achieve these. Those who smoke, for example, not only need to understand the consequences of this habit and the advisability of stopping, but may also need access to smoking cessation programs. Psychosocial support of the elderly patient with chronic chest disease involves techniques to reduce anxiety and depression. While such techniques are often used, there is no clear evidence of their efficacy (Milani and Lavie, 1998). Participation in a rehabilitation program alone often provides a degree of psychosocial support, especially when this is undertaken in a group setting and where support is maintained following discharge from the rehabilitation program.

The gains achieved through pulmonary rehabilitation are often lost over time unless specific strategies to maintain them are put in place (Spruit *et al.*, 2004). While some form of follow-up is always required, a continuous maintenance program is ideal. In this regard, self-help groups who encourage and support one another have a particularly valuable role to play.

Musculoskeletal Disorders

This is a collective term for a number of heterogeneous conditions that differ in their duration (i.e. acute, subacute or chronic), their etiology (e.g. traumatic, inflammatory, degenerative) and the tissues involved (e.g. bone, joint, muscle). They are the commonest cause of disability in old people, such that in the United States, almost 60% of people aged 65 years and over report arthritis or chronic joint symptoms (Centers for Disease Control, 2002). Such problems will affect over 21 million older Americans in 2005 and over 41 million by 2030 (Centers for Disease Control, 2003).

Despite their heterogeneity, musculoskeletal disorders tend to result in similar restrictions in activity and participation. Pain, reduced mobility, and other functional losses are prominent features, which are interlinked and tend to reinforce one another. For example, people with arthritis may avoid those activities that exacerbate joint pain. As a result, muscles are weakened and joints become unstable and easily injured. This leads to more pain and further avoidance of exercise. Cardiorespiratory fitness may then become critically reduced, particularly in the very old in whom ADLs require oxygen uptakes close to the age-associated maximum. The net result is an unfit, inactive, arthritic person whose independence is compromised.

Detailed discussion of the management of pain of musculoskeletal origin is beyond the scope of this chapter and is dealt with elsewhere. However, it should be emphasized that appropriate treatment depends on an accurate diagnosis. For example, corticosteroids are the agents of choice in polymyalgia rheumatica but must be avoided when pain is from an osteoporotic vertebral crush fracture. The timing of analgesic use is also important. For example, pain in osteoarthritis is often exacerbated by exercise, so that it may be better to take medication before a particular activity rather than to continuously use potentially toxic analgesics. Nonpharmacological approaches to pain management should also be considered. For example, protecting arthritic hand joints with moulded splints can allow pain-free function with minimal loss of dexterity. A cane held in the contralateral hand reduces weight on an arthritic hip and thereby limits pain. For knee pain, the patient should experiment with holding a cane in either hand. Cane length is important to avoid secondary problems with other joints. Length should equal the distance from the wrist crease to the floor. Stick rubbers should be regularly checked and replaced when worn, to reduce the risk of falls. Resistant pain is best managed by a multidisciplinary team approach, and nowadays, most large centers have access to a pain management team and, with it, the expertise of anesthetists, psychiatrists, and others.

Daily range-of-motion exercises are particularly important in attempting to restore function in arthritic joints. However, compliance with such measures is low for people of all ages. The additional stimulus of joining others in a group activity with an added social component increases compliance. It is essential that footwear be appropriate. Patients with painful knees will benefit from wearing soft-soled shoes with cushioned heels (e.g. jogging shoes). A rocker bottom shoe (Figure 3) can reduce pain from rigid toes by assisting in weight transfer from posterior to anterior. This reduces the force needed to propel the body over the metatarsophalangeal (MTP) joints. Metatarsalgia can be reduced by

Figure 3 Rockerbottom shoe with an insole

an internal pad placed proximal to the MTP joints. When the hind foot is involved through medial arch collapse, an orthosis designed to support the medial arch often helps. Heat, including baths and spas, has been traditionally used for arthritic joints. There is no evidence that hydrotherapy causes measurable functional improvement in arthritic joints, although it does lead to greater self-confidence (Ahern *et al.*, 1995).

With regard to loss of function, a home-based assessment by an occupational therapist is often invaluable. Simple ergonomic measures and aids (e.g. tap turners, zipper pulls, sock pulls, stretch laces, long-handled shoehorns, and Velcro fasteners) can notably reduce joint strain and consequent pain.

In the context of the arthritic patient, the importance of secondary prevention should not be forgotten. Pathological changes occur against a backdrop of age-related changes in joints and soft tissues, which themselves limit flexibility. However, these age-related changes are reversible and exercise will increase joint flexibility (Raab *et al.*, 1988) and improve the strength, size, and resilience of cartilage, ligaments, and muscles. The arthritic patient should be encouraged to seek physical fitness and set him/herself realistic goals.

In the context of musculoskeletal disorders, evidence for the efficacy of structured rehabilitation programs is lacking, perhaps because research of sufficient rigor has yet to be undertaken. Multidisciplinary rehabilitation, based on time-limited and goal-directed interventions, is only of proven benefit in the management of chronic back pain, other types of chronic pain, and following hip fracture in frail elderly people (Cameron, 2004). The prevalence and impact of musculoskeletal disorders on elderly people means that further research to identify the effective elements of rehabilitation should become an even greater priority.

The Elderly Amputee Patient

The majority of lower limb amputations in elderly patients occur as a consequence of peripheral vascular disease (Ephraim *et al.*, 2003). While limb-threatening ischemia is occasionally due to a sudden embolic event, most patients have a long period of worsening ischemia prior to amputation. Many people are diabetic and have concurrent cardiac and other vascular disease, while others have smoking-induced chronic lung disease. Despite this, rehabilitation has much to offer older people following a lower limb amputation (Esquenazi, 2004) and many rise to the challenge of walking even with bilateral below-knee prostheses.

This stated, elderly people who require a lower limb amputation are a high-risk group. Perioperative mortality is in the range of 10–30%, two-year survival is 40–50%, and five-year survival is 30–40%. These survival rates have not changed significantly in the past 50 years, even with better anesthetic and surgical techniques (Cutson and Bongiorni, 1996).

When faced with an ischemic limb that cannot be salvaged by vascular reconstruction, the surgeon often has to choose between a transfemoral (i.e. above-knee) or transtibial (i.e. below-knee) amputation. Preservation of the knee is critical for the elderly amputee so that proprioceptive and neuromuscular control can be maintained and particularly so that energy expenditure can be minimized. It takes 40% more energy to walk with an above-knee than with a below-knee prosthesis (James, 1973). However, injudicious efforts to salvage a knee joint can result in an ischemic stump, which fails to heal and later necessitates a more proximal amputation. The need for a second surgical procedure is potentially disastrous as it increases the anesthetic risk, prolongs the period of immobility, increases the risk of deconditioning, and delays entry into rehabilitation.

Following limb amputation, stump management for early prosthetic intervention should commence by the use of rigid removable dressings to reduce edema, promote healing, and protect against incidental trauma. It is important that early physical therapy be directed at strengthening the arms, the abdominal muscles, the lower back, and the remaining leg. Prescription of a lower limb prosthesis is almost always indicated, even in the presence of other major medical problems. The prosthesis helps to facilitate transfers, standing and walking, and has added cosmetic value. It used to be argued that an older amputee should have crutch-walking capacity before a prosthesis should be offered. However, as walking without bearing weight on the amputated side has a higher energy cost than walking on the prosthesis, this criterion is neither valid nor fair. While some decline the offer of a prosthesis and accept wheelchair mobility, most elderly people, and particularly those with few comorbidities, are happy with their prosthesis and use it well (Pezzin *et al.*, 2004). As with any other medical intervention, a prosthesis should never be prescribed without considering the unique needs and wishes of each patient. The demands of using a prosthesis should be fully explained. For a below-knee amputee, the full range of knee extension should be

maintained. It is therefore important to avoid prolonged periods of sitting in a chair without corrective exercises and a minimum of 20–30 minutes of prone lying should occur twice daily to promote full extension. The skin coming into contact with the prosthesis needs to be durable and toughened; this is best achieved by graded use of the prosthesis. Massaging the stump improves circulation and prevents adhesions during the healing process, and patients should be encouraged to do this.

Modern transtibial prostheses consist of a socket, a shank, and an ankle and foot mechanism (Figure 4). The socket is the major determinant of the comfort and stability of the prosthesis. In general, it is designed to transfer most of the weight onto the patellar tendon and a good fit is critical for achieving this. The stump is edematous in the early postoperative period and then shrinks over time. Temporary sockets are therefore required until this process is complete and a permanent socket is cast. The most commonly used socket materials are plastic laminate. The socket may incorporate a suction device to suspend the limb. When a nonsuction socket is used, an interface material (stump socks or other plastic resilient material) is needed. Stump socks should be washed daily with mild soap and warm water, rinsed thoroughly, and allowed to dry flat. The inner surface of the socket should be cleaned each evening with a warm soapy cloth.

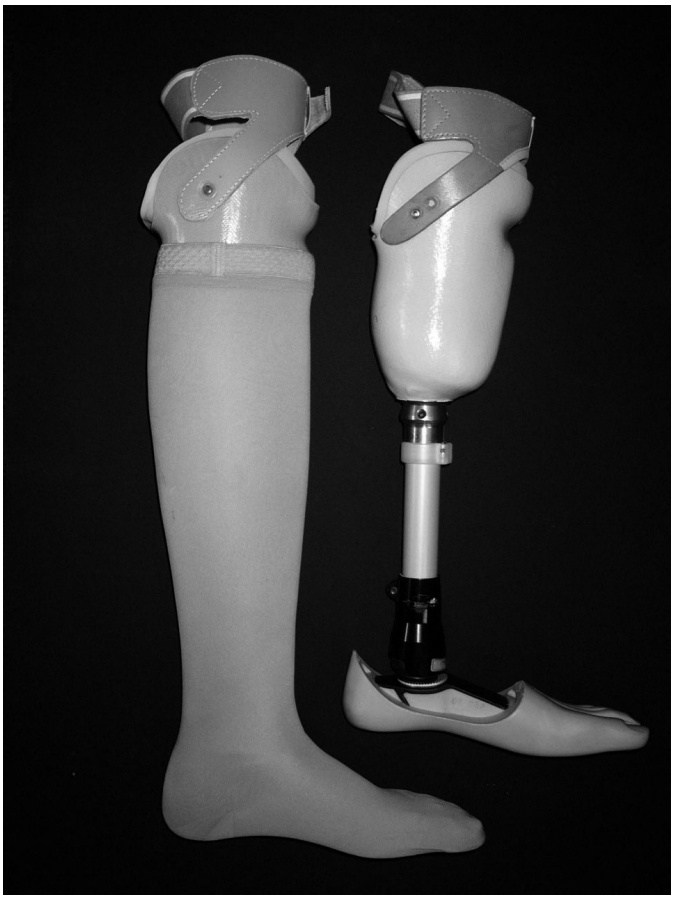

Figure 4 Two types of lower limb prostheses are shown with a solid ankle-cushion heel (SACH) foot on the left and an articulated flexible ankle mechanism fitted on the right prosthesis, which additionally shows the central pylon before final covering

Shanks have traditionally had an "exoskeletal" design, using willow or lightweight balsa wood covered with laminated plastic. A more modern "endoskeletal" limb (Figure 4) has a central pillar, made of carbon-fiber or lightweight metal to support the body weight, and is surrounded by a soft cover approximating the feel of a normal limb.

An artificial foot may be rigid or have an ankle that allows movement in one or more planes. Prescription is dependent on the level of client activity and on the condition of the stump. There is no evidence that any one design is inherently superior (Hofstad *et al.*, 2002). The advantages of a rigid ankle are lightness, low initial and maintenance cost, easy fitting, and good appearance. The solid ankle-cushion heel (SACH) foot has a rigid ankle, a compressible heel, and a light foot. It is particularly suited to the frail, less active patient who does not take long steps. SACH feet provide long service and are now almost always used for below-knee limbs.

Once a comfortable, stable, and functional limb has been provided, the next stage of training is to help the patient to walk on it properly. Gait retraining and the provision of additional mobility aids are complex subjects, discussion of which is outside the scope of this chapter.

When peripheral vascular disease leads to limb amputation, the remaining limb is often significantly ischemic so that 15–20% of people undergo a contralateral amputation within 2 years and some 40% within 4 years (Weiss *et al.*, 1990). The viability of the remaining leg can often be enhanced by surgery and by minimizing risk factors for vascular disease (e.g. poor diabetic control, cigarette smoking, etc.). Foot hygiene should be promoted and trauma to the leg should be avoided, particularly by wearing appropriate footwear.

Comprehensive rehabilitation of the elderly amputee involves more than the provision of a prosthesis. Comorbidity, prosthetic component selection and resettlement with tenuous or absent social supports all present formidable challenges. A more comprehensive review of this area, including the care of the bilateral amputee, is available (Esquenazi, 1993). The elderly amputee may draw encouragement from the life of the famed actress Sarah Bernhardt, who had an above-knee amputation at the age of 71 and thereafter continued her acting career until her death 8 years later.

The nonpainful sensation of a phantom limb is normal after amputation. Initially, this can be so deceptive that a patient inadvertently attempts to walk or reaches to scratch the missing limb. Over time, patients sense the limb retracting or "telescoping" into the stump. Phantom pain is a separate, though perhaps related phenomenon, which affects some 50–80% of people following a limb amputation (Flor, 2002).

The pathophysiology of phantom pain is poorly understood, though central and peripheral nervous system factors together with psychological factors are implicated (Halbert *et al.*, 2002). It can usually be differentiated from stump pain, as it is localized in the phantom and is variously described

as burning, crushing, or lancinating. Phantom pains may be continuous or intermittent. The limb may be perceived as twisted or deformed. Management includes explaining to the patient that such bizarre sensations are commonplace and do not indicate mental instability or illness. While patients with chronic pain before amputation have a higher incidence of phantom pain, attempts to control pain before and during surgery do not consistently reduce the subsequent development of phantom pain.

The management of phantom pain is challenging, particularly on the rare occasion when it is very debilitating. There is little evidence from randomized controlled trials to guide clinicians and, when reported, improvement rates are a little better than with placebo (Halbert *et al.*, 2002). Anesthetic and surgical techniques (e.g. local anesthesia, sympathectomy, cordotomy) are as disappointing as pharmacological approaches. Tricyclic antidepressants and sodium-channel blocks are often used because of their efficacy in neuropathic pain, but are of no proven benefit. Transcutaneous electrical nerve stimulation (TENS) seems to provide modest relief at best (Katz and Melzack, 1991). However, patients do need ongoing psychological support and help to develop coping with strategies (Hill *et al.*, 1995).

Neurological Rehabilitation

The array of pathological processes that involve the brain and other parts of the nervous system tend to divide into those that are acute and nonprogressive on the one hand and those that are chronic and progressive on the other. Examples of the former include stroke, acquired brain injury, and spinal cord injury, while examples of the latter include Parkinson's disease, Motor Neuron Disease, and the dementing illnesses. Collectively, they present an array of rehabilitation challenges, particularly relating to mobility, balance and stability, communication and swallowing, and cognition. A multidisciplinary team approach to the management of chronic pain in older people is also starting to emerge (Helme, 2001).

This brief section deals only with the rehabilitation of some common chronic progressive neurological disorders of old age. The complex area of rehabilitation following stroke is addressed elsewhere in this text (*see* **Chapter 74, Stroke Rehabilitation**), while acquired brain injury and spinal cord injury are so uncommon in elderly people as to not warrant discussion here.

Perhaps the first matter to consider is the rationale for rehabilitation in people with progressive neurological disorders as it could be argued that their relentless nature makes resource-intensive approaches to rehabilitation inappropriate. This also raises complex ethical and practical issues regarding the overlap between rehabilitation and palliative care. In the context of a progressive dementing illness, particular challenges arise when, for example, patients lack both the intellectual capacity to fully engage in rehabilitation and to provide informed consent to participate. However, the loss of intellectual capacity cannot alone justify a decision to deny a person access to therapy that can improve his or her quality of life.

With progressive neurological disorders such as Parkinson's disease, rehabilitation has tended to focus on gait and speech problems (Montgomery, 2004). While these are the most distressing aspects of the disease for many patients, they are also the most difficult to modify. This may partly explain why randomized controlled trials have failed to demonstrate a benefit from physiotherapy or occupational therapy in Parkinson's disease (Deane *et al.*, 2003a,b). However, a lack of proof of efficacy is not proof of inefficacy and all experienced clinicians will have encountered very many patients with Parkinson's disease in whom rehabilitation made a significant contribution to improved functional status and quality of life.

Dementia is by far the commonest progressive neurological disorder in older people. With dementia, two particular considerations arise: the impact of rehabilitation on the dementing process *per se* and the impact of a coincidental dementia on rehabilitation for another disorder (e.g. hip fracture or stroke). With regard to the former, most research to date has focused on the potential benefits of exercise; a recent meta-analysis of 30 trials involving over 2000 patients concluded that exercise training increases fitness, physical function, cognitive function, and positive behavior in people with dementia (Heyn *et al.*, 2004). There is also accumulating evidence that those with mild to moderate dementia at least benefit from rehabilitation for such problems as hip fracture (Huusko *et al.*, 2000).

Future Challenges

The principles and practice of rehabilitation have evolved considerably since Marjorie Warren first highlighted its potential role in geriatric medicine some 60 years ago. However, progress has been slow in at least two areas. The first concerns access to rehabilitation for elderly people even in countries with well-developed health services. For example, it is estimated that only 2% of Canadians who might benefit access pulmonary rehabilitation and only 1% of those in need access musculoskeletal rehabilitation (Brooks *et al.*, 1999; Arthritis Foundation, Association of State and Territorial Health Officers, CDC, 1999). The mismatch between resources and demand is an even greater problem in developing countries.

The second area where progress has been slow is in identifying the most cost-effective elements of the rehabilitation process in different clinical situations. Further research in this area is essential for resources to be optimally targeted, for funding to be secured, and for geriatric rehabilitation to advance as a discipline. Many health-care systems are struggling with demographic change and a consequent increased demand for hospital resources at a time when acute hospital beds are being reduced. As acute hospital care and long-term residential care tend to be separately funded and poorly coordinated, pressures to reduce lengths of acute hospital stay tend to erode rehabilitation services in the acute hospital. Community-based rehabilitation services are not expanding to fill the gap and are anyway unsuited to many elderly people who lack the live-in support of a carer.

A lack of investment in rehabilitation is also a false economy measure as it leads to avoidable and costly institutional care (Young *et al.*, 1998). Sixty years ago, Marjorie Warren highlighted the social injustice of failing to optimally meet the rehabilitation needs of elderly people and their families. Such concerns are still relevant today.

KEY POINTS

- In 2001, the WHO introduced its International Classification of Functioning, Disability and Health (ICF). This challenges traditional views on health and disability, while providing a mechanism to document the impact of the social and physical environment on a person's functioning.
- Rehabilitation is a stepwise process where the various stages often overlap, may occur concurrently, and may need to be regularly revisited.
- Education is a vital component of rehabilitation, as through it, the patient acquires the knowledge, skills, and attitudes to minimize the activity and participation restrictions that can result from impairment.
- A failure to optimally meet the rehabilitation needs of older people and their families is socially unjust, just as a lack of investment in rehabilitation is a false economy measure, leading to avoidable and costly institutional care.

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PART III

Medicine in Old Age

Section 14

Special Issues

Skin Disorders in the Elderly

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INTRODUCTION

Changing population demographics around the world, resulting in an increasing elderly population, lead to heightened awareness of health issues in this portion of the population. Among these, prevention and treatment of the highly prevalent skin disorders constitute a major concern. Approximately one in five Americans, 55 years or older, sees a physician each year for dermatologic diagnosis (Smith *et al.*, 2001): the most prevalent in both men and women is actinic keratosis, and nonmelanoma skin cancer is in the top four most common dermatologic conditions (Smith *et al.*, 2001). Moreover, fatal skin diseases like blistering disorders, malignant melanoma, and cutaneous T-cell lymphoma are disproportionately common in the elderly. A better understanding of the pathophysiology of aging processes in the skin would help prevent and treat dermatoses in the geriatric population, but much can be done even with therapies now available.

The following sections briefly outline current theories of skin aging and their implications on skin problems in the elderly, then discuss individual dermatoses and practical considerations for therapy.

MECHANISMS OF AGING

Aging is a complex process that affects the individual at different levels. At the cellular level, aging culminates in senescence (permanent loss of proliferative capacity) or apoptosis (death), leading to functional deficits as a result of cell loss, failure to replace lost cells, and compromised differentiated function of remaining cells. This continuous functional attrition, is unquestionably injurious to the individual, but appears to provide "secondary gain" as a cancer preventive mechanism (Campisi, 1996). Over time, genomic DNA is continuously exposed to damaging agents such as reactive oxygen species generated as a result of oxidative cellular metabolism and environmental carcinogens including solar irradiation, air pollution, and cigarette smoke. Cumulative DNA damage, particularly when affecting oncogenes and tumor suppressor genes, may lead to malignant transformation, but only in cells still capable of proliferation. Thus, it appears overall beneficial for the individual to lose such damaged cells and bear the resulting functional losses (*see also* **Chapter 2, A Biological Perspective on Aging**, **Chapter 3, Immunity and Aging** and **Chapter 4, Physiology of Aging**).

Telomeres and DNA Damage

Existing data suggest that aging is influenced both by inherent, genetic, as well as environmental factors. At the DNA level, telomeres, the terminal portion of eukaryotic chromosomes consisting of thousands of repeats of a tandem sequence TTAGGG, appear to govern the number of cellular divisions through progressive shortening, thus serving as the "biologic clock." (Ahmed and Tollefsbol, 2001).

It is interesting that the 3′ telomere strand is composed of DNA bases that constitute the target for DNA damaging agents such as UV irradiation, reactive oxygen species and benzo(a)pyrene, the carcinogen in cigarette smoke and automobile exhaust. UV irradiation leads to the formation of pyrimidine dimers, most commonly between adjacent thymidines (Patrick, 1977); reactive oxygen species primarily cause 8-oxo-guanine (Oikawa and Kawanishi, 1999); and benzo(a)pyrene forms adducts at guanine nucleotides (Jack and Brookes, 1980). Indeed, one-third of the 3′ strand (TTAGGG) is dithymidines (TT) and half is guanine (G) residues. This suggests a mechanism by which repeated UV irradiation or exposure to other environmental carcinogens might accelerate cellular aging through preferential telomere damage.

Indeed, human syndromes that display premature aging like Cockayne, Werner's and ataxia telangiectasia display mutations in genes that participate in DNA damage repair. In Cockayne syndrome, which is characterized by increased sensitivity to UV irradiation, developmental abnormalities,

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and premature aging (Kraemer, 2003), a DNA helicase is mutated (Troelstra *et al.*, 1992) and the patients display increased sensitivity to oxidative and UV-induced DNA lesions. In ataxia telangiectasia, progeric skin changes including xerosis, develop at a young age in the majority of patients (Paller, 2003). The ATM gene mutated in ataxia telangiectasia encodes a kinase that mediates DNA damage responses (Savitsky *et al.*, 1995). In Werner's syndrome, patients display growth arrest, senile cataracts, premature balding and graying of hair, sclerodermoid appearance of the skin, loss of subcutaneous fat, and wasting of muscles at a young age (Nehlin *et al.*, 2000). A DNA helicase is mutated in Werner's syndrome, (Yu *et al.*, 1996) associated with rapid telomere shortening and decreased telomere repair as well as hair graying, atrophic and sclerotic skin and loss of subcutaneous fat, atherosclerotic heart disease, and death in early middle age. Together, these syndromes strongly support the role of DNA damage in the aging process.

The Immune System

The immune system has a role in controlling infections and also in surveillance against cancer development. With increasing age, infections become more prevalent and constitute one of the principal causes for mortality in people 65 years or older (Mouton *et al.*, 2001). In addition, the elderly display an increased incidence of cancer and inflammatory diseases, suggesting dysregulation of the immune system. With aging, both the cell-mediated and humoral immunity deteriorate. T-cells display reduced proliferation and cytokine production in response to specific triggers (Jankovic *et al.*, 2003). Recent studies based on murine data suggest that T-cell dysfunction and impaired age-associated response to pathogens and vaccines may be the result of decreased apoptosis of naive T cells early during infection/vaccination, compromising the ability of memory T cells to proliferate and expand (Jiang *et al.*, 2003). Similarly, with regard to humoral immunity, vaccination studies show that older individuals fail to select antigen activated B cells in the germinal centers of the lymph nodes, a process that may adversely affect humoral immunity (Dunn-Walters *et al.*, 2003). These decrements in immune response render the elderly more susceptible to infections and, possibly, to cancer development.

SKIN AGING

Skin aging can be divided into intrinsic or chronologic aging, those changes in the skin that are the result of passage of time alone; and photoaging, those changes in the skin that are the result of chronic sun exposure which are compounded by chronologic aging.

Intrinsic Aging

Clinical and Histological Changes

Intrinsically, aged skin appears pale, dry, lax, displaying gravitational and expression wrinkles, and a variety of benign neoplasms. Histological modifications present in chronologically aged skin are summarized in Table 1. These include flattening of the dermal–epidermal junction with decreased contact between the epidermis and the dermis and as a result, decreased exchange of molecules between the two compartments (Kurban and Bhawan, 1990). Also, this dermal–epidermal effacement leads to easier separation of the epidermis from the dermis upon minor trauma, rendering the elderly more prone to superficial erosions. Other changes include increased variability in epidermal thickness and in individual keratinocyte size as well as widening of the spaces between the keratinocytes (Yaar and Gilchrest, 2003). Also, there is a decreased number of enzymatically active melanocytes, the neural crest derived cells that reside in the basal layer of the epidermis and produce the pigment melanin that is protective against UV irradiation. Langerhans cells, the skin immune effector cells responsible for antigen presentation also decrease with age (Yaar and Gilchrest, 2003).

In the dermis, there is loss of volume, with cell depletion and decreased vascularity. Dermal changes in collagen, elastin, and glycosaminoglycans, the latter composing the ground substance of the dermis that occupies the spaces between the fibrous components of the dermis, occur. Both collagen and elastic fibers appear more compact as a result of decreased ground substance. In addition, the number of collagen bundles and the amount of elastic fibers decrease in part because of decreased synthesis and in part because of increased degradation (Yaar and Gilchrest, 2003; Tzaphlidou, 2004). Also, there is a decrease in the number of superficial dermal capillary loops that supply the epidermis, perhaps

Table 1 Histologic features of aging human skin[a]

Epidermis	Dermis	Appendages
Flattened dermal–epidermal junction	Atrophy (loss of dermal volume)	Depigmented hair
Variable thickness	Fewer fibroblasts	Loss of hair
Variable cell size and shape	Fewer mast cells	Conversion of terminal to vellus hair
Occasional nuclear atypia	Fewer blood vessels	Atrophy of glands
Fewer melanocytes	Fewer capillary loops	
Fewer Langerhans cells	Lymphatic involution	

[a]Modified from Yaar M and Gilchrest BA, Aging of the skin, Dermatology in General Medicine (Eds Freedberg IM *et al.*), 2003, p 1386, with permission of the McGraw-Hill Companies.

in part due to decreased epidermal angiogenic cytokines like vascular endothelial growth factor, decreased receptors on blood vessels, or both (Ryan, 2004). Similarly, lymphatic involution occurs and the walls of both the vascular and lymphatic vessels show replacement of elastic fibers by more rigid collagen (Ryan, 2004). In addition, skin appendages including hair follicles, eccrine and apocrine sweat glands, and sebaceous glands, display gradual age-associated atrophy.

Physiologic Functions

Physiologic functions that decline with age are summarized in Table 2. Although barrier function is mostly retained with age, there is a significant delay in barrier recovery after trauma. Decreased wound healing in the elderly is a result of decreased cell proliferation, decreased angiogenesis, as well as decreased collagen synthesis (Yaar and Gilchrest, 2003).

Owing to changes in their structure and perhaps also as a result of decreased epidermal or dermal stimuli, aged vessels display decreased ability to constrict or dilate upon temperature change. The lymphatics which, similar to blood vessels, are already compromised, are often overloaded by a deteriorating venous system, particularly in dependent areas, leading to lymphatic malfunction. With aging, there is decreased immune responsiveness in large part because of decreased and malfunctioning Langerhans cells, but other contributing factors include decreased access of Langerhans cells to capillary loops and lymphatics as well as decreased white cell reactivity in response to antigenic stimulus. An endocrine function of human skin that declines with age, in part because of decreased epidermal 7-dehydrocholesterol, is vitamin D production (MacLaughlin and Holick, 1985). Age-associated atrophy of cutaneous appendages result in decreased sweat and sebum production. Finally, there is an age-associated decrease in DNA damage repair capacity (Goukassian *et al.*, 2000).

Photoaging

UV Effect on Cellular Membranes

In addition to UV effects on DNA, UV irradiation also directly affects cellular membranes and their components (Fisher *et al.*, 2002). UV irradiation activates cell surface receptors including epidermal growth factor, interleukin 1 and tumor necrosis factor-α receptors, leading to intracellular signaling and synthesis of transcription factors, nuclear proteins that bind the DNA to enhance or repress gene transcription. One transcription factor that is quickly and prominently induced by UV irradiation is AP-1. AP-1 interferes with collagen gene transcription in fibroblasts, decreasing the levels of the major procollagens I and III. In addition, AP-1 stimulates the transcription of genes that encode matrix degrading enzymes such as metalloproteinases which degrade collagen.

Table 2 Functions of human skin that decline with age[a]

Barrier recovery	Wound healing
Cell proliferation	Vitamin D production
Thermoregulation	Sweat production
Lymphatic drainage	Sebum production
Immune responsiveness	DNA repair

[a]Modified from Yaar M and Gilchrest BA, Aging of the skin, Dermatology in General Medicine (Eds Freedberg IM *et al.*), 2003, p 1386, with permission of the McGraw-Hill Companies.

Clinical and Histological Changes

Photodamaged skin is dry and sallow displaying coarse and fine wrinkles, irregular pigmentation in the form of lentigines, lesions that are referred to by the layperson as "liver spots", which are small macules displaying variegated light to dark brown color and slight border irregularity; gutate hypomelanosis, multiple punctate hypopigmented spots; and persistent hyperpigmentation, or permanent bronzing of the skin (Yaar and Gilchrest, 2003). It frequently displays multiple premalignant lesions (actinic keratosis) and occasionally displays malignant lesions primarily, basal cell and SCCs. At times, facial skin may display a pattern of papular, yellowish aggregations with open comedones (Favre–Racouchot disease) and telangiectasis.

The histologic characteristics that correlate with these clinical changes are listed in Table 3. The epidermis of photodamaged skin is frequently acanthotic. There is loss of keratinocyte polarity, and there are many atypical keratinocytes (Yaar and Gilchrest, 2003). Melanocyte distribution is uneven, with areas of increased density of hypertrophic dopa-positive melanocytes and areas with reduced melanocyte numbers. Generally, elastosis, which is the overgrowth of abnormal elastic fibers, is the major histologic sign of photodamaged skin (Yaar and Gilchrest, 2003). Also, collagen fibrils appear fragmented and disorganized (Fisher *et al.*, 2002). In contrast, with sun-protected skin, photodamaged skin displays increased cellularity with abundant mast cells, histiocytes, other mononuclear cells, lymphocytic infiltrate, and numerous fibroblasts. Also, in contrast with sun-protected skin, the few remaining dermal blood vessels appear dilated and tortuous.

Physiologic functions that decline with chronologic skin aging appear to be more severe in sun-exposed skin, particularly compromised wound healing capacity and decreased immune responsiveness (Yaar and Gilchrest, 2003).

INFECTIONS/INFESTATIONS

Tinea Pedis

"Athlete's foot" or tinea pedis is the most common fungal infection in the elderly. Long-standing infections are

Table 3 Features of actinically damaged skin[a,b]

Clinical abnormality	Histologic abnormality
Dryness (roughness)	Increased compaction of stratum corneum, increased thickness of granular cell layer, reduced epidermal thickness, reduced epidermal mucin content
Actinic keratoses	Nuclear atypia, loss of orderly, progressive keratinocyte maturation; irregular epidermal hyperplasia, and/or hypoplasia; occasional dermal inflammation
Irregular pigmentation	
Freckling	Reduced or increased number of hypertrophic, strongly dopa-positive melanocytes
Lentigines	Elongation of epidermal rete ridges; increases in number and melanization of melanocytes
Guttate hypomelanosis	Reduced number of atypical melanocytes
Persistent hyperpigmentation (bronzing)	Increased number of dopa-positive melanocytes, and increased melanin content per unit area, and increased number of dermal melanophages
Wrinkling	
Fine surface lines	None detected
Deep furrows	Contraction of septae in the subcutaneous fat
Stellate pseudoscars	Absence of epidermal pigmentation, altered fragmented dermal collagen
Elastosis (fine nodularity and/or coarseness)	Nodular aggregations of fibrous to amorphous material in the papillary dermis
Inelasticity	Elastotic dermis
Telangiectasia	Ectatic vessels often with atrophic walls
Venous lakes	Ectatic vessels often with atrophic walls
Purpura (easy bruising)	Extravasated erythrocytes and increased perivascular inflammation
Comedones (maladie de Favre et Racouchot)	Ectatic superficial portion of the pilosebaceous follicle
Sebaceous hyperplasia	Concentric hyperplasia of sebaceous glands

[a]Basal cell carcinoma, squamous cell carcinoma and melanoma also occur in otherwise normal actinically damaged skin but, unlike the table entries, affect only a small minority of individuals with photoaging. [b]Modified from Yaar M and Gilchrest BA, Aging of the skin, Dermatology in General Medicine (Eds Freedberg IM *et al.*), 2003, p 1386, with permission of the McGraw-Hill Companies.

frequently associated with involvement of the toenail (onychomycosis). Tinea pedis usually begins in the interdigital web spaces as erythema and scale, sometimes spreading to involve the lateral, medial, and plantar surfaces of the foot (moccasin distribution) (Figure 1). Pruritus is a frequent complaint. The differential diagnosis of interdigital tinea pedis includes erythrasma (Corynebacterium) and gram-negative toe web infection (Pseudomonas). The potassium hydroxide (KOH) preparation is a simple and quick bedside test that can help confirm the diagnosis. Dry scale is removed with a 15 blade and placed on a glass slide. One drop of KOH with 20% dimethyl sulfoxide is added before the cover slip is placed on top. Direct microscopy with the 10 × magnification reveals branching hyphae (Figure 2). Topical azole cream (ketoconazole, spectazole) applied twice daily, or terbinafine 1% cream applied once daily for 3–4 weeks is effective. Patients should be instructed to apply the cream in the toe web spaces and to the lateral, medial, and plantar surfaces of the foot. Reinfection is a common problem. Prophylactic measures include complete drying of the feet after bathing and wearing cotton socks to eliminate the moist environment in which tinea proliferates, avoiding going barefoot in public places, and once weekly application of antifungal cream to the feet.

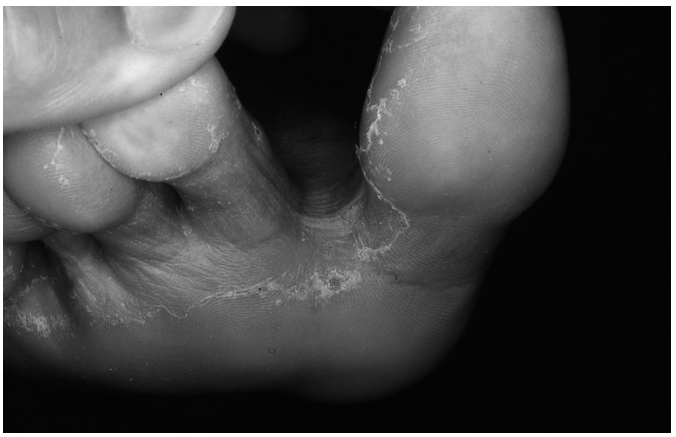

Figure 1 Interdigital tinea pedis with dry white scale

Onychomycosis

Onychomycosis is fungal infection of the nail bed with subsequent involvement of the nail plate, usually caused by contiguous spread from tinea pedis. Thus, most patients will also have clinical findings of interdigital or moccasin-type tinea pedis. Toenails are more often involved than finger nails.

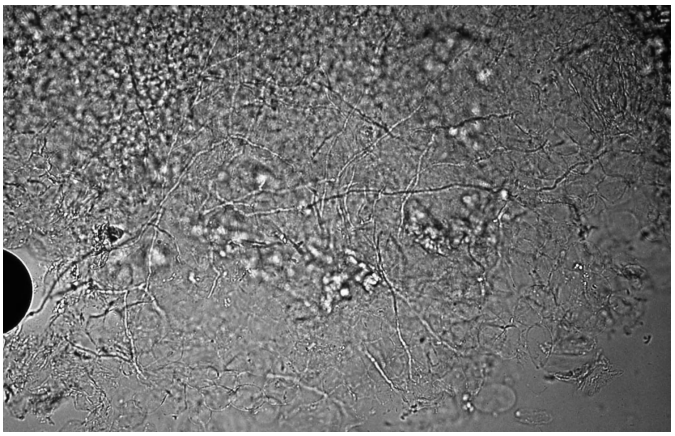

Figure 2 KOH preparation demonstrates long branching hyphae

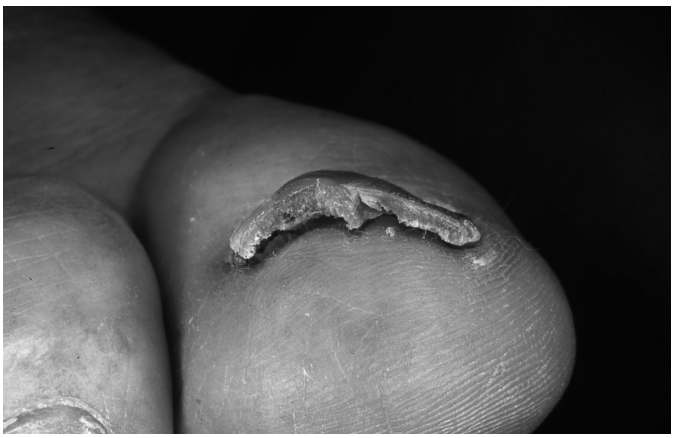

Figure 3 Onychomycosis. The nail demonstrates subungual hyperkeratosis and onycholysis

The characteristic clinical features are yellow discoloration, thickening of the nail bed (subungual hyperkeratosis) and separation of the nail bed from the nail plate (onycholysis) (Figure 3). The differential diagnosis includes pincer nail deformity, onychogryphosis, psoriasis, and lichen planus. Because only 50% of dystrophic toenails are caused by fungal infections, and systemic antifungal therapy is expensive ($400–$600), confirmatory testing is highly recommended. Sensitivity of KOH preparation and culture is highly dependent on proper specimen collection. A nail clipper is used to remove the nail proximally to the point where the nail plate meets the nail bed. This area is cleaned with an alcohol towelette and a small curette or 15 blade used to remove the soft yellow subungual debris. This specimen is placed on a glass slide for KOH preparation (as previously described) or plated on a dermatophyte test medium (DTM), which contains a pH indicator that turns the agar from yellow to red in the presence of dermatophyte. Color change is usually apparent within 2 weeks. (Elewski *et al.*, 2002) Recent studies support histologic examination of a nail clipping with periodic acid-Schiff stain (PAS) to be the most sensitive test (92%), compared to KOH preparation (80%) and fungal culture (59%) (Weinberg *et al.*, 2003).

Onychomycosis is usually asymptomatic and does not affect activities of daily living. Not all patients will require treatment, nor are all patients interested in therapy. However, onychomycosis may cause pain and limited mobility, and in diabetic patients, it can serve as a portal of entry for secondary bacterial infections. Topical antifungals are not effective because they cannot penetrate the nail bed or nail plate, and thus systemic therapy is required. Terbinafine 250 mg daily for 3–4 months is the treatment of choice for dermatophyte onychomycosis. (Sigurgeirsson *et al.*, 2002) For onychomycosis caused by yeast (Candida), the azoles must be selected (itraconazole 200 mg daily for 3–4 months, fluconazole 150 mg weekly for 6 months). Active hepatitis is a contraindication to taking these systemic therapies. For those patients at risk for liver disease, baseline liver function tests (AST, ALT) are recommended. Before the initiation of therapy, review of the patient's medication list is crucial to prevent potential drug interactions. Itraconazole is contraindicated in patients taking astemizole, terfenadine, triazolam, midazolam, cisapride, lovastatin, and simvastatin.

Herpes Zoster

Herpes zoster, commonly known as "shingles", is caused by reactivation of varicella–zoster virus in the dorsal root ganglion. Immunosuppressed individuals, particularly those with hematological malignancy and human immunodeficiency virus (HIV) infection, are at increased risk. The distribution is unilateral and dermatomal (Figure 4). The primary lesions are grouped vesicles on an erythematous base (Figure 5). Over time, the vesicles become pustules and form dried yellow or hemorrhagic crusts. The differential diagnosis includes herpes simplex, varicella, and acute contact dermatitis. Pain precedes the eruption in more than 90% of cases. Rarely, neuralgia is the only manifestation (zoster sine herpete). The classic clinical findings are usually adequate to

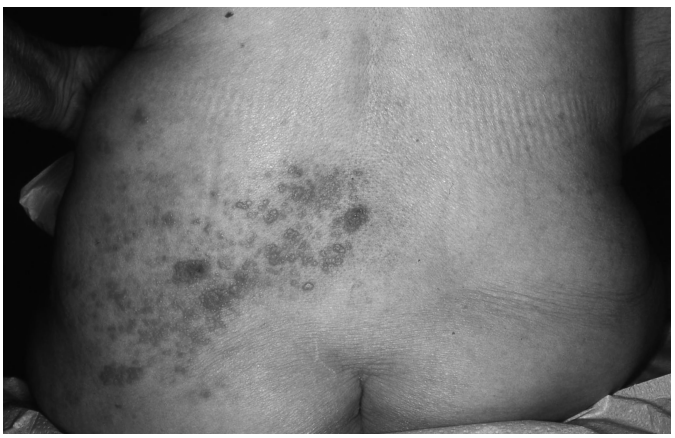

Figure 4 Herpes zoster in the classic dermatomal distribution

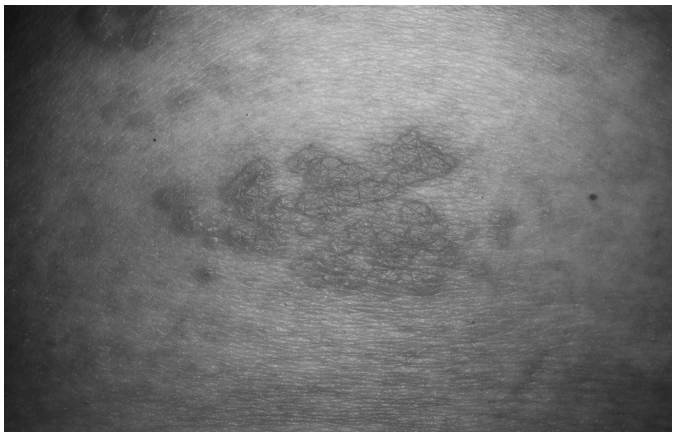

Figure 5 Herpes zoster with grouped vesicles on an erythematous base

make the diagnosis. The Tzanck smear and viral cultures are simple bedside confirmatory tests with variable sensitivity and specificity, dependent upon technique and timing of specimen collection. The Tzanck smear is performed by using iris scissors to unroof fresh vesicles and then a 15 blade is used to scrape the base of the subsequent erosion. This is smeared into a thin layer on a glass slide and briefly heated. Wright or Giemsa stain is applied for about 30 seconds and then rinsed off with water. The specimen is viewed with direct microscopy under 40 × magnification. Demonstration of multinucleated giant cells can be seen in herpes simplex and varicella–zoster infection (Figure 6). For viral cultures, the appropriate specimen is fluid from a vesicle, not dried crusts. Varicella–zoster cultures can take 1–2 weeks with frequent false-negative results. Direct fluorescent antibody is a specific and rapid test (1–2 hours), but not available in most outpatient settings.

Complications include ophthalmic involvement, dissemination, and postherpetic neuralgia. Patients with involvement of the V1 branch of the trigeminal nerve, particularly the side and tip of the nose (Hutchinson's sign), require immediate ophthalmologic consultation to rule out ocular involvement including keratitis and acute retinal necrosis. Immunocompromised patients are at risk for dissemination, defined as more than 20 vesicles outside the primary and immediately adjacent dermatomes. Rarely, this can be followed by visceral involvement (lung, liver, brain). The most common complication is postherpetic neuralgia, pain that persists after resolution of the cutaneous eruption. This affects at least half of the patients older than 60 and most frequently follows facial dermatome involvement.

Systemic antiviral therapy (acyclovir 800 mg po 5 times/day for 7–10 days, famciclovir 500 mg po 3 times/day for 7 days, valacyclovir 1 g po 3 times/day for 7 days) is effective if begun within 48–72 hours of rash onset. These drugs reduce acute pain, accelerate healing, and reduce the incidence and severity of postherpetic neuralgia. The addition of systemic corticosteroids can further reduce acute pain, but has questionable effects on the incidence and severity of postherpetic neuralgia. In immunocompromised patients and those with complications, intravenous acyclovir should be used. Postherpetic neuralgia can be treated with amitriptyline (25–75 mg po qHS) or gabapentin (900–3200 mg day^{-1}) in divided doses.

Scabies

Scabies is caused by the *Sarcoptes scabiei* mite, which burrows into the stratum corneum. It is transmitted by close body contact with other humans. Fomite transmission is rare. Risk factors include nursing home residence, HIV and acquired immunodeficiency syndrome (AIDS), and crowded living conditions. Affected patients complain of severe generalized pruritus for weeks and may report close contacts with similar symptoms. The best locations to find the mite are the interdigital web spaces between the fingers, volar wrists, penis, and areola. The primary lesions are 5–10 mm linear or serpiginous burrows, often with a gray dot at one end representing the mite (Figure 7). A generalized hypersensitivity reaction to the mite results in erythematous papules, diffuse eczematous dermatitis, lichenified plaques, and excoriations.

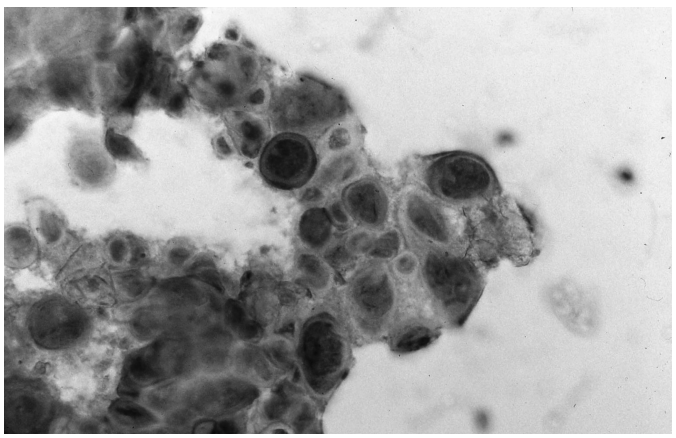

Figure 6 Tzanck smear with multinucleated giant cells

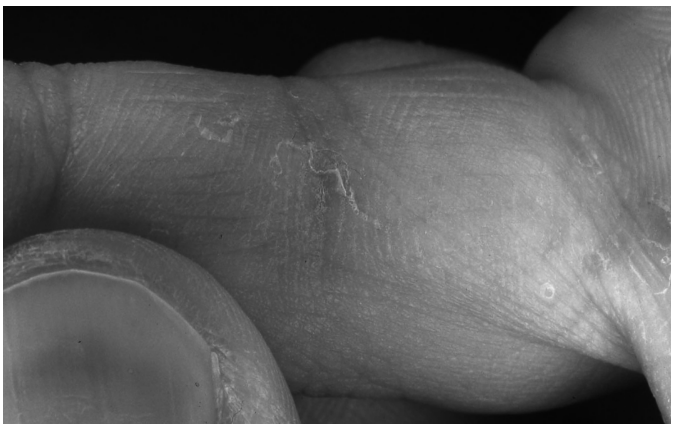

Figure 7 Serpiginous scabies burrow of the medial index finger

The differential diagnosis includes atopic dermatitis, contact dermatitis, drug eruption, and the urticarial phase of bullous pemphigoid. Less common presentations include nodules (nodular scabies), thick hyperkeratotic crusted plaques (Norwegian or crusted scabies), and vesicles or bullae (bullous scabies). Diagnosis is confirmed using direct microscopy, but proper specimen collection is essential for demonstrating the mite. Place one drop of mineral oil on the center of a glass slide. Touch this oil with the belly of a 15 blade (such that skin scrapings will adhere to the blade). Hold the blade perpendicular to the skin and scrape an epidermal burrow to remove the stratum corneum. Pinpoint bleeding occurs at the correct depth. Wipe the scrapings onto the center of the glass slide and repeat for two more burrows to increase the yield. Place a cover slip on top and view under scanning magnification (×4). Presence of the mite, mite parts, eggs or feces confirms the diagnosis (Figure 8). However, because a typical patient harbors very few mites even when severely symptomatic, a classical presentation even in the absence of a positive scraping may be adequate justification for treatment.

Nodular scabies is a prolonged hypersensitivity reaction to remnants of the mite. The lesions are pruritic firm erythematous to brown nodules often occurring on the genitals and intertriginous sites. Immunocompromised patients may develop severe thick hyperkeratotic crusts (Norwegian scabies). Compared to other scabies patients, they are extremely contagious as each crust contains hundreds of mites.

Comprehensive management includes mite eradication, alleviation of pruritus, and prevention of transmission. The patient and all close contacts should be treated simultaneously, as infected individuals may remain asymptomatic for 2 weeks or longer, until they mount a delayed hypersensitivity reaction to the mites. Topical treatments include permethrin 5% cream or lindane 1% lotion. Detailed instructions are required for proper application. A 60-g tube is prescribed for whole body application. Patients should take a bath or shower and completely dry before application. The topical agent should be applied to the entire skin surface (from the neck down), with particular attention to finger web spaces, feet, genitals, buttocks, and intertriginous sites. It should be washed off in 8 hours. This regimen should be repeated for 1 week to eradicate newly hatched mites that may have survived treatment in the egg form. For asymptomatic contacts, one application may be adequate. Overexposure to lindane has been reported to cause central nervous system (CNS) toxicity and thus small children and patients with extensively eroded skin or crusted scabies, expected to have enhanced percutaneous absorption, should not be treated with this agent. For cases resistant to topical treatment, or in the immunocompromised host (such as AIDS patients), ivermectin 0.2 mg kg^{-1} as an oral dose repeated at 10–14 days should be considered. This is a practical option for nursing home epidemics when proper application of topical agents is difficult to achieve.

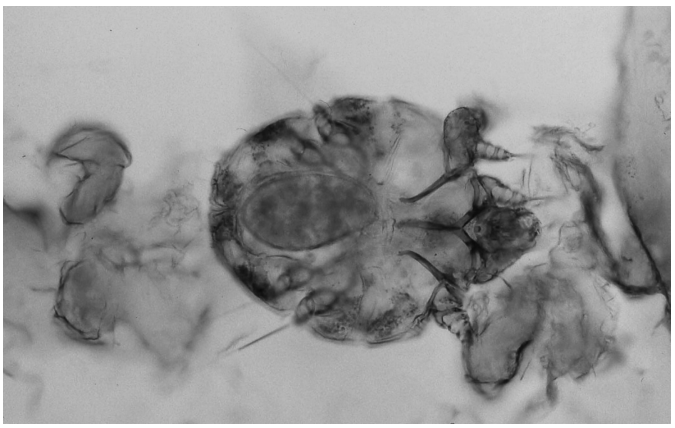

Figure 8 Scabies scrapings demonstrate gravid female mite

Table 4 Steroid compound potency rating

Class[a]	Compound
1	Clobetasol proprionate 0.05% Halobetasol proprionate 0.05%
2	Fluocinonide 0.05% Diflorasone diacetate 0.05%
3	Triamcinolone acetonide 0.5% Desoximetasone 0.05%
4	Mometasone furoate 0.1% Triamcinolone acetonide 0.1%
5	Hydrocortisone valerate 0.2% Prednicarbate 0.1%
6	Desonide 0.05% Triamcinolone acetonide 0.025%
7	Hydrocortisone 1% Hydrocortisone 2.5%

[a]Class 1 (strongest) → Class 7 (weakest).
Most steroids are available both as a cream and ointment. For the same concentration, the ointment is slightly more potent than the cream and more soothing to inflamed skin, although often less cosmetically acceptable than cream formulations. Most topical steroids are most effective if applied twice daily initially and then tapered as improvement occurs. Class 1 steroids should be used only in severe inflammatory or pruritic skin conditions.
Atrophy, telangiectasias, and striae may occur with prolonged use of potent topical steroids (class 1 & 2). The Food and Drug Administration (FDA) has approved use of all class 1 steroids for only 2 weeks (package insert). *The face, genitals, intertriginous areas, and mucosal surfaces* absorb steroids more readily and are more prone to these side effects. *Potent topical steroids should not be used >2 weeks on the face, genitals, intertriginous areas, or on mucosal surfaces.* Potent topical steroids applied to >50% total body surface area may be absorbed sufficiently to have systemic effects such as adrenal axis suppression.

Although scabicides are very effective at mite eradication, they have little short-term effect on the severe pruritus that patients experience. Class I steroid ointments (clobetasol, halobetasol) applied twice to three times daily or a systemic corticosteroid taper over 2–3 weeks will help alleviate the itching while the hypersensitivity reaction abates (Table 4). To prevent fomite transmission, all clothes worn within 2 days of treatment, towels, and bed sheets should be machine washed in hot water or dry cleaned.

INFLAMMATORY DISORDERS

Dry Skin, Pruritus, and Asteatotic Dermatitis

Dry skin or xerosis is a common problem and manifests as pruritus. This is often exacerbated by hot showers and

overuse of soaps, as well as high indoor heat and low humidity. Symptoms are more common in the winter. Extremities are more affected than the face or trunk. Erythematous patches and slightly raised plaques with fine dry scale and subsequent superficial cracking may be seen (asteatotic dermatitis) (Figure 9). The differential diagnosis includes atopic dermatitis, contact dermatitis, or a systemic cause of generalized pruritus (hepatobiliary obstruction, chronic renal failure, hypo or hyperthyroidism, Hodgkin's lymphoma). Detailed history taking and subsequent laboratory workup will help exclude internal causes of pruritus.

Patient education is the key to management of xerosis and asteatotic dermatitis. Limit application of soaps to intertriginous sites. Moisturizers containing lactic acid or urea should be applied daily to the trunk and extremities immediately after bathing or showering, to retain water in the stratum corneum. During winter months, a humidifier in the bedroom is helpful. For asteatotic patches, application of a class 3 topical steroid ointment to affected areas twice daily for 2–3 weeks is effective (Table 4).

Seborrheic Dermatitis

Seborrheic dermatitis is strongly associated with overgrowth of a commensal yeast of the *Malassezia* species. The scalp, face, and chest are involved, particularly around the ears, eyebrows, nasolabial folds, and beard areas. The primary lesion is an erythematous patch or slightly raised plaque with greasy yellow scale (Figure 10). The differential diagnosis includes scalp psoriasis, rosacea, eczema, photosensitivity disorders, or airborne allergic reaction. Anti-dandruff shampoos containing zinc pyrithione 1%, selenium sulfide 1%, or ketoconazole 1% are effective for patients with scalp and facial involvement. They should be applied daily for 1 week and then tapered to 2–3 times per week to prevent recurrences. Patients should be instructed to massage the lather into the face for a few minutes before rinsing. Ketoconazole 2% shampoo may be more effective. For facial involvement, apply ketoconazole 2% cream or a class 6 steroid cream applied twice daily for 2–3 weeks (Table 1). For scalp pruritus, a class 2 steroid solution can be applied as needed.

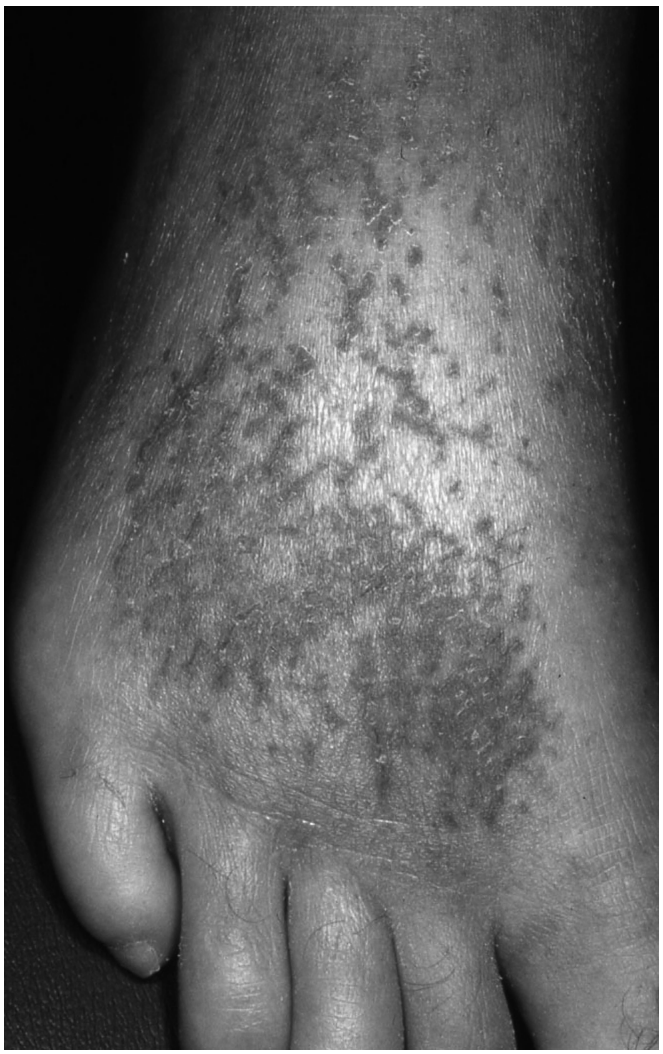

Figure 9 Asteatotic dermatitis with fine cracking of the skin surface

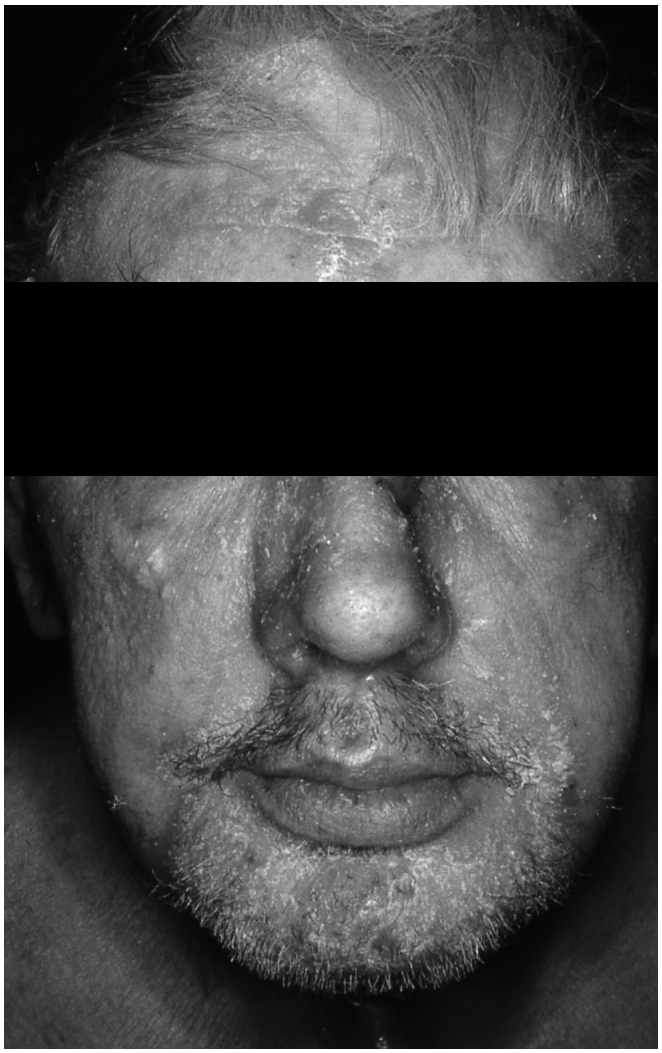

Figure 10 Seborrheic dermatitis. Erythema and scale involving the eyebrows and nasolabial creases

Psoriasis

Psoriasis is a hereditable T-cell-mediated inflammatory dermatosis; one-third of patients have a positive family history. Occasionally, it may be precipitated by an episode of streptococcal pharyngitis, classically as guttate psoriasis with many small plaques widely distributed over the body. Otherwise, psoriasis most often symmetrically affects extensor surfaces (elbows, knees, lumbosacral area), and scalp. The flexures and genital area may also be involved (inverse psoriasis). The primary lesion is an erythematous papule or plaque with thick, layered, silvery scale (Figure 11). The nails may demonstrate yellow–brown oil spots, pitting, and onycholysis (Figure 12). The differential diagnosis includes eczema, seborrheic dermatitis, and lichen planus. The diagnosis is usually made clinically, although in uncertain cases a biopsy will reveal characteristic changes. Five to thirty percent of patients with cutaneous psoriasis may also present with arthritis of the small and large joints. Rare presentations of generalized pustular psoriasis (von Zumbusch) or erythroderma (greater than 90% total body surface area involvement) may be life threatening and require hospitalization.

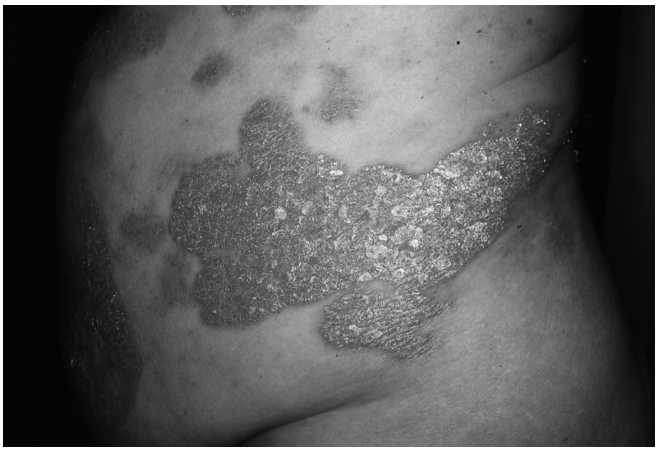

Figure 11 Plaque psoriasis. Erythematous plaque with thick, silvery scale

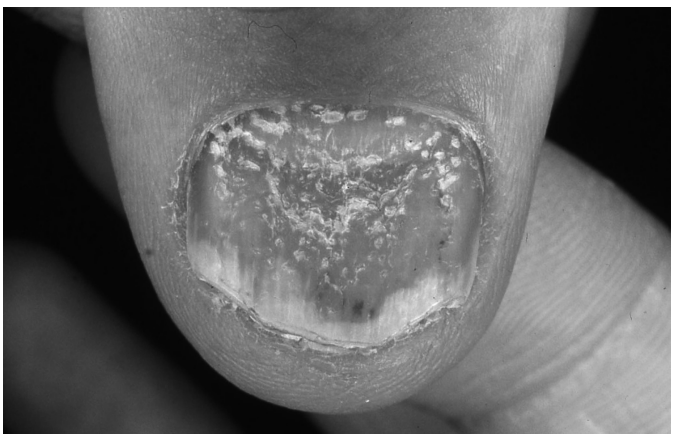

Figure 12 Nail psoriasis demonstrates pitting and onycholysis

The broad range of therapeutic options for psoriasis includes topical creams and ointments, ultraviolet light, traditional systemic agents (methotrexate, acitretin, cyclosporine) and most recently, biologic immunomodulators. Appropriate choice of therapy is largely dependent on disease severity, as determined primarily by total body surface area involvement. For patients with less than 25% involvement, topical therapies are generally effective (Lebwohl and Ali, 2001). Class 1 or 2 corticosteroid ointments are applied to affected areas of the trunk and extremities twice daily, whereas class 4 or 5 corticosteroid creams are preferred for the face or intertriginous sites to avoid steroid side effects (Table 1). Previously untreated patients usually respond best, allowing treatments to be tapered or even discontinued after a few weeks, but long-standing disease may require near-constant steroid use for good control. Calcipotriene 0.005% cream or ointment, and tazarotene 0.05/0.1% cream or ointment have a different mechanism of action and work synergistically when used in combination with topical steroids. They should be applied at different times, as simultaneous application may compromise efficacy of one or both agents. Monotherapy with calcipotriene or tazarotene is not as effective as use of a class 1 steroid. Cutaneous irritation is a common side effect of both of these steroid-sparing agents.

For patients with greater than 25% involvement and/or minimal improvement with topical treatment, ultraviolet light is an effective alternative. Oral psoralen and UVA (PUVA) or narrow band UVA (311 nm) treatments are administered 2–3 times per week, usually with substantial improvement in 1 month. For some patients, systemic therapies may be more appropriate or convenient than phototherapy or topical treatment (Lebwohl and Ali, 2001). Methotrexate, acitretin, and cyclosporine may result in adverse effects of hepatic fibrosis, hypertriglyceridemia, and renal failure, respectively. Thus, each of these medications requires appropriate monthly lab monitoring. The newest biologic agents (etanercept, alefacept, efalizumab) target specific T-cell interactions including antigen presentation, leukocyte trafficking, and cytokine production (Singri *et al.*, 2002). These agents demonstrate rapid improvement with comparable efficacy to traditional systemic therapies, without damage to internal organs. However, they are also immunosuppressive and very expensive, $12 000 to $20 000 per year per patient (Craze and Young, 2003).

Rosacea

"Adult acne" is characterized by vascular hyperreactivity and inflammatory papules and pustules. It occurs most commonly in women aged 40 to 50. The central face is predominantly involved (forehead, nose, cheeks, chin). The primary lesions are erythematous papules and pustules (Figure 13). Many patients present only with erythema, telangiectasias, and a history of flushing. Secondary bulbous deformity of the nose occurs rarely (rhinophyma). Ocular involvement with scleral injection and discomfort may occur in up to 50% of patients.

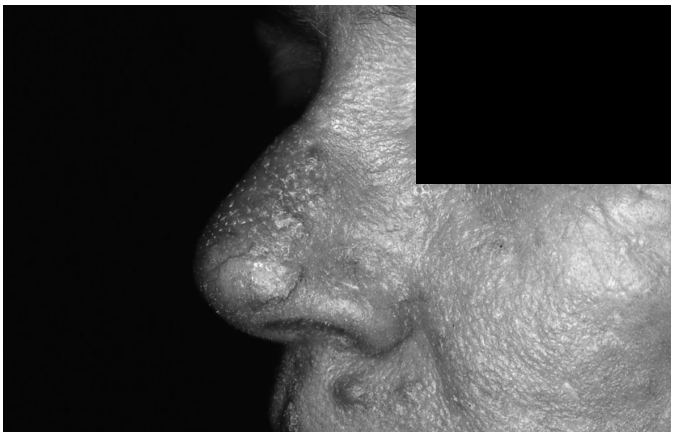

Figure 13 Rosacea. Papules and pustules of the central face and cheeks

A standard clinical classification system into erythematotelangiectatic, papulopustular, phymatous, and ocular subtypes has been suggested (Wilkin *et al.*, 2002).

Flushing is known to be triggered by any environmental stimulus that increases skin temperature of the head and neck including sunlight, hot showers, exercise, alcohol, hot beverages, and spicy food. All patients should be advised to apply daily sunscreen with a sun protection factor of 15 or greater. Physical blockers that contain titanium dioxide and zinc oxide are well tolerated. Topical antibiotics including metronidazole 0.75% cream or gel and sodium sulfacetamide 10%/sulfur 5% lotion applied twice daily are first line therapies that can reduce the number of inflammatory lesions and also the erythema (Pelle, 2003). Systemic antibiotics (tetracycline 500 mg po twice daily on an empty stomach, doxycycline 100 mg twice daily) work well for patients with more severe or extensive papules and pustules. Pulsed-dye laser treatments are very effective for the telangiectasias of rosacea, although it will not prevent development of new telangiectasias.

Stasis Dermatitis

This inflammation and discoloration of the lower extremities results from chronic venous insufficiency. Pooling of fluid in the lower extremities increases capillary pressure, causing extravasation of red blood cells and hemosiderin deposition in the dermis. The anterior shins are most commonly affected, followed by the calves, dorsal feet, and ankles. Primary lesions are red to brown hyperpigmented macules coalescing into larger patches (Figure 14). Varicosities and pedal edema are often present. Secondary changes include erythema, fine cracking, and scales. Ulceration may occur in up to 30% of patients. The differential diagnosis includes pigmented purpuric dermatosis, minocycline induced hyperpigmentation, and contact dermatitis.

Compression and leg elevation are mainstays in the management of chronic venous insufficiency and may help reduce development of ulcers. Open toe, below the knee compression stockings at 20–30 mm Hg should be worn daily. Elevation of the legs above the level of the heart when the patient is sitting or lying down will reduce venous pooling. Although the brown discoloration from hemosiderin rarely resolves, eczematous patches or plaques can be successfully treated with a class 4 topical steroid cream applied twice daily.

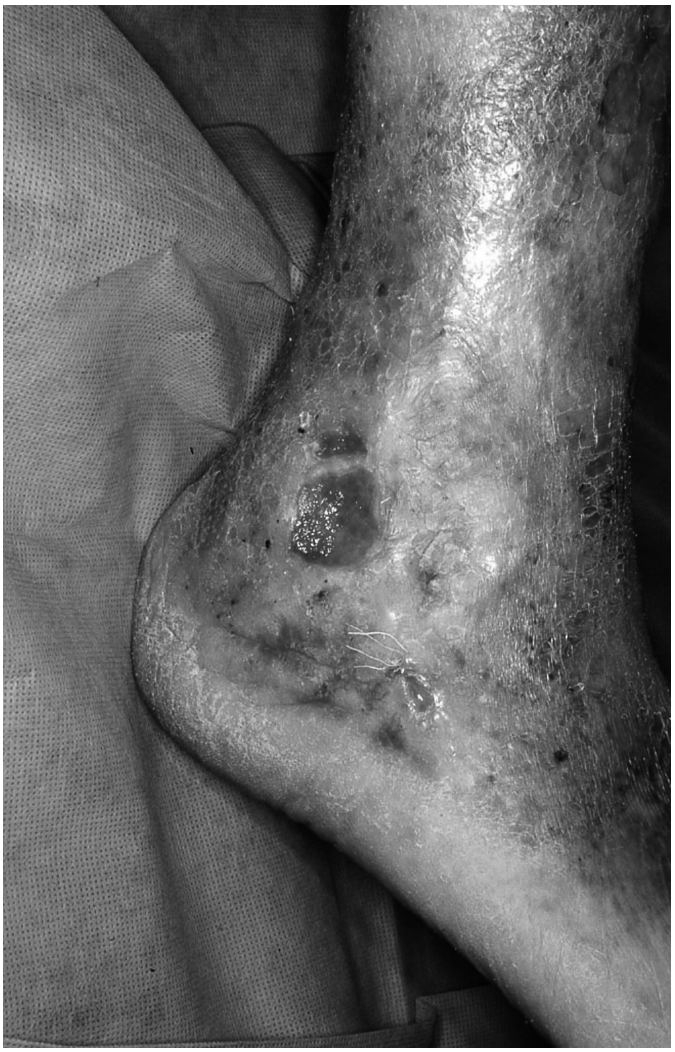

Figure 14 Stasis dermatitis. Brown discoloration with ulcer of the lateral malleolus

Drug Eruption (Morbilliform)

Maculopapular eruptions are the most common types of cutaneous drug reactions, occurring during the first 2 weeks of a new medication. The most common drugs implicated are penicillins (ampicillin, amoxicillin), sulfonamides (trimethoprim–sulfamethoxazole), nonsteroidal antiinflammatory drugs (naproxen, piroxicam), anticonvulsants (carbamazepine, phenytoin), and antihypertensives (captopril, diltiazem). The distribution is symmetric, usually beginning on the head and neck or upper trunk and progressing down the limbs. Primary lesions are erythematous macules and

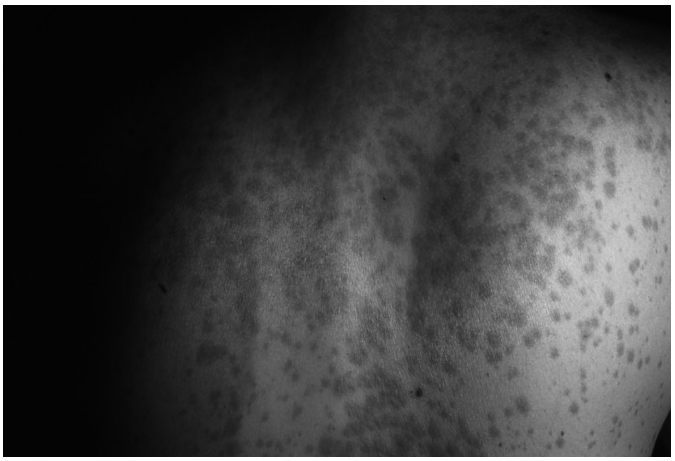

Figure 15 Morbilliform drug eruption from trimethoprim–sulfamethoxazole

papules forming areas of confluence (Figure 15). Pruritus is often present. The differential diagnosis includes viral exanthem.

Drug hypersensitivity syndrome is a potentially life threatening complication and presents as a triad of fever, cutaneous eruption (80% morbilliform), and internal organ involvement (hepatitis, nephritis, lymphadenopathy). This occurs on first exposure to the drug, with symptoms starting 1–6 weeks after exposure. In suspected cases, laboratory tests to evaluate potential asymptomatic internal organ involvement include transaminases, complete blood cell count, urinalysis, creatinine. The first step in managing a suspected drug reaction is to immediately discontinue the most likely culprit along with any unnecessary medications. Application of cool compresses or, in severe cases, a class I steroid cream applied twice daily or a predisone taper for 2–3 weeks may provide symptomatic relief of accompanying pruritus.

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune blistering disease resulting from IgG autoantibodies and C3 binding to specific antigens at the dermal–epidermal junction (BP180, BP230) with subsequent inflammatory response and bulla formation. It predominantly affects individuals over the age of 60. The distribution favors the flexures including the medial thighs, groin, axilla, abdominal folds, neck, antecubital, and popliteal fossa. Pruritus is a common symptom. The blisters are often preceded by an "urticarial phase" of erythematous and edematous papules and plaques. The primary lesions are tense bullae, ranging from 0.5 to 3 cm in size, in contrast to the smaller flaccid blisters of pemphigus vulgaris (Figure 16). After the blisters rupture, secondary changes of erosions and dried yellow to hemorrhagic crust may also be observed. These lesions heal with dyspigmentation, but rarely scarring. The differential diagnosis includes porphyria cutanea tarda, arthropod bite reaction, acute contact dermatitis, scabies (urticarial phase), and epidermolysis bullosa.

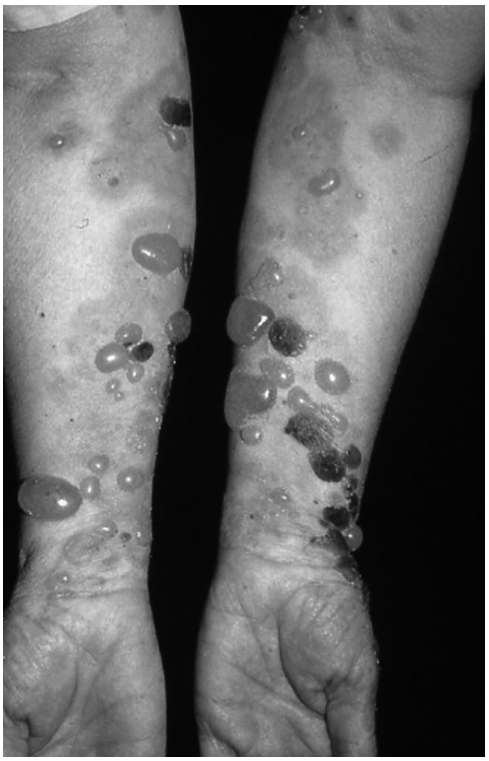

Figure 16 Volar forearms of a patient with bullous pemphigoid demonstrating tense blisters, ruptured bullae, and hemorrhagic crusts

Two biopsies are required to confirm the diagnosis. One biopsy of the blister for H&E (hematoxylin and eosin) demonstrates the subepidermal split and the eosinophil-rich infiltrate. Another biopsy of perilesional skin for immunofluorescence demonstrates linear deposition of IgG and C3 along the basement membrane zone.

Suppression of the immune system is the cornerstone of therapy. Prednisone at 0.5 to 1.0 $mg\,kg^{-1}\,day^{-1}$ gradually tapered over 3 to 6 months is the first choice. For patients not responding rapidly, or requiring a high maintenance dose of predisone, a steroid-sparing agent such as mycophenolate mofetil or azathioprine should be given in combination with prednisone to allow a reduction in dose, and eventual discontinuation of the steroid. Tetracycline (500 mg 4 times/day) with nicotinamide (500 mg 3 times/day) may be effective in patients with limited disease.

BENIGN NEOPLASMS

Seborrheic Keratosis

This common growth of adulthood occurs after the age of thirty on face and trunk. The primary lesion is a 5–15 mm brown papule or plaque with a warty surface and a greasy feel on palpation. There is often a variety of colors in a single lesion ranging from beige to dark brown to black. On closer inspection, small 1 mm horn cysts may be apparent

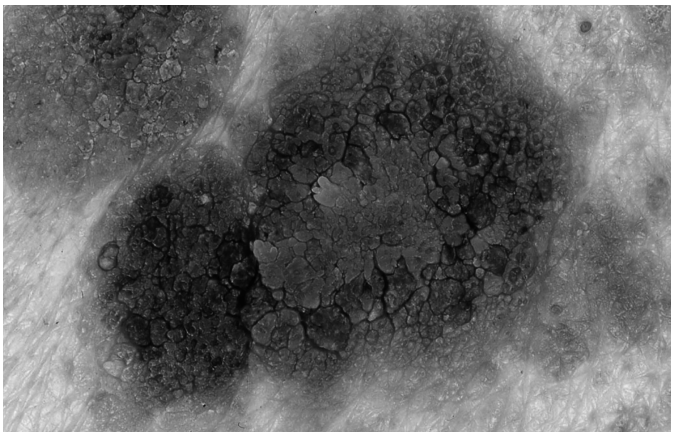

Figure 17 Seborrheic keratosis with horn cysts

(Figure 17). The pathogenesis of seborrheic keratosis is not well established, although the lesions occur more commonly on sun-exposed sites. The differential diagnosis includes pigmented basal cell carcinoma (BCC), melanoma, and warts (verruca vulgaris). Diagnosis is usually made clinically. However, if pigmented BCC or melanoma is highly suspected, a biopsy is recommended. Seborrheic keratoses are usually asymptomatic and require no treatment. If the lesions are inflamed, irritated, or cosmetically undesirable, they can easily be removed by cryotherapy, curettage, or shave excision.

Epidermoid Cyst

Synonyms for epidermoid cyst include wen, sebaceous cyst, or epidermal inclusion cyst. This common cutaneous cyst is usually located on the face, scalp, or trunk. The primary lesion is 5–30 mm flesh-colored to yellow, dermal to subcutaneous nodule (Figure 18). It often has a central punctum that may express foul smelling cheese-like keratin when pressure is applied. Epidermoid cysts are freely mobile over the underlying tissues. They can arise primarily from sebaceous follicles or from traumatically implanted epithelium. Although these cysts are usually asymptomatic and require no treatment, they can be cosmetically annoying or rupture from pressure. Ruptured cysts extrude keratin into the dermis and the resulting foreign body reaction leads to erythema, swelling, and pain. Incision and drainage followed by tetracycline 500 mg po twice daily for 2 weeks or intralesional triamcinolone acetonide 5 mg ml^{-1} will relieve the acute inflammation. Definitive treatment requires excision with removal of the entire cyst wall.

PREMALIGNANT AND MALIGNANT NEOPLASMS

Actinic Keratosis

Actinic keratosis is a precursor lesion to SCC. Actinic keratoses are seen commonly in middle-aged, fair-skinned Caucasians in a photo-distribution including the face, lips, ears, dorsal hands, and forearms, the result of cumulative lifetime of sun exposure. The primary lesion is a 5–10-mm rough, adherent, white scaly papule or plaque, often on an erythematous base (Figure 19). On palpation, it feels gritty, with a sandpaper-like texture. Early lesions are often more readily detected by palpation than visual inspection. The differential diagnosis includes seborrheic keratosis. Immunosuppressed patients, particularly transplant recipients, are at higher risk for actinic keratoses. There is a low risk of progression to invasive carcinoma for an individual lesion, estimated at far less than 1% per year by most authorities, but individuals with multiple actinic keratoses are at high risk of skin cancer by virtue of their diffused photodamage.

Regular sun avoidance prevents progression of actinic keratoses and allows regression of many. Daily application of sunscreen with sun protective factor 15 or greater, long-sleeve shirts, and broad-brimmed hats are recommended. Isolated lesions are often frozen with liquid nitrogen in the office setting. Liquid nitrogen can be applied with a

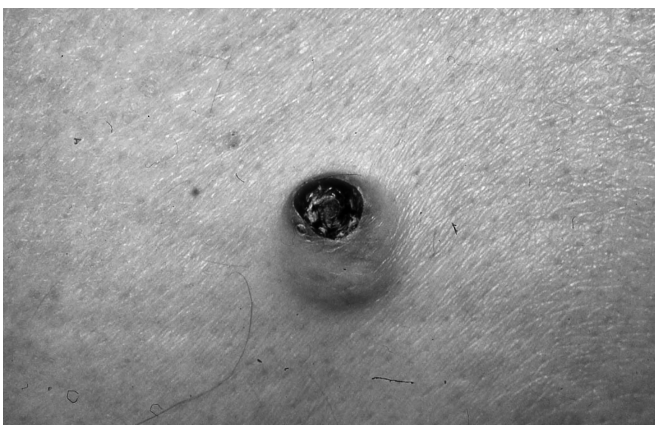

Figure 18 Epidermoid cyst with central punctum

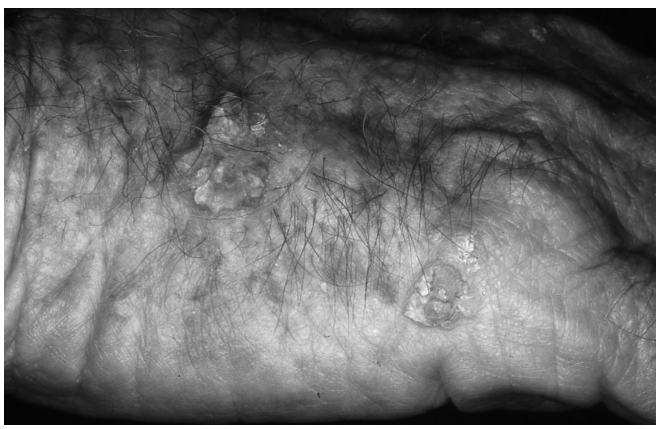

Figure 19 Hypertrophic actinic keratoses of the dorsal hand

cotton-tipped applicator or an open-spray technique with a handheld nitrogen unit, until the lesion turns white. This is repeated for a second cycle. Patients will experience stinging or burning during the treatment followed by erythema and sometimes blistering of the treated lesion. Other treatments include 5-fluorouracil 5% cream, imiquimod 5% cream, chemical peels, and photodynamic therapy. 5-fluorouracil 5% cream is applied twice daily for 3 weeks. Patients must be informed that treated areas will become progressively and often severely inflamed and eroded. A return visit scheduled in 1–2 weeks for patient assessment and reassurance is recommended. Compliance can be improved by dividing the affected area into smaller subunits and treating one subunit at a time to minimize the inflammatory reaction. Imiquimod 5% cream, recently approved in the United States for the treatment of actinic keratoses, is applied to the entire treatment area before bedtime and left on for 8 hours, twice weekly for 16 weeks (Lebwohl *et al.*, 2004). Side effects are similar to 5-fluorouracil. Recent studies with photodynamic therapy (application of a photosensitizing drug with exposure to its activating wavelength of light to achieve destruction of target tissue) demonstrate efficacy comparable to topical therapies and cryotherapy, with approximately 90% disappearance of lesions (Touma *et al.*, 2004; Piacquadio *et al.*, 2004). Advantages of this procedure include rapid healing and disappearance of treated lesions within 1 month, physician-controlled delivery allowing complete and homogeneous treatment of the face and/or scalp, eliminating the need for patient compliance. Because patients with actinic keratoses are also at risk for skin cancer, including melanoma, they should be examined annually.

Basal Cell Carcinoma (BCC)

BCC accounts for approximately 75% of all skin cancer, more than 1 million cases per year in the United States. It is also related to chronic ultraviolet light exposure, affecting predominantly fair-skinned Caucasians and involving the head and neck more often than the trunk and extremities. The nose is the most common site. The primary lesion is a translucent or pearly papule with visible telangiectasias (Figure 20). Late changes include central crusting or ulceration. Patients often complain that these lesions "do not heal" and they may break down or bleed. Histologic confirmation by shave or punch biopsy techniques is required to confirm the diagnosis. The differential diagnosis includes SCC, keratoacanthoma, and sebaceous hyperplasia. BCC is a very slow growing tumor that rarely metastasizes. However, if left untreated, significant morbidity can result from local invasion and extension to underlying cartilage, fascia, muscle, and bone.

Appropriate choice of therapy is dependent on the risk for recurrence and metastasis (Miller, 2000). Low risk tumors are defined as primary tumors measuring up to 2 cm on the trunk and extremities or up to 1 cm on the head and neck, with well-defined clinical borders, and occurring in an immunocompetent patient. Excision with 4-mm margins and electrodesiccation, and curettage (ED&C) have comparable cure rates of 90%. High-risk tumors have one or more of the following characteristics: recurrent tumor; size greater then 2 cm on the trunk and extremities or greater than 1 cm on the head and neck; poorly defined clinical borders; occurring in an immunosuppressed patient. These are best excised with concurrent histologic confirmation of clear margins before closure (Mohs surgery). Cure rates at 5 years are then 98–100%. For patients with a prior BCC, the 3-year cumulative risk for recurrence is 44% (Marcil and Stern, 2000). An annual skin examination is sufficient for detecting new BCCs. The number of prior skin cancers is a strong risk factor for development of subsequent skin cancers; thus patients with multiple BCCs should be examined more frequently.

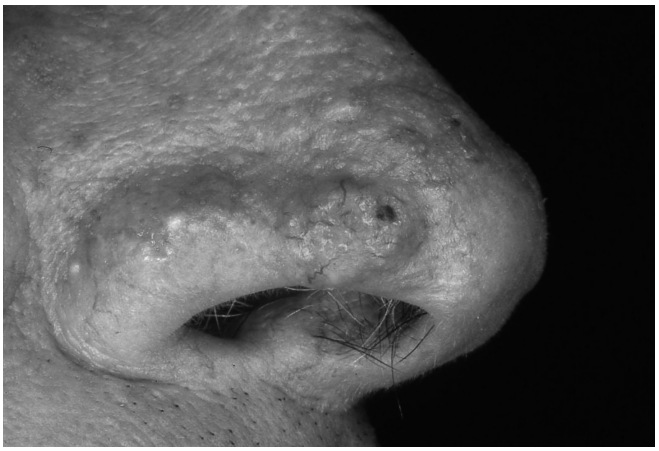

Figure 20 Nodular basal cell carcinoma with telangiectasias

Squamous Cell Carcinoma (SCC)

SCC is the second most common skin cancer, approximately 20% of the total, and derives from keratinocytes above the basal layer of the epidermis, often with actinic keratoses as precursor lesions. It predominantly affects the habitually sun-exposed head, neck, and dorsal hands, although SCC can also arise at sites of chronic inflammation, in areas of prior radiation or old burn scars, or on the genitals. The primary lesion is a firm indurated papule, plaque, or nodule (Figure 21). Secondary changes include hyperkeratotic scale or central ulceration with crust. These lesions do not heal and often break down and bleed. Biopsy with shave or punch technique is required to confirm the diagnosis. The differential diagnosis includes BCC and keratoacanthoma. SCC on the lips or ears has a 10–15% risk of spread to cervical nodes. SCC should be suspected in any persistent nodule, plaque or ulcer, especially when occurring in sun-damaged skin or on the lower lip. Immunosuppressed patients (transplant recipients) are at higher risk for SCC due to impaired cell-mediated immunity.

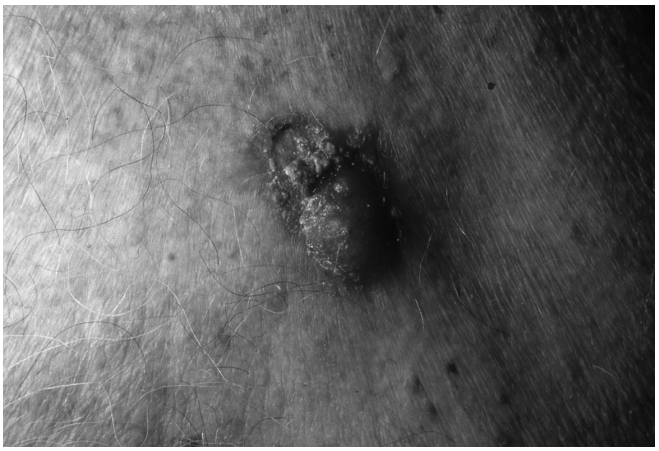

Figure 21 Squamous cell carcinoma of central chest

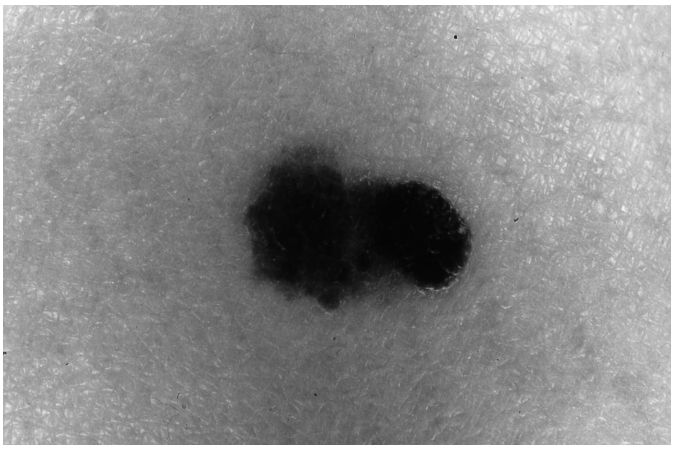

Figure 22 Superficial spreading melanoma demonstrating a nodular area likely to represent deep invasion

ED&C and excision have comparable cure rates of 90% for low risk tumors (defined for BCC). Mohs surgery is suggested for high-risk tumors defined as having one or more of the following: recurrent tumor; tumor measuring >2 cm on the trunk and extremities, or >1 cm on the head and neck; location on the genitals, lips, ears, site of prior radiation or scar; tumor with poorly defined clinical borders; and tumor occurring in an immunosuppresed host (Miller, 2000). For patients with a prior SCC, the 3-year cumulative risk for another SCC is 18% (Marcil and Stern, 2000). Annual follow-up examinations for at least 3 years are recommended. Patients with multiple SCCs should be seen more frequently.

Melanoma

Melanoma comprises 5% of all skin cancers. It is derived from melanocytes and has the greatest potential for metastasis. The incidence of melanoma is increasing faster than any other cancer. The lifetime risk of melanoma in an individual in the United States born in 2004 is estimated at greater than 1 in 70. Older men have the highest incidence of melanoma and the highest mortality rates from melanoma. In the United States, the incidence of thick tumors (>4 mm) has continued to increase in men 60 years and older (Jemal *et al.*, 2001). Nearly 50% of all melanoma deaths involve white men 50 years and older. Risk factors include light complexion (red-blonde hair), blistering sunburns during childhood, tendency to tan poorly and sunburn easily, and a positive family history. Additional risk factors in the middle-aged population include age greater than 50 years, male sex, and history of actinic keratoses or nonmelanoma skin cancer.

There are three clinical and histologic subtypes of melanoma: nodular (15%), superficial spreading (70%), and lentigo maligna melanoma (15%). The latter usually evolve after many years from a variegate, gradually enlarging macule on the face and neck of the elderly. The other types arise most commonly on the trunk or legs. The primary lesion is a brown to black macule, papule, plaque, or nodule with one or more of the following features: asymmetry, border irregularity, color variegation, and diameter greater than 6 mm (Figure 22). Patients may notice an increase in size of a pigmented lesion and bleeding. The differential diagnosis includes solar lentigo, seborrheic keratosis, dysplastic nevus, and pigmented BCC. If possible, suspected lesions should be excised with 1–2 mm margin of normal skin down to the subcutaneous fat.

Melanoma is treated by surgical excision with margins determined by histological tumor thickness (Breslow depth). (Balch *et al.*, 2001) Tumor thickness and presence or absence of histologic ulceration are the most important prognostic factors (Balch *et al.*, 2001). Patients with thin melanomas (<1.0 mm) have the best prognosis ($>90\%$ five-year survival rate), whereas those with thick tumors (>4 mm) have a 50% five-year survival rate. Evaluation of nodal involvement with sentinel lymph node biopsy provides regional lymph node staging information for patients at high risk for metastatic melanoma (primary melanomas >1.0 mm in depth, and for tumors ≤ 1 mm when histological ulceration is present) (Perrott *et al.*, 2003). Newly diagnosed and established melanoma patients require periodic complete skin examinations including mucosal sites, genitals, buttocks, palms and soles, lymph nodes, and palpation for hepatosplenomegaly. They should also be instructed on how to perform monthly self-skin exams. Frequency of follow-up, laboratory tests, and imaging studies depend on the stage of disease.

CUTANEOUS MANIFESTATIONS OF INTERNAL MALIGNANCY

There is a variety of skin signs associated with internal malignancy. Although uncommon, these findings with subsequent diagnostic testing may help one to discover an otherwise occult malignancy. Some cutaneous markers for malignancy are listed in Table 5.

Table 5 Cutaneous manifestations of internal malignancy

Skin sign	Physical findings	Associated malignancies
Metastases	≥1 cm firm nodule(s) on the scalp, flesh-colored to pink to black	Breast, lung, genitourinary
Bazex syndrome	Erythematous scaly plaques on the ears, nose, cheeks, hand, feet and knees. Hyperkeratosis of the palms & soles	Upper respiratory & digestive tracts
Paget's disease	Unilateral erythematous sharply defined plaque of the nipple and areola. Unresponsive to potent topical steroids	Breast
Generalized pruritus	Unexplained itching not associated with dry skin	Hodgkin's disease Leukemia/ lymphoma Mycosis fungoides
Dermatomyositis	Swelling of the face & eyelids with a pink to violaceous hue. Flat-topped violaceous papules over the PIP and DIP joints. Proximal muscle weakness	Lungs Gastrointestinal Breast
Erythema gyratum repens	Wavy erythematous plaques with fine peripheral scale in a concentric pattern (wood grain appearance). Lesions migrate over the skin surface	Lung, breast, stomach, other
Erythroderma	Erythematous patches or plaques with exfoliative scale covering ≥90% of total body surface area	Lymphoma, leukemia, Sezary syndrome
Acquired ichthyosis	Dry fish-like scale involving the extremities	Lymphoma, multiple myeloma, Lung, breast, cervical cancer
Acanthosis nigricans	Hyperpigmented velvety plaques involving the flexures (axilla, groin, neck)	Stomach Other gastrointestinal or genitourinary

KEY POINTS

- Successful management of dermatophyte infections (tinea pedis, onychomycosis) requires adequate patient education, correction of underlying predisposing factors, and prophylactic measures against recurrence.
- Inflammatory disorders are chronic, but can be effectively controlled with a routine skin care regimen (application of moisturizer, sunscreen) and topical therapies.
- Benign lesions may be biopsied or removed if they become irritated or cosmetically undesirable.
- Recommendations for skin cancer prevention include regular sun avoidance, daily application of sunscreen, long-sleeve shirts, and broad-brimmed hats.
- Patient education, early detection, and adequate monitoring are the keys to timely diagnosis of skin cancer.

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Pressure Ulceration

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INTRODUCTION

A pressure ulcer may be defined as an area of localized damage to the skin and underlying tissue caused by pressure, shear, friction or a combination of these (European Pressure Ulcer Advisory Panel). Pressure Ulcers are known by a variety of other terms including bed sore, decubitus ulcer, pressure sore, and dermal ulcer. However, these terms do not accurately reflect the nature or etiology of the wound and are thus best avoided. Pressure ulcers arise as a local breakdown of soft tissue as a result of compression between a bony prominence and an external surface. The majority of pressure ulcers develop on the lower half of the body: two-thirds of these occur around the pelvis and one-third on the lower limbs. Common sites of pressure ulceration are shown in Figure 1. Pressure ulcers are most common in the elderly population, especially those older than 70 years, up to one-third of whom will have undergone surgery for a hip fracture. A second distinct population are those with spinal cord injuries with a reported prevalence of 20–30% 1–5 years after injury.

Over four hundred thousand people develop a pressure ulcer annually in the United Kingdom. Pressure ulcers most commonly arise in the hospital setting with a prevalence ranging from 3 to 14% in the acute setting. This rate varies between specialties; 2% in general surgical patients and 10% in orthopedic patients, reflecting, in part, the age differences of the two groups (Clark and Watts, 1994). The incidence in the acute setting is between 1 and 5%, though in patients who are bed- or chair-bound for more than 1 week, the incidence rises to almost 8%. Development of a new pressure ulcer is associated with a fivefold increase in length of hospital stay (Lazarus *et al.*, 1994).

In long-term facilities, the prevalence ranges from 1.5 to 25%. The prevalence of pressure ulceration in nursing homes is not appreciably higher than in the acute hospital setting. Around 20% of pressure ulcers develop at home and a further 20% in nursing homes. Pressure ulceration in an elderly person carries a fivefold increase in mortality, with the in-hospital mortality rate of 25 to 33%. By 2020, the number of people aged over 65 years in the United Kingdom will rise by 20%: The incidence of pressure ulceration will rise concomitantly.

Pressure ulcers are responsible for a significant degree of morbidity, both physical and psychological. Moreover, they represent a huge financial burden, both to the individual and to society as a whole. In 1993, the cost of pressure ulcers to the NHS was estimated at between £180 and £321 million (Touche, 1993). More recent studies have shown that this cost has escalated to between £1.4 and £2.1 billion annually, equivalent to 4% of the total NHS expenditure (Bennett *et al.*, 2004): This was believed to be a conservative estimate as the figures did not reflect the cost of associated problems such as methicillin resistant staphylococcus aureus (MRSA) infection, heel pressure ulcers associated with peripheral vascular disease and pressure ulcers in diabetics.

The cost of healing a grade IV pressure ulcer was found to be ten times that of healing a grade I pressure ulcer (Bennett *et al.*, 2004). Osteomyelitis complicating pressure ulceration significantly increases the need for hospital admission with a lengthy in-patient course and increased financial cost, mostly reflecting nursing time. Most pressure ulcers are avoidable, with the cost of preventing pressure ulceration representing a significant potential cost saving to the patient and to the health-care system. The cost to society of pressure ulceration continues to increase as a result of increased litigation. In the United States, development of a pressure ulcer in a care home or hospital may be regarded in a court of law as evidence of clinical negligence.

PATHOGENESIS

The four main extrinsic factors implicated in the etiology of pressure ulceration include interface pressure (the load perpendicular to the tissue surface), shear (the load parallel

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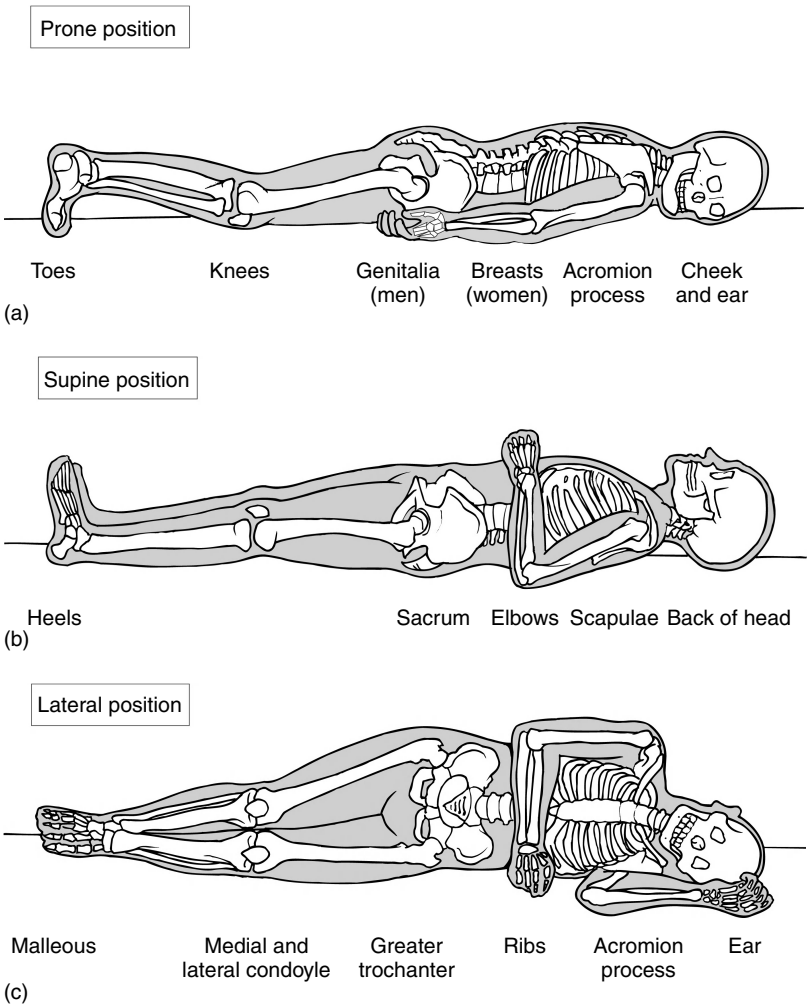


Figure 1 Common sites of pressure ulceration in the at-risk individual in (a) the prone position, (b) the supine position, (c) the lateral position

to the tissue surface), friction (the load acting tangentially to the tissue surface), and moisture. While direct (interface) pressure is the most important etiological factor, all four are closely interrelated.

In the 1930s, Landis estimated, in healthy volunteers, that normal capillary pressure ranged from 32 mm of mercury (mmHg) on the arterial side of the circulation to 12 mmHg on the venous side (Landis, 1930). When pressure of short duration is relieved, the tissue demonstrates reactive hyperemia, reflecting increased blood flow to the area. A sustained high closing pressure in excess of 32 mmHg was postulated to lead to decreased capillary blood flow, occlusion of blood vessels and lymphatics and tissue ischemia (Figure 2). The closing pressure was revised in later work by Landis to between 45 and 50 mmHg. Pressure as low as 40 mmHg has, however, been found to cause tissue anoxia in some elderly patients (Bader and Gant, 1988).

Dermal capillaries are coiled at their bases and are thus more resistant to occlusion by pressure. The subcutaneous vessels run parallel to the deep fascial planes and are more likely to be occluded by external pressure leading to tissue damage (Bliss, 1993). Prolonged pressure may, therefore, lead to ischemic changes and pressure ulceration due to perfusion/reperfusion injury from build up of inflammatory molecules.

The highest pressures occur over bony prominences at the bone/muscle interface (Figure 3). Thus, an external pressure of 50 mmHg may rise to over 200 mmHg at a bony prominence, leading, with time, to deep tissue destruction, which may not be evident on the surface of the skin. Such pressures may decrease transcutaneous oxygen tensions to almost zero. Pressures as high as 150 mmHg have been recorded from patients lying on ordinary mattresses (Lindan, 1961; Houle, 1969); regular relief from high pressures in the at-risk patient is, therefore, essential to prevent pressure ulceration.

Such changes are ultimately responsible for necrosis of muscle, subcutaneous tissue, dermis and epidermis and consequent pressure ulcer formation. It will be apparent though, that high pressure of short duration will lead to more rapid tissue damage while low pressure leads to a more insidious onset of tissue damage and ulceration

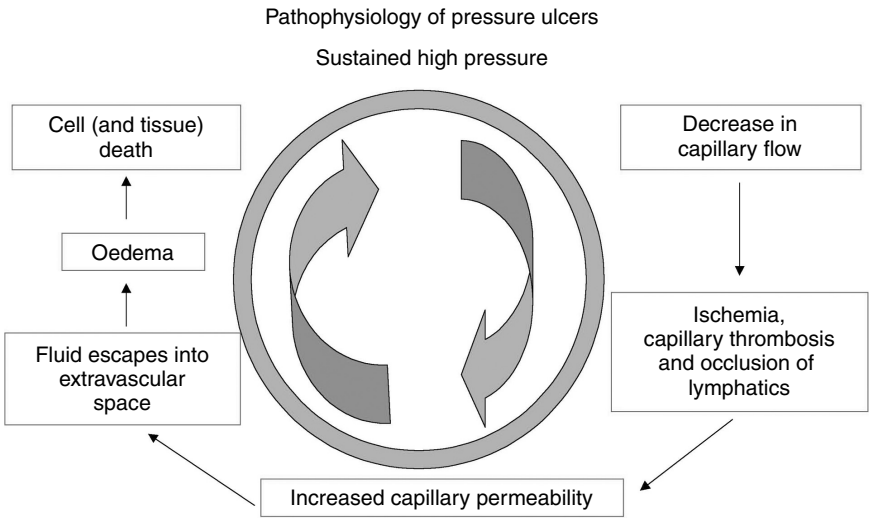


Figure 2 Schematic representation of the mechanism of pressure-induced tissue damage

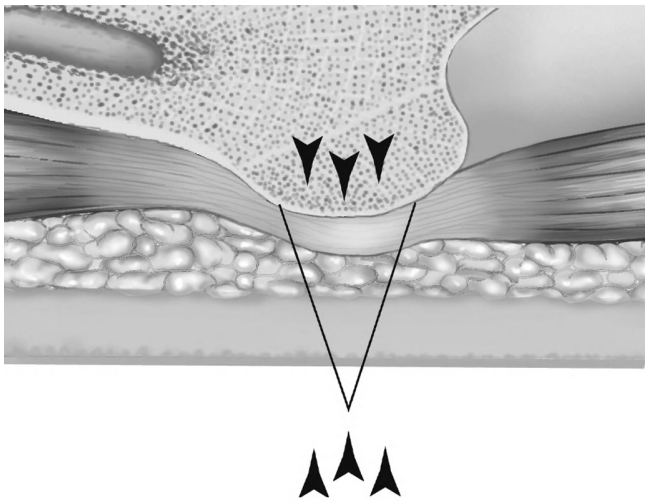


Figure 3 Conical pattern of pressure distribution over a bony prominence, illustrating the fact that seemingly low external pressure rises to a much higher pressure at the bone/muscle interface. Thus, tissue damage may be unrecognized as the skin may still be intact

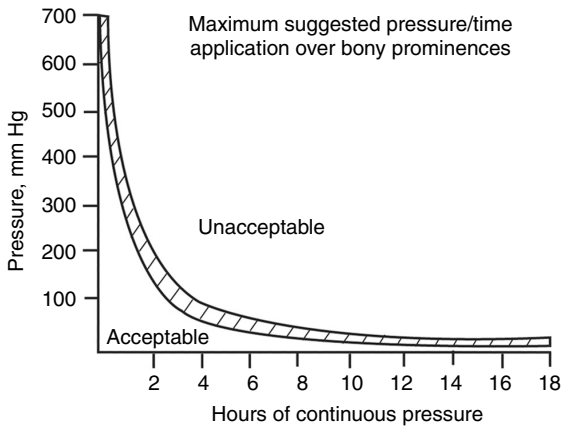


Figure 4 Guidelines on sitting tolerance based on the magnitude of localised pressure (From Reswick J and Rogers J. Experiences at Rancho Los Amigos Hospital with Devices and Techniques to Prevent Pressure Sores. Bedsore Biomechanics. Baltimore: University Park Press)

(Figure 4). However, duration of pressure is also important and tissue damage may be avoided in the face of sustained pressure, which is relieved intermittently. This forms the basis of the rationale of regular turning of patients at risk of pressure ulceration, though the minimum frequency is still a matter of debate. Clinically, pressures of 70–100 mmHg have been recorded over bony prominences supported by standard NHS mattresses (Collier, 2004). Pressure-reducing mattresses reduce this pressure to between 30 and 40 mmHg (Collier, 1996).

Shear force (the load parallel to the tissue surface) is generated owing to the motion of bone and subcutaneous tissue relative to the skin, which is restrained from moving due to frictional forces (Figure 5). For example, when a seated patient slides down the chair or when the head of a bed is elevated to greater than 30°, the sacral skin remains fixed with respect to the support surface while the sacrum moves, and the deep fascial blood vessels are stretched and distorted. In such circumstances, the pressure required to occlude the blood vessels is greatly reduced, which reduces the rate of recovery from tissue anoxia (Schubert and Héraudj, 1994). In the elderly individual, reduced skin elastin content predisposes to the adverse effects of shear. While interface pressure is of more importance in generating tissue damage, the concomitant presence of shear increases the risk of ischemic damage. The effect of shear may be reduced through the use of vapor-permeable mattress covers, which reduce the amount of moisture.

Friction, acting tangentially to the tissue surface, opposes the movement of one surface against another (Figure 6). Frictional forces may lead to the formation of intraepidermal

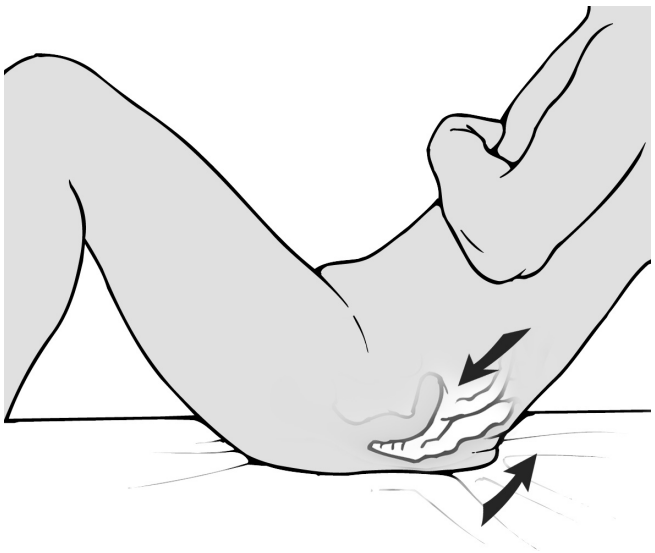


Figure 5 Shear force

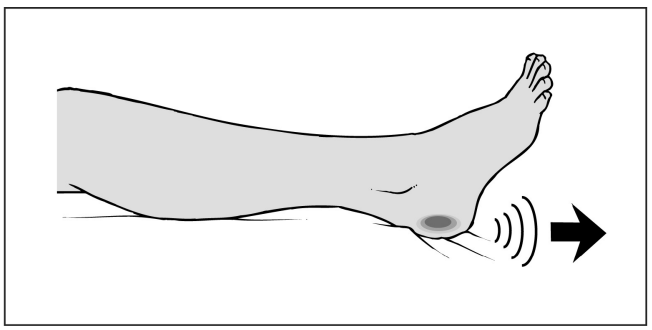


Figure 6 Friction force

blisters, which in turn lead to superficial skin erosions, initiating or accelerating pressure ulceration. Such forces occur, for example, when a patient is dragged across a bedsheet, pulling the sheet under the patient, sliding transfer from bed to chair, or as a result of ill-fitting prosthetic devices or footwear. Friction reduces the amount of pressure required for ulceration to occur.

It must be emphasized that pressure damage reflects a complex interplay of these three forces, each playing a greater or lesser role depending on the situation pertaining at that time and also affected by the presence of moisture.

While moisture, by itself, does not cause pressure ulceration, an excessively moist environment caused by, for example, perspiration, urinary or fecal incontinence or excessive wound drainage enhances the deleterious effects of pressure, friction, and shear. It also causes maceration of the skin, which compounds these factors. Friction and moisture are important factors leading to superficial skin breakdown and produce the greatest effects in areas of high pressure: The effects of friction are increased up to fivefold in the presence of moisture. Pressure and shear forces exert their effects on deeper structures (Hall, 1984; Herman and Rothman, 1989).

RISK FACTORS

Many groups, including the Tissue Viability Society (UK), the National Pressure Ulcer Advisory Panel (NPUAP) (USA) and the European Pressure Ulcer Advisory Panel, have developed guidelines and protocols on pressure ulcer prevention and treatment. The main such body in the United Kingdom is The National Institute for Clinical Excellence (NICE). NICE has developed guidelines on pressure ulcer prevention (NICE, 2003) and is also developing guidelines on the treatment of pressure ulceration. NICE has identified various risk factors associated with the development of pressure ulceration (Table 1).

Acute Illness

Pressure Ulceration is more common in immobile patients who develop pyrexia (Bar and Pathy, 1998). This leads to an increased metabolic rate and increased demand for oxygen by the compromised tissues, making pressure ulceration more likely. Acute illness also leads to general metabolic disturbance which is further compromised by, for example, poor nutrition and drug therapy, which may lead to reduced tolerance of pressure and, in patients with established pressure ulceration, to impaired healing. The precise extent to which such systemic conditions increase the risk of developing pressure damage and difficulties in healing remain to be quantified.

Limited Mobility/Immobility

Immobility (the inability to reposition without assistance) or limited mobility are probably the major factors leading to pressure ulcer formation and may occur for a variety of reasons. These include paralysis (the inability to move due to loss of motor nerve function) due to neurological problems such as stroke and spinal cord injury, which lead to hemi-, para- or quadriplegia. Paralysis also leads to decreased muscle bulk and reduction of subcutaneous tissue, which, in turn, predisposes to pressure ulceration. Physical illness, including arthritis and orthopedic problems, leads to difficulty in changing position due, for example, to pain as well as joint deformity and lack of strength. The elderly are

Table 1 Risk factors for pressure ulceration

Acute illness
Extremes of age
Level of consciousness
Malnutrition/dehydration
Limited mobility/immobility
History of pressure damage
Sensory impairment
Severe chronic or terminal disease
Vascular disease

particularly prone to such problems. Obesity may lead to reduced mobility.

One of the commonest reasons for immobility in the elderly is fracture of the neck of femur. Fractured neck of femur has been shown in a cross-sectional study to be a risk factor for the development of a pressure ulcer (Scheckler and Peterson, 1986). Between 50 and 60% of patients with fracture of the femur develop a pressure ulcer, most of which develop within five days to two weeks of admission and occupying 20% of orthopedic beds (Versluysen, 1985, 1986).

Being bed- or chair-bound significantly increases the risk of pressure ulceration; appropriate pressure-relieving surfaces should be provided. Individuals with increased limb tone (spasticity) may benefit from interventions such as physiotherapy, muscle relaxants, nerve block, or surgery.

The number of nocturnal movements is correlated with development of pressure ulcers. One study has shown that 90% of ulceration in older patients occurred in those who have less than 20 spontaneous movements per night: No pressure ulcers were recorded in those patients with more than 50 movements per night (Exton-Smith and Sherwin, 1961). Reduced nocturnal mobility is associated with use of sedative medication and a high-pressure ulcer risk score (Barbenel *et al.*, 1986).

Other risk factors, which have been found to increase the incidence of pressure ulceration in the immobile patient, include dry skin, a preexisting grade I pressure ulcer (non-blanchable erythema of intact skin) and fecal incontinence (Allman *et al.*, 1995). In patients with spinal cord injuries who develop pressure ulcers, the serum albumin, prealbumin and cellular adhesion molecules (which have a role in immunity and wound healing) have been shown to be lower than those without injuries (Cruse *et al.*, 2000).

Impact of Age

Age alone is not an independent risk factor for pressure ulcer development. The fact that the frequency of pressure ulcer rises with age is a consequence of the comorbidities associated with advancing age (Allman *et al.*, 1995). The effects of all such risk factors should be minimized through their optimal management. The elderly are more likely to have underlying chronic disease, which may be severe, contribute to immobility, increase the risk of pressure ulceration and may impair healing. As many as 70% of patients with pressure ulcers are over 70 years of age (Barbenel *et al.*, 1977). Individuals between 70 and 75 years of age have double the incidence of pressure ulcers compared with 55–69 year-olds. The greatest incidence of pressure ulcers occurs in the 80–84-year age-group (Ek and Bowman, 1982). More than two-thirds of the elderly with pressure ulcers are female (Nyquist and Hawthorn, 1987).

Age-related susceptibility to skin breakdown in the face of other comorbidities may occur owing to loss of dermal vessels, thinned epidermis, flattening of the dermo-epidermal junction, decreased elastin content and increased skin permeability (Carter and Balin, 1983). Significant risk factors for the development of pressure ulcers in the chronically sick patient include cerebrovascular accident (CVA), impaired nutritional intake, being bed- or chair-bound and having fecal incontinence (Berlowitz and Wilking, 1989). The incidence of fracture of the neck of femur increases with age and is a significant risk factor for pressure ulcer development.

Severe Chronic or Terminal Illness

Chronic and terminal illnesses are, by nature, more common with increasing age. In hospitals, the main focus of treatment is the underlying illness, and the prevention and treatment of pressure ulcers may be seen as a lower priority. Caution should be exercised in the use of drugs used in such diseases: Drugs such as sedatives and analgesics may lead to immobility, while antihypertensives may cause alteration of skin blood flow (Kanj *et al.*, 1998).

Diabetes is a major cause of morbidity and may be associated with pressure ulcer formation. Diabetics are at risk of vascular disease, which may lead to reduced tissue perfusion. Diabetic sensory neuropathy impairs the ability to sense and react to pressure, pain, and temperature. Autonomic and motor neuropathy lead to dry skin, which cracks easily, and to altered foot architecture, which itself predisposes to diabetic foot ulceration as a result of altered foot pressure.

Chronic respiratory disease such as chronic obstructive pulmonary disease (COPD) may lead to decreased tissue oxygenation and thus tissue that is more prone to pressure damage. Chronic cardiovascular disease and peripheral edema may also predispose to pressure ulceration. Inadequate circulation due, for example, to cardiovascular or peripheral vascular disease will lead to poor tissue oxygenation and may predispose to pressure ulcer formation. Anemia, similarly, leads to reduced oxygenation and increased susceptibility to pressure damage: Pragmatically, the hemoglobin should, if possible, be maintained above $10\,\mathrm{g\,dl^{-1}}$.

Individuals with terminal illness are at high risk of pressure ulceration. Prevalence of pressure ulcers in such patients ranges from 37 to 50% (Hatcliffe and Dawe, 1996) and reflect the severity of the underlying disease. While most pressure ulcers are avoidable, they may reflect the multisystem failure that often accompanies terminal illness. In these cases, aggressive preventative measures may be inappropriate; patient comfort and dignity should be of prime concern.

Vascular Disease

Peripheral vascular disease is particularly associated with smoking and diabetes. It leads to reduced blood perfusion and increased risk of pressure ulceration: The heels, feet, and toes are at particular risk (Figure 7).

Malnutrition and Dehydration

Attention to nutrition is critical in the prevention and management of pressure ulcers. There is a correlation between

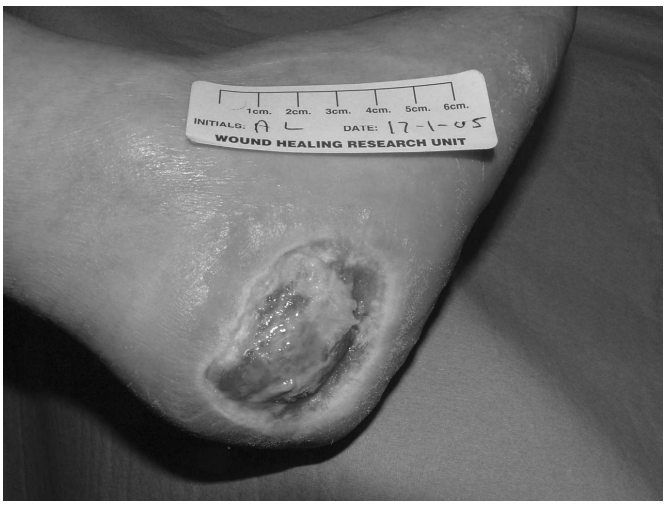


Figure 7 Heel pressure ulcer

the degree of malnutrition and the extent and severity of pressure ulceration (Allman *et al.*, 1986). In addition, malnutrition retards the healing of established pressure ulcers (Herman and Rothman, 1989). Malnutrition (protein-energy), impaired oral intake, and the development of pressure ulceration are closely interrelated. The relative risk of pressure ulcer development in high-risk malnourished patients is more than double that of patients with normal nutritional status (Thomas *et al.*, 1996). Two-thirds of severely malnourished nursing home residents were found in one study to have pressure ulcers, compared with none in mild to moderately malnourished residents (Pinchcofsky-Devin and Kaminski, 1986). Furthermore, malnutrition is associated with increased mortality in nursing home residents (Bourdel-Marchasson *et al.*, 2000).

Studies on the prevention of pressure ulceration through nutritional intervention are inconclusive (Mathus-Vliegen, 2004). However, it is generally accepted that, in order to prevent pressure ulceration in undernourished and malnourished patients, an energy intake of 35 kcal per kg body weight is required. $1.5\,g\,kg^{-1}$ of protein and 1 ml per kcal per day fluid intake with the addition of the recommended daily allowance of micronutrient should be provided (though there are no good data on the amount or type) (EPUAP; Chernoff *et al.*, 1990; Breslow *et al.*, 1993; Mathus-Vliegen, 2004). In individuals with established pressure ulceration, the nutritional demands may be greater.

Patients at high risk and those with established pressure ulceration should be assessed and reviewed by a dietician. Provision of adequate nutrition may involve supplementary feeding, either assisted or enteral (via a nasogastric or PEG tube), though there may be a degree of morbidity associated, including diarrhea, incontinence, and limited mobility while attached to the feed – in themselves risk factors for pressure ulcer formation. Supplementation with high protein dietary supplements for 15 days to older, critically ill patients has shown a reduction in pressure ulcer development (Bourdel-Marchasson *et al.*, 2000). Practically, however, this may prove difficult to maintain in many patients.

Serum Albumin concentration is often used to assess the degree of nutrition. A concentration of less than $35\,g\,l^{-1}$ is generally taken as a reflection of poor nutrition and a risk factor for the development of pressure ulcers. It should be remembered that this is at best a crude surrogate for degree of nutrition as the half-life of albumin is relatively long (of the order of 21 days) and hypoalbuminemia may be encountered in a variety of acute illnesses. Serum prealbumin, transferrin and lymphocyte count may be better markers of (mal) nutrition. Other measures of nutritional status predictive of pressure ulcer formation include decreased body weight, reduced triceps, skin-fold thickness, and lymphocytopenia (Allman *et al.*, 1995).

Sensory Problems

Sensory deficits give rise to altered ability to perceive the pain and discomfort associated with persistent local pressure, leading to reduced repositioning. Such deficits occur in individuals with neurological problems such as neuropathies (e.g. diabetic), which especially predispose to heel ulceration. Medical or psychological conditions may lead to altered conscious levels with resultant decrease in mobility. Medication is an especially common cause of altered conscious levels; these include sedatives, analgesics, and anesthetics. The effects of sensory loss in patients with stroke or spinal cord injury may be compounded by motor deficits or increased tone (spasticity), which limit mobility and the ability to reposition.

RISK ASSESSMENT

There are a plethora of pressure ulcer risk assessment scales in use, though there is little evidence that any one is superior to another or that their use has led to a reduction in pressure ulcer incidence (Whitfield *et al.*, 2000). The scales attempt to stratify the risk according to the number of known risk factors present, in order that preventive measures are instituted. They are designed for use in individuals who are bed- or chair-bound or who have limited ability to reposition themselves. Some are more comprehensive than others. They all contain a core of basic components (Table 2).

Table 2 Components of risk assessment scales

Age
Mobility
Activity
Level of consciousness
Nutrition
Continence
Skin status
Illness severity

However, some of the grading of the risk factors is subjective and observer dependent (Healey, 1996). This may be reflected in the low sensitivity (ability of the tool to correctly identify those patients who will develop a pressure ulcer) and specificity (ability of the tool to correctly identify those patients who will not develop a pressure ulcer) that the assessment scales exhibit. When using a risk assessment scale, it is judicious to consider whether it is valid, reliable, applicable to the patient group being assessed, subjective or objective, user friendly, and useful (Collier, 2004). It should be self evident that risk assessment scales are of use only if the at-risk patient identified receives appropriate intervention.

NICE has, echoing advice from the Department of Health (Essence of Care) in the United Kingdom, made suggestions on the use of pressure ulcer assessment scales (Table 3).

In Europe, the commonest scales used are Waterlow, Norton, and Braden. Others used include Gosnell and Knoll. The Waterlow scale is commonly used in the United Kingdom (Table 4).

Table 3 Points to be considered when choosing support surface

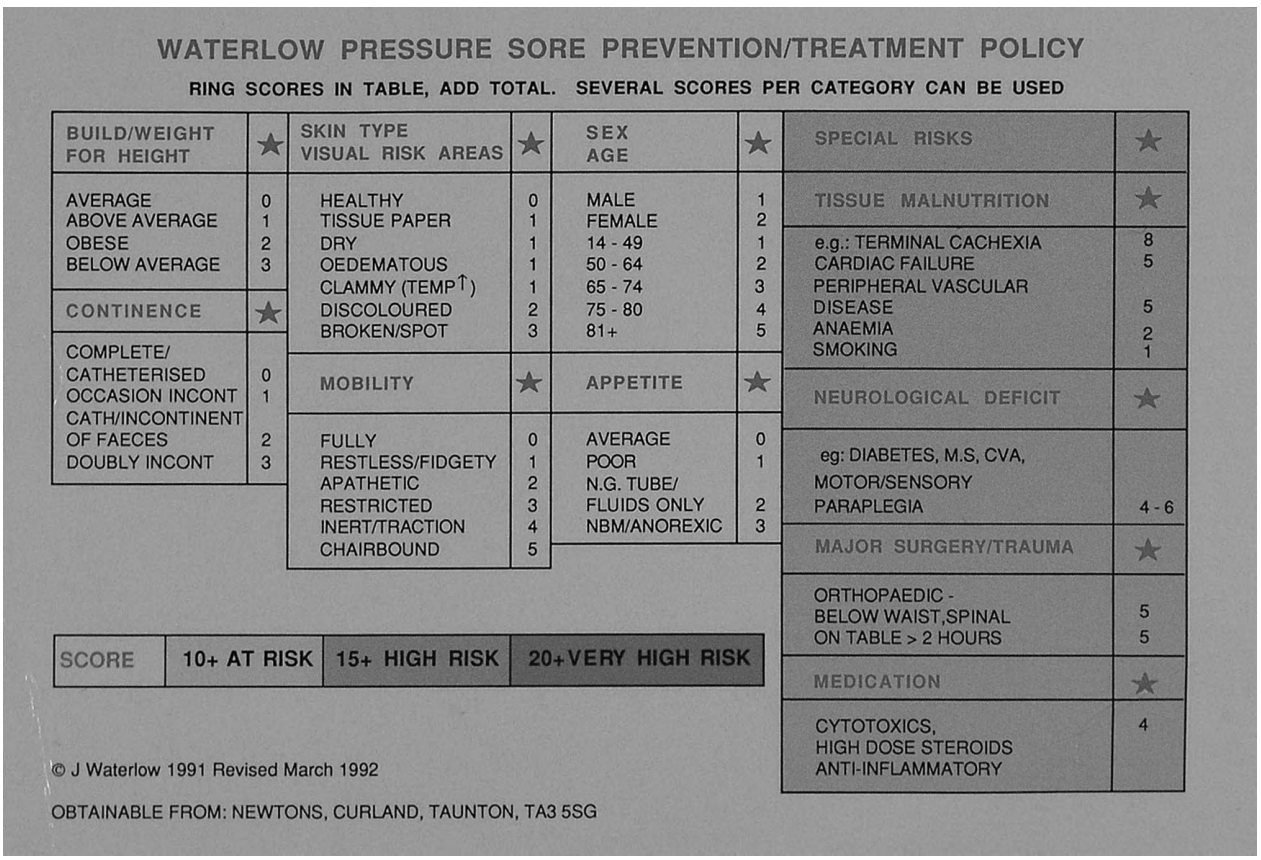
Identified level of risk
Skin assessment
Comfort
General health state
Lifestyle and abilities
Critical care needs
Acceptability of the pressure-relieving equipment to patient and/or carer

Prevention of Pressure Ulcers

Since direct pressure, shear forces, friction, and moisture are prerequisites for the development of pressure ulceration, pressure relief or redistribution should be the mainstay of any preventive strategy. Prevention may reduce the incidence of pressure ulceration by up to 50% (Anderson *et al.*, 1983; Seiler, 1985). Pressure ulcer prevention is further aided by the recognition that patients with limited or no mobility are at risk. Patients, carers, and health-care workers should be educated in this respect and also in recognizing early signs of pressure damage. While risk assessment tools will aid in this respect, they are no substitute for good clinical care and observation.

At-risk patients should have daily evaluations of the skin, concentrating particularly on the common at-risk areas, especially the bony prominences, including the sacral, ischial, trochanteric, and heel areas (Ayello, 1992). The skin should be kept clean and well hydrated (DeLisa and Mikulic 1985). Excess moisture should be minimized and may require the use of barrier creams or sprays and the use of absorbent pads for fecal and/or urinary incontinence. The skin over bony

Table 4 Waterlow risk assessment scale



WATERLOW PRESSURE SORE PREVENTION/TREATMENT POLICY

RING SCORES IN TABLE, ADD TOTAL. SEVERAL SCORES PER CATEGORY CAN BE USED

BUILD/WEIGHT FOR HEIGHT	★	SKIN TYPE VISUAL RISK AREAS	★	SEX AGE	★	SPECIAL RISKS	★
AVERAGE	0	HEALTHY	0	MALE	1	TISSUE MALNUTRITION	★
ABOVE AVERAGE	1	TISSUE PAPER	1	FEMALE	2		
OBESE	2	DRY	1	14 - 49	1	e.g.: TERMINAL CACHEXIA	8
BELOW AVERAGE	3	OEDEMATOUS	1	50 - 64	2	CARDIAC FAILURE	5
CONTINENCE	★	CLAMMY (TEMP↑)	1	65 - 74	3	PERIPHERAL VASCULAR DISEASE	5
		DISCOLOURED	2	75 - 80	4	ANAEMIA	2
COMPLETE/ CATHETERISED	0	BROKEN/SPOT	3	81+	5	SMOKING	1
OCCASION INCONT	1	MOBILITY	★	APPETITE	★	NEUROLOGICAL DEFICIT	★
CATH/INCONTINENT OF FAECES	2	FULLY	0	AVERAGE	0		
DOUBLY INCONT	3	RESTLESS/FIDGETY	1	POOR	1	eg: DIABETES, M.S, CVA, MOTOR/SENSORY PARAPLEGIA	4 - 6
		APATHETIC	2	N.G. TUBE/			
		RESTRICTED	3	FLUIDS ONLY	2	MAJOR SURGERY/TRAUMA	★
		INERT/TRACTION	4	NBM/ANOREXIC	3	ORTHOPAEDIC - BELOW WAIST,SPINAL	5
		CHAIRBOUND	5			ON TABLE > 2 HOURS	5
						MEDICATION	★
						CYTOTOXICS, HIGH DOSE STEROIDS ANTI-INFLAMMATORY	4

SCORE	10+ AT RISK	15+ HIGH RISK	20+VERY HIGH RISK

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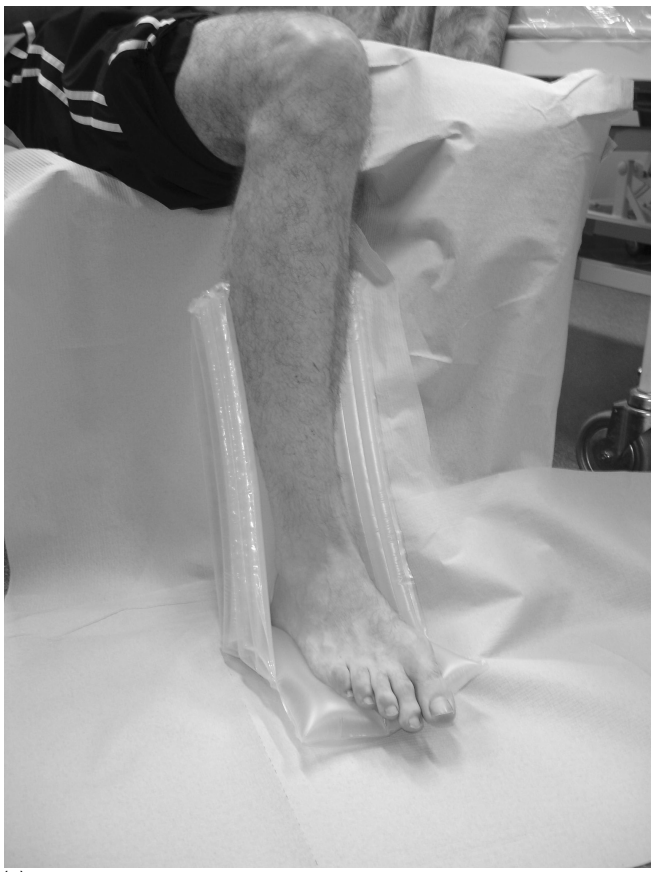
prominences should not be massaged deeply, as this may cause, rather than prevent, damage (Ek *et al.*, 1985, 1987).

In individuals not at risk of pressure ulceration, pressure relief or redistribution is an automatic, frequent, and usually reflex reaction to pressure, while in bed or seated. Individuals who are unwell or immobile turn much less frequently. These at-risk individuals should be repositioned regularly. While there are no firm data on frequency of repositioning, current practice suggests that a minimum 2-hourly repositioning schedule should be instituted, alternating the individual between lying on their back and then alternate sides (Knox *et al.*, 1994).

When positioned on the side, the individual's back should be angled at 30° with respect to the support surface in order to minimize pressure over the greater trochanter and lateral malleolus (Seiler and Stahelin, 1985). Direct ("kissing") contact of the bony prominences such as knees and ankles should be avoided through judicious use of cushions and foam wedges. "Doughnut" cushions should be avoided as they may lead to, rather than prevent, ulceration, possibly as a result of reduction of blood flow to the area of tissue which herniates through the center of the "doughnut" (Allman, 1989a,b).

Friction and shear forces should be minimized; abolition of these forces is neither possible nor desirable, else the patient would slip off the support surface! While repositioning, the individual should be lifted, rather than dragged across the bed or out of a wheelchair. The support surface should be kept clean and free of any debris (e.g. food), which may exacerbate any pressure damage. Shear damage may be diminished by keeping the head of the bed at 30° or less, thus preventing undue pressure on the sacrum, ischial tuberosities, and heels. A variety of heel (Figure 8) and elbow protectors are in use (e.g. sheepskin) but evidence on their efficacy is lacking.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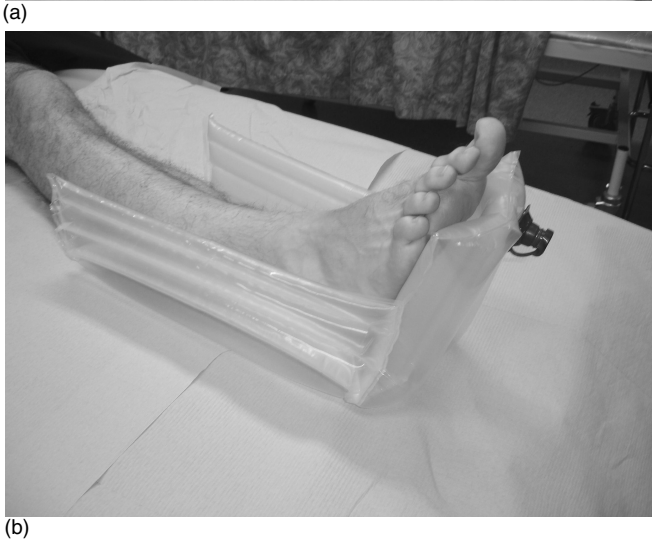
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Figure 8 Repose Bootee, heel protector

Pressure-relieving Devices

There is a bewildering array of pressure-relieving and pressure-reducing support surfaces available. These include beds, mattresses, mattress overlays, cushions, chairs, and wheelchairs. There is, however, very little good-quality data supporting the use of particular pieces of equipment (Rycroft-Malone and Duff, 2000; Rithalia, 2004a). Furthermore, there appears to be a deal of uncertainty as to what the equipment actually achieves (Collins, 2004). There is also potential conflict in trying to combine a piece of equipment that is liked by the patient, meets the treatment objective, and is suitable for a particular care setting (Fletcher, 1995).

NICE in the United Kingdom has, in its guidelines, stated that pressure-relieving devices should be based on cost considerations as well as an overall assessment of the individual. They further state that holistic assessment should include the points listed in Table 3 and should not be based solely on scores derived from risk assessment scales (NICE).

However, much clinical practice in identifying the patient at risk of pressure ulcers and provision of the appropriate pressure-relieving surface continues to be dependent on the risk assessment scales. Indeed, the Waterlow scale, for example, links a risk score to a particular intervention (Watts and Clark, 1993; Winman and Clark, 1997). Moreover, many pressure ulcer prevention protocols and manufacturers of pressure-relieving surfaces imply that there are reliable cut-off points for identifying appropriate surfaces dependent on the degree of risk determined by the risk assessment scale.

NICE guidelines advocate the use of the terms "vulnerable to pressure ulcers" and "at elevated risk of pressure ulcers" in recognition of the limitations of risk assessment scales (NICE).

The implementation of holistic prevention programs, including provision of support surfaces, use of risk assessment tools, repositioning schedules, nutrition, and education programs have all resulted in reductions in pressure ulcer incidence (Xakellis *et al.*, 1998; Lyder *et al.*, 2002). This highlights the fact that good care is essential in both prevention and treatment of pressure ulcers. All prevention strategies require staff education. There should be a written pressure ulcer prevention and treatment policy. There should also be a multidisciplinary approach to prevention and treatment strategies including doctors, nurses, dieticians, physiotherapists, occupational therapists, speech and language therapists, housekeeping staff, catering, and supplies officers.

Figure 9 Standard hospital mattress

Mattresses

NICE guidelines recognize that there is little good-quality data on what support surface should be used in a particular circumstance. They suggest, as a minimum provision, that those individuals vulnerable to pressure ulcers should be placed on a high-specification (though low-tech) foam mattress with pressure-relieving properties. The guidelines further advise that alternating pressure or other high pressure-relieving systems should be considered in the following circumstances:

1. as a first-line preventive strategy for people at elevated risk (based on holistic assessment);
2. when the individual's previous history of pressure ulcer prevention and/or clinical condition indicates that they are best cared for on a high-tech device;
3. when a low-tech device has failed.

Support surfaces may be broadly divided into those that provide pressure reduction and those that provide pressure relief. Pressure-reducing systems produce the effect by increasing the surface area in contact with the support surface brackets (pressure = force/area). This is often the reason cited for nursing the patients in bed rather than in a chair, sitting for long periods (Gebhardt and Bliss, 1994). Pressure-relieving systems sequentially remove the source of pressure from parts of the body, usually by alternately inflating and deflating cells within mattress or mattress overlays.

Support systems are more commonly classified as static or dynamic systems. Static systems are generally, but not exclusively, nonpowered, low-tech devices of which the hospital mattress is the most basic example (Figure 9). They commonly comprise a sandwich of different densities of foam or other surfaces which are profiled (Collins, 2004). Other examples of static, pressure-reducing services include foam overlays and water-, gel- and air-filled devices designed to be placed over a standard mattress.

Figure 10 "Repose" mattress overlay

Comparative studies of some overlays have shown that they are no better than good-quality foam mattresses (Medical Devices Agency, 1994). However, a randomized, controlled, prospective trial comparing a low cost, low-pressure inflatable mattress ("Repose", Figure 10) designed to be placed on a standard hospital mattress showed no difference when compared to a high-tech dynamic support mattress and patients at high risk of pressure ulceration indicating that certain low-tech static pressure-relieving systems can be as effective as high-tech pressure-relieving systems in treating certain patient groups (Price *et al.*, 1999).

Static systems (Figure 11) are generally suitable for those individuals able to adopt a variety of positions. The system should not be able to "bottom out", that is, the mattress (or overlay) or any part of it providing less than 2.5 cm of support. The surfaces are appropriate for patients at low risk of pressure ulcer development.

Figure 11 Static mattress

Figure 12 Dynamic mattress

Dynamic support surfaces (Figure 12) may be either pressure-reducing or pressure-relieving devices. They are generally powered and high tech in nature. They are available as mattresses, mattress overlays and whole-bed systems. Low air-loss (pressure-reducing) mattresses have air pumped into the cells making up the mattress, some of which escapes via tiny holes in proportion to the weight placed upon it. Each cell deflates slightly, conforming to and supporting the body evenly. Care should be taken not to let the system "bottom out" (Young and Cotter, 1990; Phillips, 1999). It has been postulated that pressure-relieving devices may be useful in preventing tissue ischemia via their cyclical "zero pressure" areas (Russ and Motta, 1991).

Dynamic pressure-relieving surfaces are also powered high-tech devices. The pressure relief is generally facilitated by alternately inflating and deflating cells, so that one set of cells cyclically supports the body. The body is, therefore, relieved of pressure when a set of cells deflates. Usually, the two or three cells under the head of the patient are static, thus promoting patient comfort. Cell layers, sizes, shapes, and cell cycles vary between mattresses, depending on the manufacturer. Some dynamic systems adopt a static mode which is useful when carrying out certain procedures, for example, in the event of power failure or when transferring the patient from area to area. Table 5 lists the characteristics of different types of mattresses (Kanj *et al.*, 1998; Lyder, 2003).

Air-fluidized systems (pressure reducing) are filled with small silicone-coated beads through which air is pumped on a continuous basis, providing a dynamic surface (Figure 13). The patient's pressure points are, therefore, constantly moving. The dry particles are able to absorb fluid, which are then removed from the system, thus helping to prevent maceration and decrease the effect of moisture on the various forms of pressure.

Dynamic support surfaces are indicated for patients at elevated risk of developing a pressure ulcer, those patients with pressure ulcers who are unable to be nursed completely off the pressure ulcers, those with very large or multiple ulcers, and those with ulcers which are not healing.

In the United States, the center for Medicare and Medicaid to services has divided support services into three categories based upon reimbursement costs (Lyder, 2003).

Table 5 Selected characteristics for classes of support surfaces

Performance characteristics	Air-fluidized (high air loss)	Low-air loss	Alternating air (dynamic)	Static flotation (air or water)	Foam	Standard hospital mattress
Increased support area	Yes	Yes	Yes	Yes	Yes	No
Low moisture retention	Yes	Yes	No	No	No	No
Reduced heat accumulation	Yes	Yes	No	No	No	No
Shear reduction	Yes	?	Yes	Yes	No	No
Pressure reduction	Yes	Yes	Yes	Yes	Yes	No
Dynamic	Yes	Yes	Yes	No	No	No
Cost per day	High	High	Moderate	Low	Low	Low

From Bergstrom *et al.*, 1994.

Figure 13 Air-fluidized mattress

Group 1 – Static support surfaces not requiring electricity.
Group 2 – Dynamic surfaces powered by electricity or pump including alternating and low air-loss mattresses.
Group 3 – Air-fluidized beds.

While such devices have been shown to reduce the incidence of pressure ulceration, there is no data to show that one particular type is better than another (Rithalia, 2004b). Furthermore, there is no evidence that high-tech pressure-relieving mattresses and overlays are more effective than high specification (low-tech) mattresses and overlays (NICE; Price *et al.*, 1999).

Seating

An often-neglected area of pressure-relieving support surfaces is seating, including both chairs and cushions. Again, however, there is a paucity of clinical evidence that one seat or cushion (from the enormous array of both that are available) is better than another. Suitable seating is essential to prevent pressure damage and to maintain a balanced, symmetrical seating posture (Collins, 2004). The provision of adequate seating in an acute hospital is generally very poor. A "one size fits all" approach seems to have been adopted with little thought given to providing pressure relief or reduction. All too often the seating is in poor condition (Versluysen, 1986). There is very little access to pressure-relieving cushions. In the person's own home and care homes, the elderly and disabled are often expected to sit for long periods in unsuitable chairs.

Ideally, provision of seating, including pressure-relieving cushions, should promote good sitting balance (Figure 14) and provide comfort by taking into account the individual's postural alignment, weight distribution, balance and stability and pressure relief or redistribution factors. The pelvis provides the interface between the seat and or cushion and the rest of the body. The main points of contact between the pelvis and seat are the ischial tuberosities, the tissue over which, not surprisingly, is the area particularly prone to pressure ulceration. In people without mobility problems, sitting is a dynamic process, the individuals changing their position when they become uncomfortable and thus relieving pressure, particularly over the ischial tuberosities.

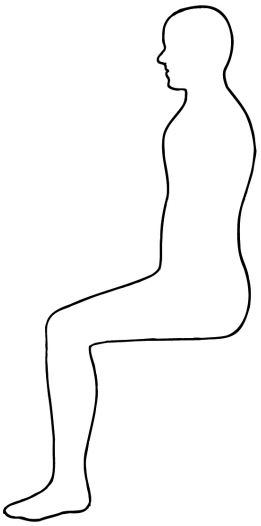


Figure 14 Ideal sitting position

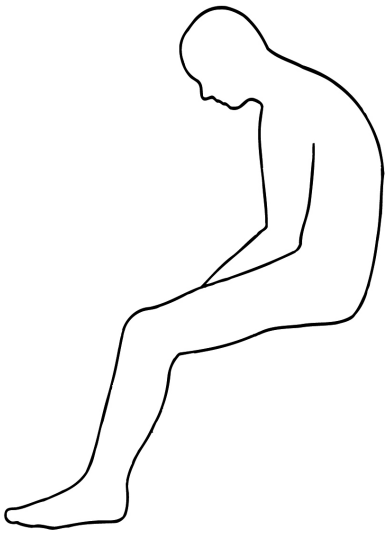


Figure 15 Posterior pelvic tilt

Elderly, immobile, and disabled individuals often have a poor sitting posture, leading to what is known as *posterior pelvic tilt* (Figure 15). This may arise as a result of gravity, an unsupportive or inappropriate chair or wheelchair and poor trunk control, amongst other factors. Since the pelvis rotates posteriorly, the sacrum becomes more at risk of pressure damage. In addition, the ischial tuberosities slide forward, increasing shear and friction forces with a concomitant increase in the risk of pressure ulceration. A further consequence of the body slipping forward is that the heels become prone to further shear and frictional pressure, increasing the risk of pressure ulceration.

If the seat of the chair sags, the pelvis may tilt laterally (Figure 16), leading to increased risk of pressure ulceration

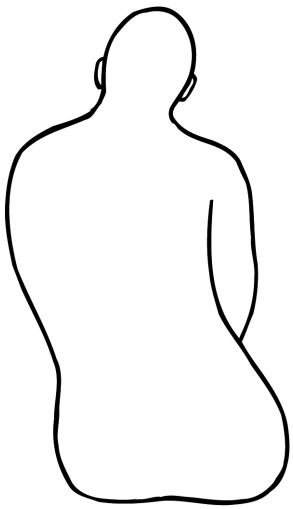


Figure 16 Lateral pelvic tilt

over one ischial tuberosity (as most of the body weight is supported through this tuberosity) as well as the ipsilateral greater trochanter.

While turning schedules for people nursed in bed are well established, scant attention has been paid to repositioning schedules for at-risk individuals sitting in chairs or wheelchairs. Again, there is little data on the optimum frequency of posture change: if possible, the person should be encouraged to shift position every 15–30 minutes. If they are unable to do this independently, they should be repositioned at least hourly.

The immobile and ill elderly person is more at risk of pressure ulceration when seated, as they often have reduced muscle bulk around the pelvis, with reduced skin elasticity. This leads to higher pressures around the ischial tuberosities. Pressure-relieving cushions may help reduce the risk of pressure damage in these individuals. Wheelchair users in the United Kingdom with postural problems and who are at risk of pressure ulceration, are entitled to be assessed for and provided with a suitable cushion or seating system (Collins, 2004).

The wide range pressure-relieving cushions available reflects, in part, a degree of lack of evidence of efficacy (Bar and Pathy, 1998). However, studies have shown that cushions markedly reduce interface pressure, shear and friction forces (Palmieri *et al.*, 1984). In addition, cushions provide support and stability for the pelvis and enable the individuals to maintain their balance when reaching for things (Fletcher, 1995). Cushions should enhance the ability to transfer either independently or with assistance and should be comfortable (Bennett *et al.*, 1981). The cushion choice is dependent on the degree of pressure relief needed, lifestyle factors, postural stability, continence (bladder and/or bowel) and cost. The cushion should also be compatible with the chair or wheelchair (Garber *et al.*, 1996, 2000). When choosing an armchair, attention should be paid to the seat base, cushion, backrest (with or without recline) and armrests.

Table 6 Cushion characteristics

Cushion type	Suitability	Benefits/drawbacks
Static	Low- to high-risk individuals	• Supports ischial tuberosities • Thighs supported and isolated • Inexpensive, lightweight, many variations • Bottoms out with time • High interface pressures • Difficult to clean • Wears readily • Some flammable
Air filled Gel filled Fluid filled	Low- to high-risk individuals	• Pressure redistribution and reduction • Good stability • Absorbs dynamic movements • Good for wheelchairs • Air filled – lightweight and cleanable • Dependent on correct inflation • Liable to puncture • More difficult transfers • Fluid filled – heavy
Dynamic	High-risk individuals Individuals with pressure ulcers	• Pressure relieving • Increase sitting tolerance • Varying inflation • Mechanical breakdown • Leaks • Regular battery charging

Cushions, like mattresses and mattress overlays, may be classified as either static or dynamic (Figure 17). The static cushions are used mainly for pressure ulcer prevention, while dynamic cushions are used for individuals at elevated risk of pressure ulceration and those with established pressure ulcers. Table 6 illustrates the advantages and disadvantages of a range of cushions.

MANAGEMENT OF ESTABLISHED PRESSURE ULCERATION

The management of established pressure ulcers has much in common with their prevention. The aim of treatment of pressure ulceration is to provide adequate pressure relief and further protection of vulnerable areas, prevent progression, and facilitate rapid healing within a multidisciplinary, holistic approach to the individual. Apart from treating the pressure ulcer, attention should focus on treatment of any underlying diseases, especially those that may adversely affect wound healing and mobility. Review of medication should ensure that there is no inappropriate sedation (which could lead to immobility). Similar nutritional regimes should be instituted in patients with pressure ulcers as for those at risk of pressure ulceration.

Pressure Relief

The type of pressure relief for individuals with pressure ulcers is dependent on their needs. If the individual is

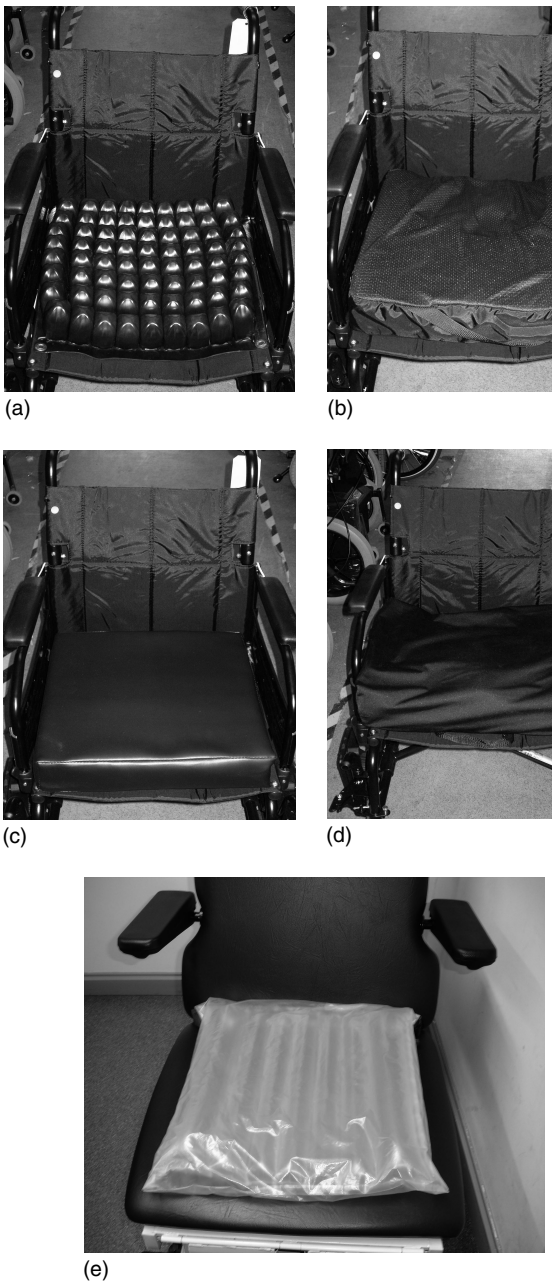


Figure 17 Pressure-relieving cushions

able to be nursed off the pressure ulcer, a static support surface accompanied by a regular turning schedule may be appropriate (Hanan and Scheele, 1991). Should it not be possible to nurse the patient off the ulcer and if the pressure ulcer demonstrates no evidence of healing or deteriorates on a static surface, a dynamic support system should be employed (Table 5).

Some studies in both long- and short-term care settings have demonstrated that dynamic mattresses promote healing of pressure ulcers compared to static foam mattresses, regardless of the size and depth of pressure ulcer (Allman *et al.*, 1987; Ferrell *et al.*, 1993). The major drawback of many dynamic mattresses is their expense, which is felt by some to be excessive compared to their benefits (Lubin and Powell, 1991; Kanj *et al.*, 1998).

Pressure Ulcer Classification

There are several classification schemes for established pressure ulceration. The European Pressure Ulcer Advisory Panel (EPUAP) has developed a simple to use, four-grade classification of pressure ulcers, reflecting increasing severity of pressure damage (Table 7, Figure 18). There is no "ideal" classification system; for example, grade 1 ulceration may go unnoticed in people with darkly pigmented skin. Clinicians should also beware the pressure ulcer covered with eschar: Such wounds cannot be accurately graded until the eschar has been removed. Undermining and sinuses commonly occur and affect grading as well as healing potential.

With moist wound healing techniques and optimal management of other medical conditions and nutrition, most grade 2 ulcers will heal after two weeks' treatment: Grades 3 and 4 ulcers take an average of 6 weeks to 3 months to heal (65% grade 2, 14% grade 3 and 0% grade 4 over a 6-week follow-up period) (Xakellis and Chrischilles, 1992; Xakellis and Frantz, 1996, Xakellis *et al.*, 1998). Generally, grades 1, 2, and 3 pressure ulcers are most amenable to local therapy, whereas grade 4 ulcers may require surgical repair (Kanj *et al.*, 1998). It has been suggested, however, that if there is not a 30% reduction in the area of a deep pressure ulcer after 2 weeks of treatment, the wound will be unlikely to heal in any reasonable period of time without reevaluation of treatment modalities (van Rijswijk, 1993).

Tools have been developed in an attempt to assess the healing of pressure ulcers. Two that have been evaluated include (1) the pressure sore status tool (PSST) (r 17 lyder) which is made up of 13 wound characteristics (e.g. edema, depth, size, exudate, etc.) and can be used to assess any chronic wound and (2) the pressure ulcer scale for healing (PUSH) tool (Stotts *et al.*, 2001) which is similar to the PSST, comprising only three wound characteristics (length and width of the ulcer, exudate amount, and tissue type); it also takes less time to complete than the PSST. These tools, however, are not widely used.

Photography of the pressure ulcer, made much easier with the advent of digital technology, is a key part of

Table 7 Pressure Ulcer Classification

Grade 1:	Nonblanchable erythema of intact skin. Discoloration of the skin, warmth, induration or hardness may also be used as indicators, particularly on individuals with darker skin
Grade 2:	Partial-thickness skin loss involving epidermis, dermis, or both. The ulcer is superficial and presents clinically as an abrasion or blister
Grade 3:	Full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia
Grade 4:	Extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures with or without full thickness skin loss.

the assessment process. However, consistent methodology is essential. Documenting the distance from which the photo was taken is important in order to obtain an accurate representation of the actual size of the ulcer (Lyder, 2003). Patient identification, date, and location should be recorded on the photo.

Local Wound Management

A key measure in effective management of pressure ulcers is comprehensive evaluation of the wound and surrounding skin (Table 8). Other causes of skin ulceration should be excluded, including ischemia, vasculitis, radiation injury, and pyoderma gangrenosum: A detailed history and careful examination should help distinguish these.

Wound Debridement

Moist necrotic tissue is yellow or gray (Figure 19): dry necrotic tissue is thick, hard, leathery and black (eschar) (Maklebust and Sieggreen, 2001). In the presence of necrotic tissue, wound healing is usually impossible. Removal of necrotic tissue, eschar, and debris is essential, both to facilitate wound healing and to accurately stage a pressure ulcer. While the use of debridement is largely based on expert opinion (Vowden, 2004), there is evidence that debridement stimulates healing by removing the necrotic tissue that impedes healing (Brem and Lyder, 2004).

Chronic wound exudate has high levels of pro-inflammatory cytokines, which keep the wound in the inflammatory stage (Harris *et al.*, 1995; Schultz and Mast, 1998). There are also high levels of matrix metalloproteinases

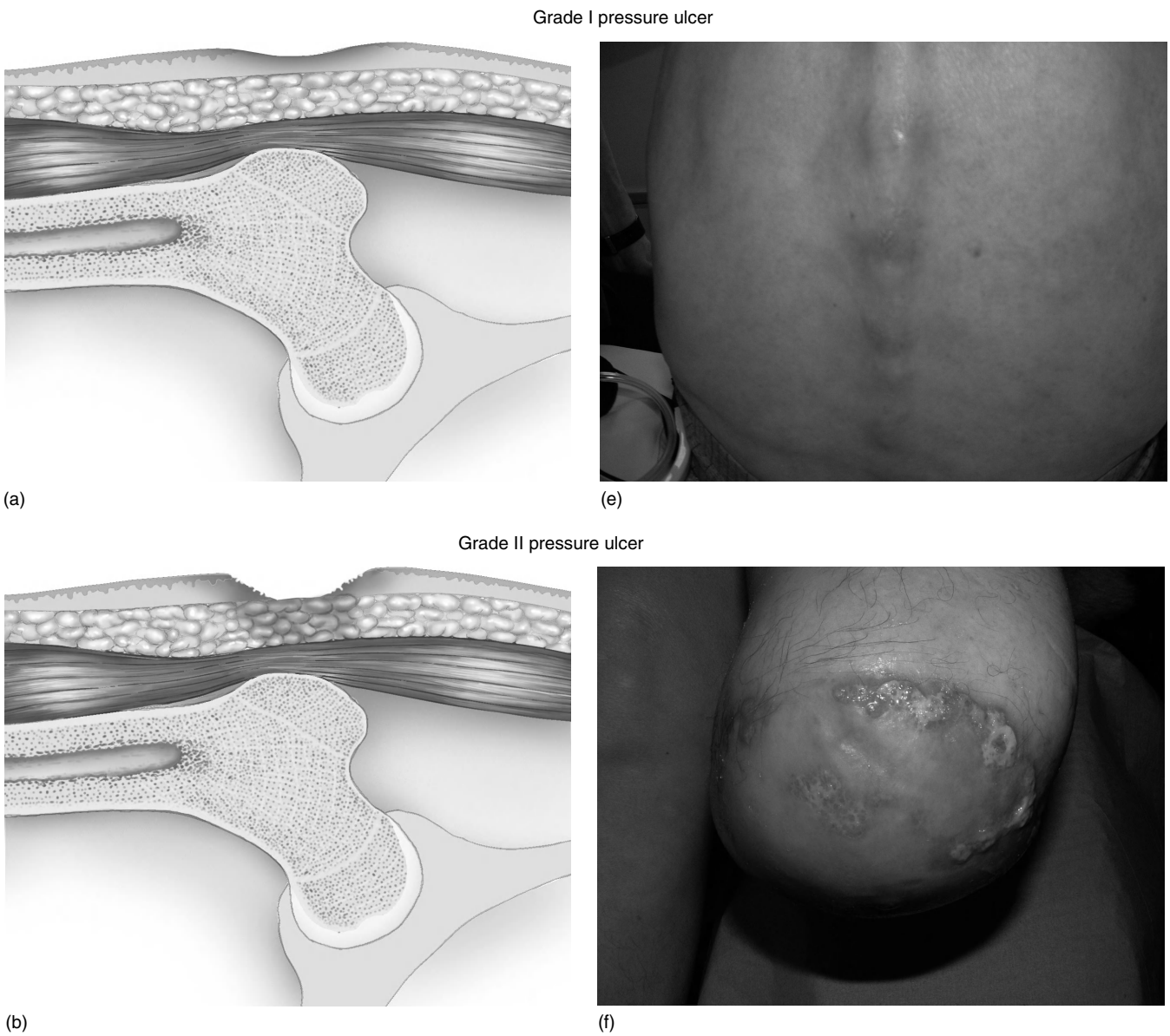
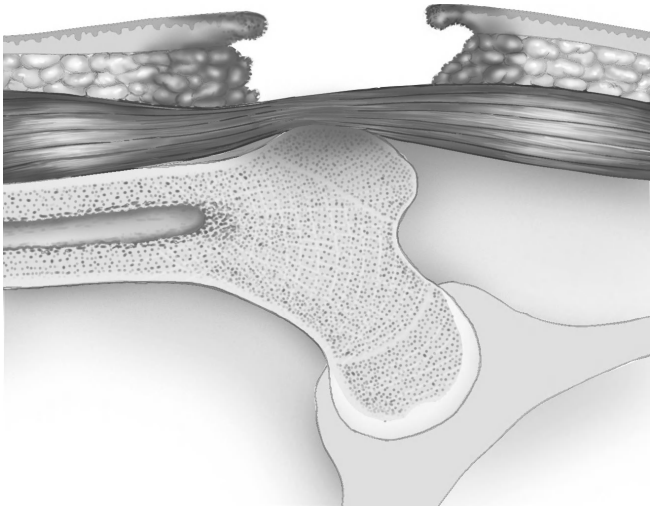
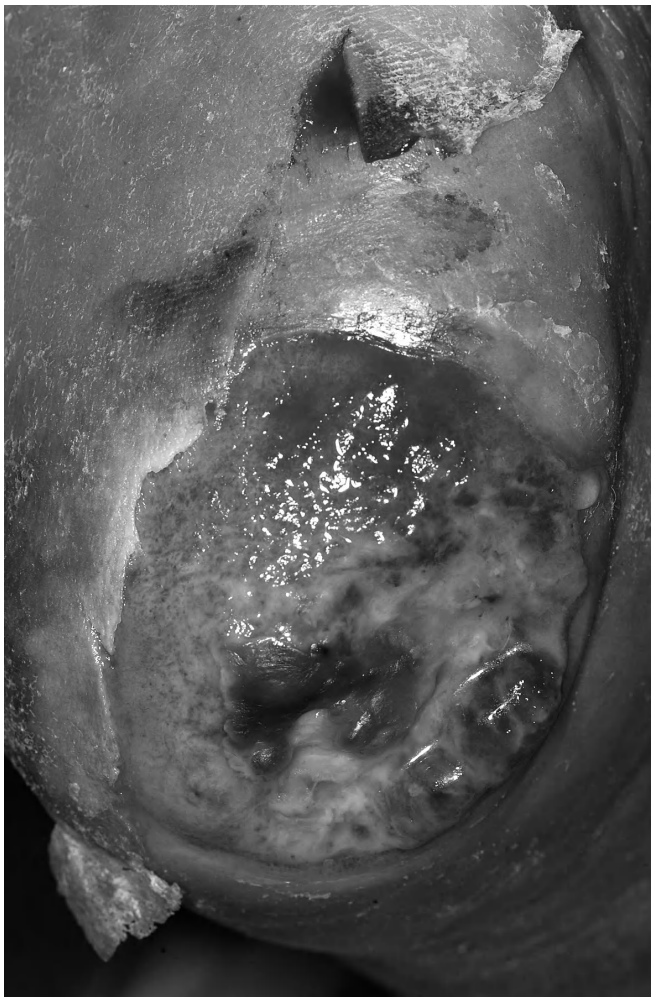


Figure 18 (a–h) Diagrammatic representations and pictures of the four grades of pressure ulcers

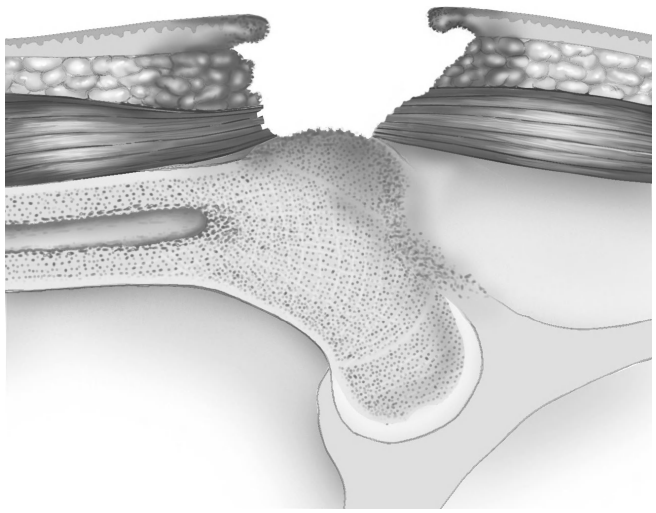


(c)

Grade III pressure ulcer

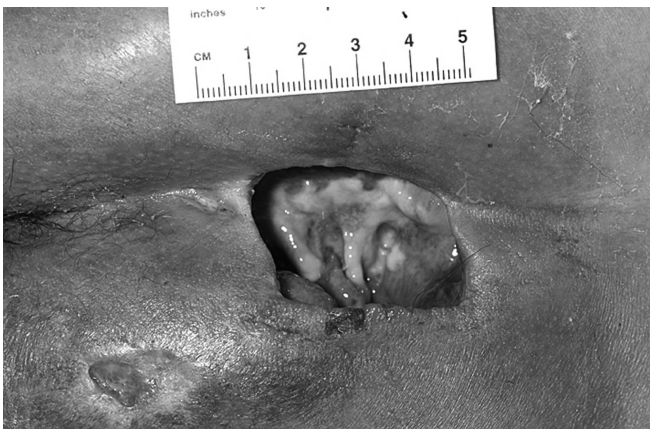


(g)



(d)

Grade IV pressure ulcer



(h)

Figure 18 (*Continued*)

(MMPs), which destroy or alter the newly formed wound matrix (Grinnell and Zhu, 1996). Debridement and wound cleansing helps to remove the exudate and stimulate wound healing. Necrotic wounds are also associated with high levels of bacterial contamination. A direct correlation between high bacterial levels in wound tissues and delay in healing has been documented in pressure ulcers (Stotts and Hunt, 1997).

Eschar (Figure 20), devitalized and infected tissue may be removed by sharp, autolytic, enzymatic, or surgical debridement. Simple sharp debridement (Figure 21) at the bedside or in the treatment room using a scalpel, scissors or curette is useful when dealing with thick eschar and extensive areas of devitalized tissue. Prior treatment with local or block anesthetic may be required. Debrided tissue may be sent for microbiological or histological analysis. Minor bleeding usually accompanies sharp debridement, resulting in the release of cytokines, which may stimulate the wound healing process (Dräger and Winter, 1999).

Table 8 Wound characteristics

Size
Depth
Wound bed
Undermining
Amount and type of exudates
Surrounding skin

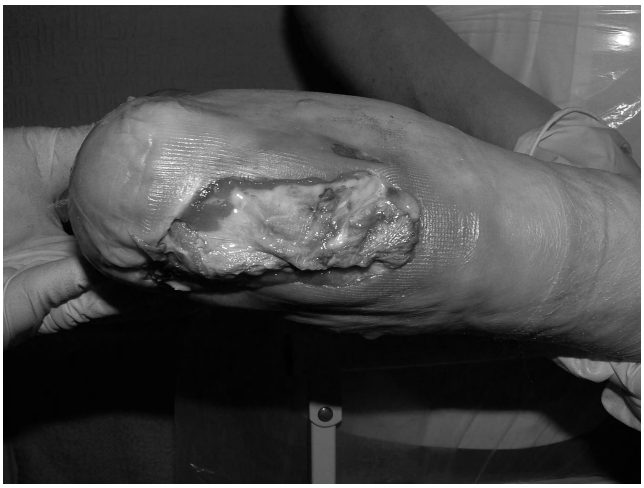


Figure 19 Moist necrotic tissue

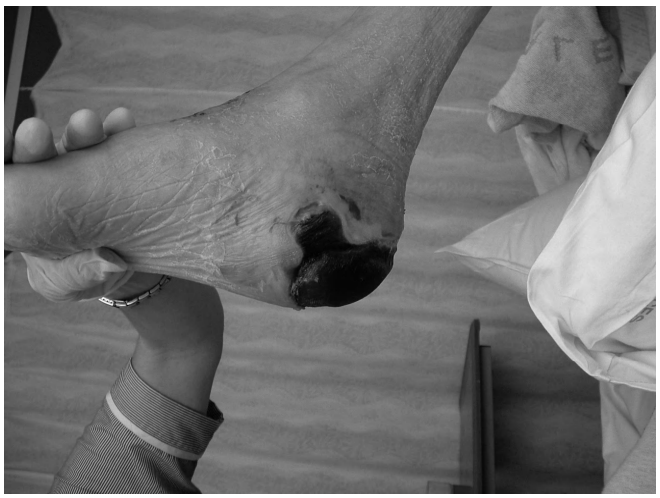


Figure 20 Wound covered with eschar

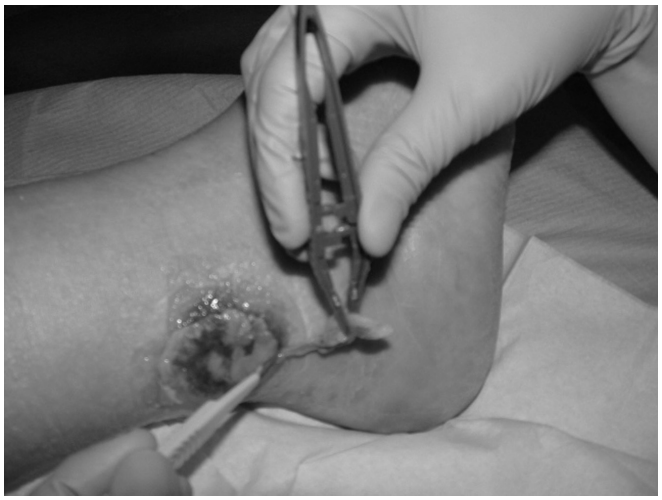


Figure 21 Sharp debridement

Commercially prepared enzymatic debriding agents may be available in some countries and used for those individuals with uninfected ulcers. They include streptokinase, streptodornase, fibrinolysin and deoxyribonuclease, sutilans, collagenase, and papain. Depending on the type, these debriding agents digest collagens (native and denatured), fibrinous material and nucleoproteins (Berger, 1993). They are usually delivered as an ointment onto the surface of the necrotic tissue. They should be avoided in wounds with exposed tendons. They have the potential for contact sensitization. They are not very effective on hard eschar or large amounts of necrotic material. It has been shown, however, in a randomized controlled study, that cheaper, amorphous Hydrogels (which promote autolytic debridement; see below) may be just as effective in debridement as enzyme preparations (Martin *et al.*, 1996).

Maggots are increasingly being used to debride chronic wounds (Sherman *et al.*, 2000; Thomas *et al.*, 1998) and may be considered a form of enzymatic debridement, though the mouth parts of the maggot also cause some mechanical irritation which is believed to aid wound healing. Such larval therapy makes use of the larvae of several species of fly, one of the commonest being the Green Bottle (*Lucilia sericata*). The larvae secrete an enzymatic liquor which selectively digests necrotic tissue and nonviable tissue: The digested products are then absorbed by the maggots. The liquor also contains cytokines, antiseptic substances, and proteases. The maggots have also been shown to ingest and kill bacteria (Fleischmann, 2004). Between 100 and 200 sterile maggots are used to debride wounds and are left in place for two to three days.

Mechanical debridement is still commonly used in some countries. The most common method is the wet to dry technique, usually using woven cotton gauze. This is soaked in saline and allowed to dry out and become adherent to the wound surface. However, this method can lead to damage of healthy viable tissue when the dressing is removed and should be avoided (Kanj *et al.*, 1998). Hydrotherapy and wound irrigation have been used to debride wounds, but evidence is limited (Palmier and Trial, 2004).

Autolytic debridement occurs in all wounds and is the body's own way of clearing necrotic tissue and debris from the area by the activity of the native enzymes within the ulcer (Thomas *et al.*, 1999). The process relies on leucocytic activity and endogenous proteolytic enzymes. Bacterial proteases also contribute to the process (Baharestani, 1999). The intrinsic process is slow and further delayed by aging, malnutrition, and chronic disease (Himel 1995).

Autolytic debridement may be promoted through the maintenance of a moist wound environment and is enhanced by the use of modern dressings, which are either moisture retentive or which hydrate the devitalized tissue. Frequent wound cleansing to eliminate the partially degraded tissue fragments is a necessary part of effective autolytic debridement. Several studies have shown that autolytic debridement is effective in digesting nonmobile tissue and more selective and less traumatic than mechanical techniques (Mulder *et al.*, 1993; Flanagan, 1995, Bale *et al.*, 1998, Colin *et al.*, 1996). Autolytic debridement is painless; easy to use; able to be combined with other forms of debridement; suitable for most wounds and patients; cost-effective; and widely available (Vowden, 2004; Mulder, 1995).

Wound Cleansing

This has been defined as "a process, which removes less adherent inflammatory molecules (such as cytokines and MMPs) from the wound surfaces and renders the wound less conducive to microbial growth" (Gardner and Frantz, 2004). The EPUAP in Europe and the American NPUAP have developed guidelines for cleansing pressure ulcers (Table 9).

Although not isotonic, and since contact with the wound is brief, tap water suitable for drinking may be used to cleanse pressure ulcers. While sterile saline (0.91% sodium chloride) is more commonly used, it is more expensive and some studies have shown that there is a lower wound infection rate in wounds irrigated with tap water compared with wounds irrigated with sterile saline (Angeras *et al.*, 1992).

Antiseptics have long been used in an attempt to kill bacteria within a wound. However, they are also toxic to nonbacterial cells found in the wound such as fibroblasts and macrophages. In addition, they may have limited effect on bacteria within wound tissue (Ayello, 2004). In general, antiseptics should not be routinely used and when they are, it should be for a limited period only. Systemic antibiotics should be used if the wound is infected.

Topical antimicrobial treatments demonstrated to enhance wound bed preparation without inhibiting the wound healing process include iodine-based dressings (e.g. Iodosorb) and noncrystalline silver-based dressings (for example, Acticoat (Smith and nephew); Actisorb 220 (Johnson and Johnson) and Aquacel Ag (Convatec)): the latter reported to minimize the potential of fungal infection (Johnson, 1991; Wright *et al.*, 1999; Thomas and McCubbin, 2003). Silver compounds may be of use to treat wounds that have developed a bio-film, which is produced by some bacteria (Ziegler *et al.*, 2004). Cadexomer iodine and silver compounds have been shown to reduce the bacterial burden.

Table 9 EPUAP and AHCPR guidelines for cleansing pressure ulcers (Bergstrom *et al.*, 1994; Fletcher, 2001)

European Pressure Ulcers Advisory Panel:

1. Cleanse wounds as necessary with tap water or with water, which is suitable for drinking, or with saline (strength of evidence = C).
2. Use minimal mechanical force when cleansing or irrigating the ulcer. Showering is appropriate. Irrigation can be useful for cleaning a cavity ulcer (C).
3. Antiseptics should not routinely be used to clean wounds but may be considered when bacterial load needs to be controlled after clinical assessment. Ideally, antiseptics should only be used for a limited period of time until the wound is clean and surrounding inflammation reduced (C).

Agency for Health Care Policy and Research (AHCPR):

1. Cleanse wounds initially and at each dressing change (strength of evidence = C).
2. Use minimal mechanical force when cleansing the ulcer with gauze, cloth or sponges (C).
3. Do not clean ulcer wounds with skin cleansers or antiseptic agents (e.g. povidone iodine, iodophor, sodium hypochlorite solution (Dakin's solution), hydrogen peroxide, acetic acid) (B).
4. Use normal saline for cleansing most pressure ulcers (C).

Wound irrigation is sometimes employed to help cleanse and debride a pressure ulcer. This ranges from use of saline filled syringes to pulsatile, battery-operated irrigation systems. The EPUAP and American Agency for Health Care Policy and Research, AHCPR (Bergstrom *et al.*, 1994; Fletcher, 2001), recommend 4–50 psi as safe and effective irrigation pressures (the health-care professional carrying out wound irrigation should ensure that they and the patient are protected from splashback and splatter).

Frequent showering with large amounts of water helps reduce the bacterial burden on the wound surface and provides psychological benefits to the patient (Bauer *et al.*, 2000). The shower should not be aimed directly at the wound, rather directed above it, so that the water irrigates the wound without too much force (Ayello, 2004).

Dressings

Dressings play a major role in the treatment of pressure ulcers. The occlusion that dressings provide promotes moist wound healing, facilitates re-epithelialization, reduces associated pain, enhances autolytic debridement and provides a barrier to bacteria (Leipziger *et al.*, 1985; Alvarez *et al.*, 1989; Friedman and Su, 1984, Mertz *et al.*, 1985). There are estimated to be more than 300 different dressings marketed for pressure ulcer care (Lyder, 2003). The major dressing classification and their uses are identified in Table 10.

Table 10 Dressings suitable for pressure ulcers

Dressing type	Pressure ulcer grade	Advantages/disadvantages
Semipermeable film	1 Minimally exuding 2	Promote moist environment Adheres to healthy skin but not to wound Allows visual checks May be left in place for several days No cushioning Not for infected or heavily exuding wounds
Foams	Low to moderately exuding, noninfected 2–3	Degree of cushioning May be left in place 2–3 days Needs secondary dressing
Hydrogels	Low to moderately exuding 2–4	Supplies moisture to low exuding wounds Useful for cavities and sinuses May be left in place for several days Needs secondary dressing May cause maceration
Hydrocolloids	Low to moderately exuding 3–4	Absorbable Conformable Good in "difficult areas" – heel, elbow, sacrum May be left in place for several days May cause maceration
Hydrofibres	Moderate to Highly exuding 2–4	Useful in cavities, sinuses, undermining wounds Highly absorbent Nonadherent May be left in place for several days Needs secondary dressing
Alginates	Moderate to Highly exuding 2–4	Useful in cavities, sinuses, undermining wounds Highly absorbent Needs secondary dressing Needs to be changed daily

Semipermeable (polyurethane) films are thin, transparent, nonabsorbent and coated on one side with hypoallergenic adhesive. They are suitable for grade 1 and minimally exuding grade 2 pressure ulcers. They are applied directly to the wound.

Hydrogels are insoluble polymers with hydrophilic sites containing more than 80% water and are available as an amorphous gel or translucent sheet. They are semitransparent and absorbent. They are nonadherent and dry out easily. They require a secondary dressing. They feel cool and soothing when applied to the wound. They are suitable for low to moderately exuding grades 2–4 ulcers. They are also suitable for wounds not spontaneously exuding, providing a moist environment.

Hydrocolloids are adherent, conformable, absorbent dressings: pastes and granules are also available and are especially suited to deeper wounds. Their conformability makes them suitable for use on "difficult" areas of the body including the sacrum, heels, and elbows. They can be left in place for several days. They are suitable for low to moderately exuding grades 3 and 4 ulcers. As they liquefy, Hydrocolloids form a yellowish gel-like material with a characteristic odor, which may, in the unwary, be mistaken for infection. They may stimulate excess granulation. They should be used with care if muscle, tendon, or bone is exposed. Hydrocolloids may be used on a range of wound beds, from ulcers that are infected to those that are epithelialising.

Alginates are polymers, which are derived from seaweed, either as calcium or sodium alginate. They are particularly useful in cavities, sinuses, and undermining grade 4 ulcers and moderately to highly exuding grades 2–4 ulcers. They are also suitable for sloughy and granulating wounds. They require a secondary dressing. They are hemostatic and useful for wounds that bleed.

Hydrofibre dressings are a form of hydrocolloid. They are highly absorbent and form a cohesive gel through interaction with wound exudates, thereby also maintaining a moist wound environment. They may be used on sloughy to granulating wounds. Hydrofibres are nonadherent and may be left in place for several days. They require a secondary dressing. They are used in similar situations as alginate dressings.

There are a plethora of other wounds dressings available. Their use should be guided by the characteristics of the wound, for example, site, size, depth, undermining, stage, drainage, surrounding skin involvement, wound infection, sinuses, underlying osteomyelitis, and so no. Dressing availability, cost, and ease of application may also need to be considered (Mulder and LaPan 1988; Eaglstein, 2001).

Infection

It is important to realize that all pressure ulcers will be colonized with bacteria. This does not, however, equate with infection. Wound cultures from pressure ulcer swabs are polymicrobial. Aerobic bacteria include, *Staphylococcus aureus*, *Staphylococcus epidermis*, β-hemolytic streptococcus Group A, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Providentia stuartii*, *Serratia marcescens*, *Enterococcus species*, *Enterobacter species*, and *Acenetobacter species* (Parish and Witkowski, 1989; Witkowski and Parish, 2000). Anaerobic organisms may also be present. Even when heavily colonized, most pressure ulcers eventually go on to heal (Mertz and Eaglestein, 1984; Dagher *et al.*, 1987; Hutchinson, 1989). Colonized wounds lack the signs of infection, which may include all or any of the features listed in Table 11.

Table 11 Signs of pressure ulcer infection

Warmth
Redness
Pain
Swelling
Odor
Increased wound exudate – serous, sero-sanguinous, purulent
Contact bleeding

When a pressure sore is infected, there is invasion of previously healthy tissue by microorganisms. A bacterial load of greater than 10^6 bacteria per gram of tissue has been found to impair wound healing (Sapico *et al.*, 1986; Parish and Witkowski, 1989; Witkowski and Parish, 2000). Infection is usually accompanied by at least some of the signs listed in Table 11. However, some of the signs may be attenuated or absent in patients with, for example, decreased sensation, abnormal neurological function or disturbed immunological response such as may occur in an elderly patient or patient with spinal cord injury. Cellulitis may complicate pressure ulcer infection as a result of spread of infection to surrounding tissue.

Bacteremia is a further serious complication of infected pressure ulcers. Bacteremia may lead to sepsis, endocarditis and death, with mortality rates between 50 and 70% (Sugarman *et al.*, 1982). Approximately one-quarter to one-third of nonhealing pressure ulcers are associated with underlying osteomyelitis arising through direct extension from an infected pressure ulcer or blood dissemination (Sugarman, 1987; Allman, 1989a,b).

Systemic treatment of an infected pressure ulcer and/or accompanying cellulitis, bacteremia, or osteomyelitis should be guided by culture and sensitivity of the organism(s). It may be prudent to start broad-spectrum antibiotic therapy while awaiting the results of tissue culture and sensitivity or blood cultures. However, swab results may not accurately reflect deep tissue cultures, which themselves may vary from one part of the ulcer to another (Kanj *et al.*, 1998). Curettage of the ulcer base following debridement is more reliable than swab samples (Sapico *et al.*, 1984; Lipsky *et al.*, 1990). Ulcer biopsy, if possible, will yield better tissue cultures (Daltrey *et al.*, 1981). Common pathogenic organisms include *S. aureus*, Bacteroides species, and gram-negative rods (Brown and Smith, 1999). A malodorous wound may be a sign of infection with anaerobes or *Bacteroides fragilis* (a facultative anaerobe). Gross tissue necrosis is usually caused by a combination of aerobic and anaerobic bacteria (Kanj *et al.*, 1998). Treatment should initially be with parenteral antibiotics.

Diagnosis of osteomyelitis and identification of the responsible pathogen is similarly fraught with difficulty. The traditional investigation of X-ray changes, elevated erythrocyte sedimentation rate and leucocytosis has a specificity of 33% and sensitivity of 60% (Darouiche *et al.*, 1994; Brown and Smith, 1999). More sensitive investigations include bone scans and MRI or CT scanning (Figure 22). Bone scans may be difficult to interpret, as the soft tissue inflammation from an infected wound is associated with a high false-positive rate. If the bone scan is abnormal, bone biopsy and culture may be necessary to determine infection and to identify the causative organism. A negative bone scan, however, makes osteomyelitis unlikely (Sugarman, 1987). MRI is now considered the investigation of choice for osteomyelitis (Sugarman, 1985). There is no consensus as to the duration of antibiotic treatment of osteomyelitis. Initial parenteral administration of antibiotics followed by oral antibiotics for a minimum of four to eight weeks is usual. Treatment may be monitored by measuring inflammatory markers such as ESR and CRP. Surgical debridement of the bone may be necessary.

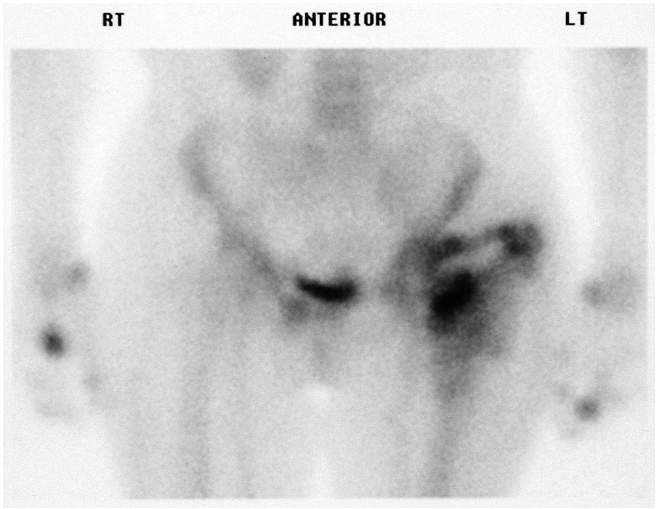


Figure 22 Bone scan of osteomyelitis underlying pressure ulcer of left hip

Sinus tracks may occur as a result of pressure ulceration. They occur in both superficial and deep ulcers and may extend to joint space and cause osteomyelitis. The sinuses may communicate with other structures including viscera (e.g. bowel and bladder). A sinogram or MRI may be necessary to delineate the extent and communication of these sinuses.

Other complications of pressure ulcers include squamous cell carcinoma (which may metastasize), with an estimated incident of 0.5%. Septic arthritis, amyloidosis, endocarditis, meningitis, and pseudoaneurysm formation may occur rarely.

Surgical Treatment of Pressure Ulcers

Surgical reconstruction may be appropriate treatment for some grade 3 and 4 pressure ulcers and may reduce healing times. An average healing time of 13 weeks has been demonstrated for grade 3 pressure ulcers if treated by skin grafting, and five weeks for those treated with musculocutaneous flaps (Brandeis *et al.*, 1990). It has been suggested that surgery is the preferred method of treatment when the rate of healing with conservative management is less than 40% (Siegler and Lavisso-Mourey, 1991).

Surgical treatment of pressure ulcers is usually reserved for those patients whose health outcomes and quality of life would significantly be improved by such intervention. There is, by extension, a definite place for palliative care for some patients with pressure ulcers whose medical and nutritional status is severely compromised, with control of symptoms rather than healing being the priority.

Successful reconstructive surgery is predicated on the optimization of the individual's medical and nutritional status. Surgery to close the defects is of long duration, with a potential for significant blood loss: postoperative immobilization is also protracted.

Adequate pre-and postoperative nutrition is essential to facilitate wound healing. Patients should give up or refrain from smoking as this hinders wound healing and may increase the risk of flap failure (Read, 1984). Spasticity leading to contractions may need to be addressed prior to surgery for pressure ulceration, as these may interfere with the pressure relief necessary postoperatively (Haher *et al.*, 1983). Exposure to feces and urine should be avoided and fecal or urinary diversion may be necessary in the preoperative planning process, especially in the paralyzed or neurologically compromised patient (Ferrell *et al.*, 1993; Brown and Smith, 1999).

There are various methods of surgical reconstruction of pressure ulcers largely dictated by their location and size of the defect. Primary closure with sutures is rarely of benefit and has high recurrence rates (Lewis, 1989). Skin grafts, similarly, are seldom used as they do not provide any padding and only provide a superficial barrier. Additionally, they exhibit "poor take" over exposed bone (Granick *et al.*, 1994).

Musculocutaneous and fasciocutaneous flaps are the most widely used method for reconstructing pressure ulcers. A fascial or muscular unit, the overlying skin and their blood supply, in a pedicle of tissue, is used to fill the defect made by the pressure ulcer (after debridement of devitalized tissue). Such flaps are, as a consequence of their preserved blood supply, able to withstand pressure and shear trauma. They are also particularly useful when treating pressure ulcers complicated by osteomyelitis by bringing highly vascularized muscle into the area of infection, which has been removed at the time of surgery (Daniel *et al.*, 1979; Mathes *et al.*, 1993; Bruck *et al.*, 1991; Anthony *et al.*, 1992).

Other flaps used include axial flaps – a vascularized segment of skin and subcutaneous tissue is raised and rotated into the defect; microvascular flaps – tissue with a single arteriovenous pedicle is raised, the vessels transected, and anastamosed to recipient vessels adjacent to the pressure ulcer defect; free flaps – muscle flaps where the original blood supply is disconnected and reconnected to vessels at the tissue defect site – rarely used, chiefly since less complicated options are usually available (Kostako-glu *et al.*, 1993).

Postoperatively, patients require immobilization, remaining in bed with vigilant pressure relief. A low air-loss mattress or an air-fluidized bed may be necessary. Immobilization for 2 to 4 weeks is usual. Flap viability must closely be monitored. Postoperative complications include hematoma (most common, therefore, meticulous intraoperative hemostasis is necessary), wound infection, flap necrosis, dehiscence, seroma, and infection.

Adjunctive Therapies

Adjunctive therapies are increasingly being employed in an attempt to heal pressure ulcers. Some of these are very effective and are becoming part of the armoury of standard treatment. Yet others are experimental or in the research stage.

VAC Therapy

Vacuum assisted closure (VAC) therapy is one of many synonyms in use for topical negative pressure therapy (TNP); though the term VAC is widely used in the United Kingdom (Figure 23). The technique has found an increasing role in the treatment of chronic wounds with large amounts of exudates, such as pressure ulcers (Philbeck *et al.*, 1999). The VAC dressing is open pored (polyurethane or polyvinyl chloride), shaped to fit the wound and sealed within it using a semiocclusive dressing. A negative pressure is delivered across the wound bed via a drainage tube embedded within the foam and connected to a negative pressure device (Banwell, 1999).

The negative pressure promotes granulation tissue formation (Morykwas *et al.*, 1997). This may be facilitated by reducing tissue edema directly, by removing fluid, or indirectly by eliminating factors that promote edema, thus preventing microvascular compromise (Morykwas *et al.*, 1997, 1999). Reduced edema may, however, reflect increase in local blood flow (Thomas and Banwell, 2004). Removal of fluid has also been postulated to remove factors inhibitory to wound healing (Banwell, 1999). Furthermore, TNP has been shown to reduce bacterial colonization of wounds both experimentally and clinically (Mullner *et al.*, 1997; Morykwas *et al.*, 1997; Obdeijn *et al.*, 1999; Giovanni *et al.*, 2001), which may further enhance wound healing.

Several studies have demonstrated the efficacy of VAC therapy in the treatment of pressure ulcers (Baynham *et al.*, 1999; Azad and Nishikawa, 2002; Coggrave *et al.*, 2002). Dressings may only need to be changed twice weekly, thus reducing patient discomfort and cost (Schneider *et al.*, 1998). The duration of VAC therapy depends on clinical improvement, patient compliance, and resources. VAC therapy has been advocated by some in the treatment of pressure ulcers complicated by underlying osteomyelitis (Ford *et al.*, 2002), while others feel that osteomyelitis is a contraindication to its use (Lyder, 2003); other relative contraindications

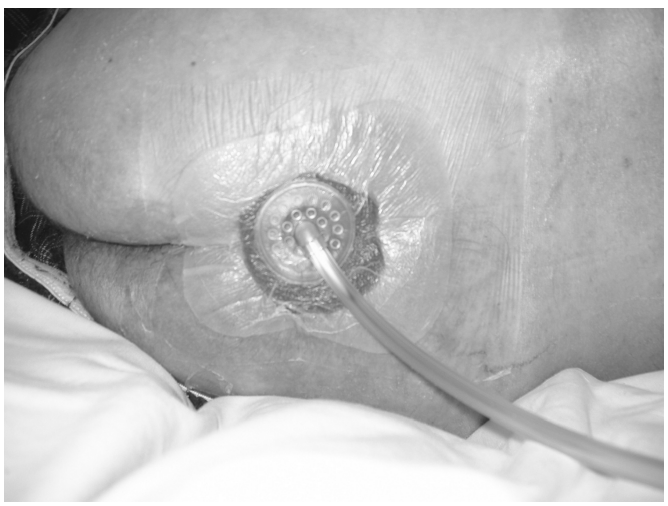


Figure 23 VAC therapy on sacral pressure ulcer

include application over an open joint; peritoneal or pleural space; in patients with a coagulopathy; over a tumor, though it may be considered as part of palliative wound control (Banwell, 1999).

Physical Modalities

Many physical therapies have been used to treat pressure ulcers. However, the therapeutic efficacy of hyperbaric oxygen, infrared, UV, low energy and laser irradiation, and ultrasonography has little evidence to support their use in the treatment of pressure ulceration (Bello and Phillips, 2000). Radiant heat (Normotherapy) is thought to increase blood flow and promote fibroblast and other factors associated with pressure ulcer healing (Xia *et al.*, 2000; Kloth *et al.*, 2000): Further evaluation with controlled trials is required.

Electrical stimulation has been recommended by the Agency for Health Care Research (USA) for stages 2 to 4 pressure ulcers which have not responded to conventional therapy (Ovington, 1999). The basis of the therapy is founded on the observation that when tissue is damaged, a current of injury is generated that may trigger biological repair (Weiss *et al.*, 1990). Electrical stimulation has been shown to enhance wound healing in human and animal models: This is thought to affect the migration, proliferation, and functional capacity of fibroblasts, neutrophils, and macrophages; promote collagen and DNA synthesis and increase the number of receptor sites for specific growth factors (Falanga *et al.*, 1997; Gentzkow *et al.*, 1993; Kloth and McCulloch, 1996; Baker *et al.*, 1996). However, it has been postulated that it is in fact the occlusive dressing used which may enhance wound healing by providing the moist environment necessary to maintain endogenous current flow (Jaffe and Vanable, 1984).

Larval Therapy

Sterile larvae (maggots, Figure 24) were first used as a treatment for infected or chronic wounds in the early twentieth century. Over recent years, there has been a resurgence of interest in their use for the debridement of a variety of infected or necrotic acute and chronic wounds including pressure ulcers. Two species of larvae are commonly used: *Lucilia species* and *Phaenicia species*.

While they often have a significant effect on sloughy and infected wounds, their exact mechanism of action is not fully understood. Maggots have been shown to ingest and kill some bacteria and studies have also shown that larval secretions kill or inhibit the growth of a number of bacterial species including *S. aureus* (including MRSA) and *Streptococcus*. Furthermore, the metabolic activity of the maggots increases wound pH, preventing the growth of such bacteria (Thomas and Jones, 1998).

The digestive juices of the larvae contain growth factors, antiseptic substances, and enzymes such as proteases (Fleischmann, 2004). Fibroblast growth stimulating factor has been demonstrated in the hemolymph and alimentary secretions of larvae (Prete, 1997). The presence of larvae or their metabolites may stimulate cytokine production by wound macrophages, thus stimulating the wound-healing process (Thomas and Jones, 1998). Larvae secrete powerful proteases, mainly of the serine class, which break down dead tissue, which is used for sustenance by the larvae (Young *et al.*, 1996).

Despite promising reports and widespread use, there are as yet, no large randomized, controlled trials to support the use of larvae in the treatment of pressure ulcers.

Growth Factors

Growth factors are secreted regulatory proteins that control survival, growth, differentiation, and effector function of tissue cells. They require a receptor, which may not be constitutive, to exert their effect. A large number of growth factors have been described and characterized. Since wound healing is an inflammatory process, much research has been carried out to determine whether they may be useful clinically in the treatment of chronic wounds including pressure ulcers. Initial promise, however, has not translated into clinical reality to any great extent.

Platelet-derived growth factor (PDGF) is one of the first growth factors released in acute wounds and as such has been investigated as a potential therapy to promote healing of chronic wounds. PDGF is a dimeric glycoprotein, released predominantly by platelet alpha granules. Topically applied recombinant PDGF-BB (rh PDGF-BB) has been shown in various small trials to produce a statistically significant reduction in pressure ulcer volume in the treatment group (Mustoe *et al.*, 1994). Other trials have shown an improvement in the rate of re-epithelialization of pressure ulcers with exogenously applied PDGF-BB (Robson, 1991; Cox, 1993). The trials highlighted the importance of simple good basic care in the treatment of pressure ulcers.

A further small, placebo controlled, double-blind study using recombinant basic fibroblast growth factor (rh b-FGF) in patients with chronic grades 3 and 4 pressure ulcers demonstrated no difference in the percentage volume reduction between different arms of the study. The volume reduction compared to baseline in the actively treated group was, however, significant (Robson *et al.*, 1992a,b).

Drawbacks of such trials are that they tend to be small and of short duration; large randomized, controlled trials are needed.

It is perhaps not surprising that growth factors have not proved the panacea in the healing of chronic wounds. Growth factors are present at different stages of healing and exert their effects depending on the wound microenvironment at a particular time and presence, or absence, of other growth factors. In addition, there is a balance between growth factors and enzymes responsible for their activation and degradation, which also vary at different stages in the wound healing cascade. Ideally, a diagnostic test to ascertain which of the wounds are deficient in specific growth factors is needed:

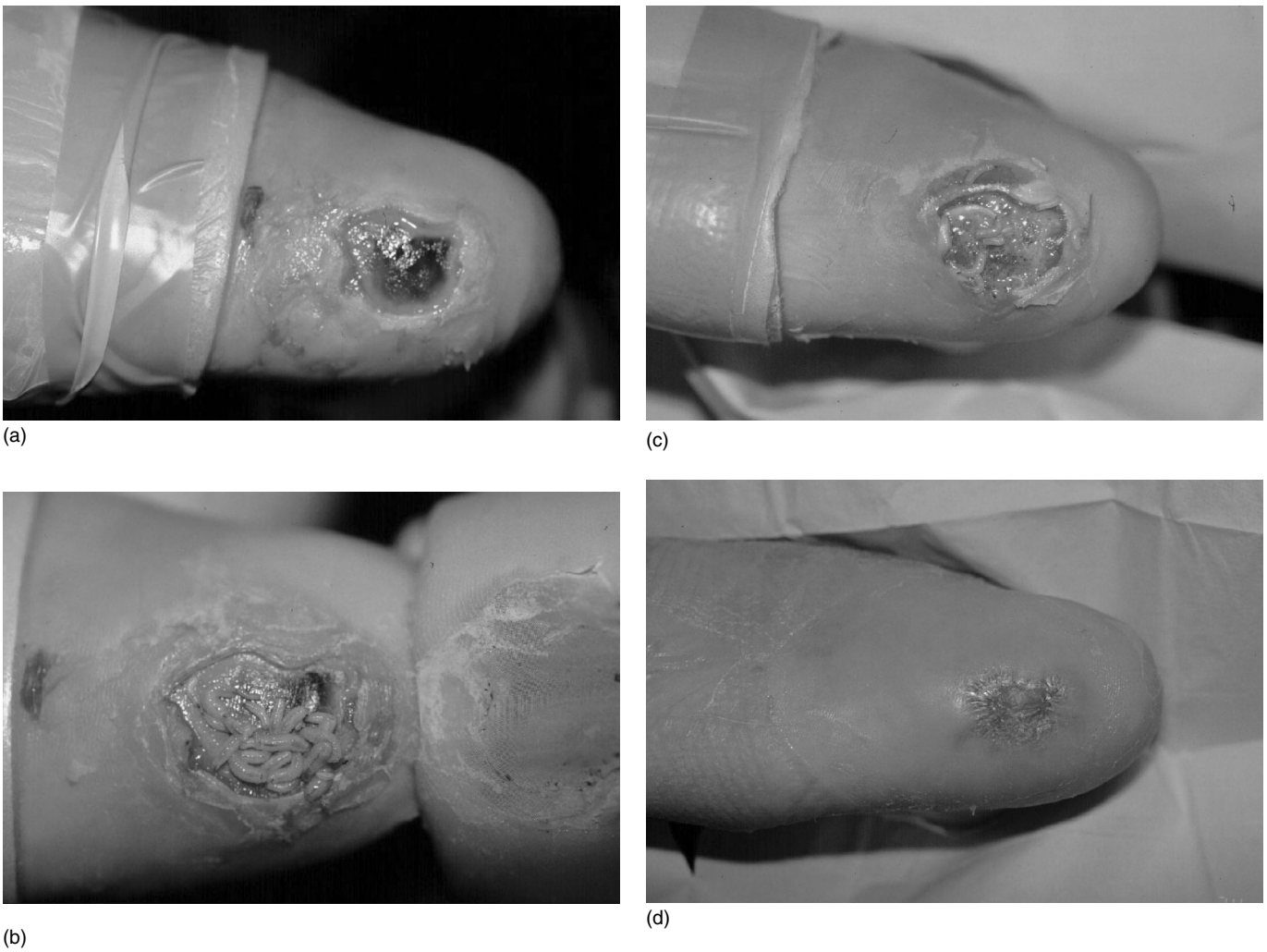


Figure 24 Debridement of heel pressure ulcer with Larval therapy (a) Pre-treatment, (b) 3 days post larval therapy, (c) 7 days post larval therapy, (d) Healed pressure ulcer (Pictures courtesy of Dr S Thomas, Zoobiotic Ltd.)

Then, perhaps, the promise of exogenously applied growth factors will be fulfilled.

Tissue Engineering

Tissue engineered "skin equivalents" have been developed to treat both acute and chronic wounds: They are formed by growing allogeneic cells in a synthetic matrix *in vitro*. The "skin equivalents" may be categorized as (1) those containing epidermal elements alone; (2) those comprising dermal elements, and (3) composite grafts containing both epidermal and dermal elements (Phillips, 1998). Most of the allogeneic cells are derived from neonatal foreskins and are seeded into a variety of collagen gels or bioabsorbable meshes. Much work has been carried out into their use on chronic wounds such as venous leg ulcers and diabetic foot ulcers with good effect. There have been some promising small trials using "skin equivalents" to treat pressure ulcers, but no large trials have been undertaken. It is an area that merits further study.

Other Therapies

Many other therapies for the treatment of pressure ulcers have been investigated. Topical agents include honey, sugar, vitamins, zinc, magnesium, gold, phenytoin, yeast extract, insulin, and aloe vera gel. Light therapy and ultrasound have also been tried (Kanj *et al.*, 1998). All require further evaluation and large-scale trials to establish their efficacy.

KEY POINTS

- Pressure ulcers are common, especially in the elderly patient.

- Pressure ulcers are caused by direct pressure, friction and shear forces, individually or often acting in concert with each other: Moisture exacerbates the effects of pressure, friction and shear.
- At-risk individuals should have regular risk assessments: Risk assessment scales are not a substitute for clinical judgment.
- The effects of risk factors should be minimized through optimal management.
- Adequate pressure relief is essential in the prevention and treatment of pressure ulcers.
- Accurate pressure ulcer grading assists in the choice of treatment, dressings, and adjunctive therapies.

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Perioperative and Postoperative Medical Assessment

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INTRODUCTION

Over the past 25 years, almost all surgical specialities have seen a dramatic increase in admissions of elderly and very elderly patients. The numbers being referred have been over and above that which would have been expected from demographic change alone and the rate of increase has usually been faster than the rise in surgical activity seen in younger adults, particularly in regard to elective procedures. Trends for two operations having a major effect on quality of life are shown in Figures 1 and 2. It seems that old people themselves, and their lay and professional advisers, are increasingly willing to consider surgery in old age. On the other hand, the idea that there are individuals who are "too old for surgery" is still very pervasive. There is concern that rates of surgery may be suboptimal, especially for higher technology interventions such as coronary surgery (Wood and Bain, 2001), and there is also evidence that elderly patients in lower socioeconomic groups have lower rates of surgery than their contemporaries in higher socioeconomic groups (Seymour and Garthwaite, 1999).

This chapter discusses the approach that needs to be taken in elderly patients in the immediate preoperative and postoperative period, concentrating on the medical aspects of assessment. However, it must not be forgotten that the fundamental aim of a preoperative assessment is the same whatever the patient's age: there is a need to estimate whether the likely benefits of the surgical procedure in that particular individual will outweigh the likely risks.

The chapter begins with a discussion of the relationship between old age and postoperative morbidity and mortality. This is followed by a brief discussion of the causes and consequences of emergency surgery in older people. Consideration is then given to the major organ systems that are of particular relevance in the medical assessment of the older surgical patient, and pointers are given to active research areas that are likely to affect practice in the near future. The problems of surgical diagnosis, strategies for the management of individual surgical conditions, and details of the technical aspects of surgery and anesthesia are not considered here, but have been reviewed by Crosby *et al.* (1992) and in a recent multiauthor book by Rosenthal *et al.* (2001). Additionally, a policy document on "Anaesthesia and Peri-operative Care of the Elderly" has been produced by a Working Party of the Association of Anaesthetists of Great Britain and Ireland (2001). Finally, the recent (Scottish Intercollegiate Guidelines Network, 2004) Guideline on Postoperative Management in Adults, while not confined to the older surgical patient, is of considerable relevance to older people as they make up a major proportion of patients who develop problems following surgery. The SIGN (Scottish Intercollegiate Guidelines Network) Guidelines are intended for use by nonspecialists in the early postoperative period, giving advice on early detection and management of common problems, and, equally importantly, indicating when more specialist help should be sought.

AGE AND POSTOPERATIVE OUTCOME

Where age is the only risk factor studied, most statistical analyses in adult patients show a positive correlation between age and the rate of adverse postoperative outcome, and a simple interpretation would be that surgery should be discouraged in extreme old age. However, there are a number of flaws in this simplistic analysis. Firstly, there is the assumption that the outcome in an elderly individual can be predicted with accuracy from the "average" outcome of patients of the same age. As shown in the following, age as a risk factor for predicting adverse outcome in *individual* surgical patients lacks both sensitivity and specificity. Secondly, mortality figures do not tell us about the balance of risk and

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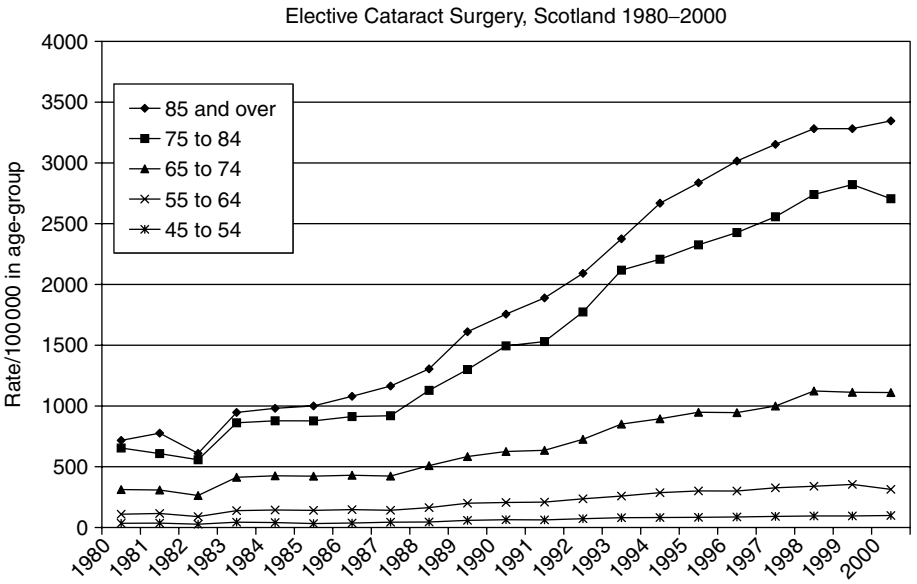

Figure 1 Elective Cataract Surgery, Scotland 1980–2000. On the basis of data supplied by the Information and Statistics Division of NHS Scotland

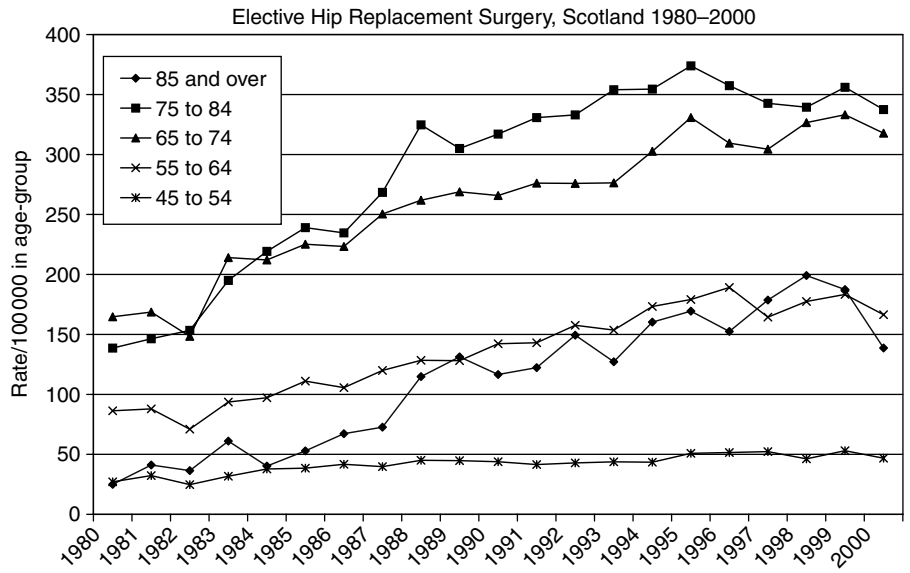

Figure 2 Elective Hip Replacement Surgery, Scotland 1980–2000. On the basis of data supplied by the Information and Statistics Division of NHS Scotland

benefits in individual patients. For example, in extreme circumstances, such as a ruptured aortic aneurysm, the mortality rate for nonoperative therapy is nearly 100% and so a postoperative mortality rate of 25–40% might be highly acceptable. Thirdly, outcome data related to broad surgical categories of disease do not take into account the tendency for more serious pathology to occur with advancing age. For example, young adults admitted urgently with abdominal pain tend to have conditions such as uncomplicated appendicitis or nonspecific abdominal pain, where mortality rates are low. As patients get older, an "acute abdomen" often turns out to be because of a perforated viscus, carcinoma, vascular events, or other major pathology which have a much higher rate of mortality and morbidity (de Dombal, 1991).

It is also wrong to assume that a positive correlation between age and postoperative adverse outcome indicates that the adverse outcome is a direct result of the aging process. In fact, there is little evidence that age *in the absence of disease* is a major risk factor for postoperative morbidity and mortality. This assertion is supported by several lines of evidence. For instance, a study from the United States, which used the Medisgroups system to grade the severity of preoperative medical problems of general surgical patients aged 65 years and over, found no relationship between age

and outcome, once the preoperative status had been taken into account (Dunlop *et al.*, 1993). Similarly, the APACHE III (Acure Physiology and Chronic Health Evaluation) prognostic system, which has been applied widely in intensive care units, indicated that around 47% of the variability in mortality was associated with the severity of illness, 6% with a type of disease, while only 3% appeared to be attributable to age (Knaus *et al.*, 1991).

Thus, the great body of evidence suggests that the major factor in the association between age and adverse postoperative outcome comes about *not as a result of aging itself, but through a secondary association with age-associated disease* (Lubin, 1993; Seymour, 1999).

AGE, EMERGENCY SURGERY, AND POSTOPERATIVE OUTCOME

It has been known for many years that nonelective surgery is associated with a higher rate of postoperative problems than is elective surgery. Survival curves from a study of elderly general surgical patients in North Wales (Edwards *et al.*, 1996) have suggested that, while both age and nonelective surgery were associated with postoperative mortality, nonelective surgery had a strong association with short- and medium-term survival, while age had a major effect on long-term postoperative survival. However, the interpretation of the association between nonelective surgery and adverse outcome in older patients is complicated by the fact that there is also a positive correlation between increasing age and the tendency to be admitted nonelectively.

An excellent series of reports produced in England and Wales by the National Confidential Enquiry into Perioperative Deaths (NCEPOD) have focused attention on postoperative deaths which might have been preventable. They have pointed to deaths following emergency surgery (often carried out out-of-hours by less experienced staff on medically unstable patients) as a continuing cause for concern. The reports also show that over two-thirds of postoperative deaths occur in patients aged 71 years and over. Within Scotland, the SASM (Scottish Audit of Surgical Mortality) audits all postoperative deaths and has come to similar conclusions.

CARDIAC PROBLEMS

Cardiac Surgery (*see* Chapter 52, Cardiac Surgery in the Elderly)

In patients who are undergoing cardiac operations such as coronary artery bypass grafts or valve replacement, surgery is usually carried out under elective conditions and detailed information about cardiac status is available preoperatively. Furthermore, such patients tend to be treated postoperatively in intensive care units. Under such circumstances postoperative mortality rates tend to be gratifyingly low even in older patients. In the previous edition of this textbook, reference was made to a survey of patients undergoing cardiac operations in Washington DC. Even at that time, a quarter of patients were aged 70 years and over and they had a 30-day mortality of 5.3%, compared with a 2.7% 30-day mortality in patients aged 69 years or under (Katz *et al.*, 1995). Around the same time, Unsworth-White and colleagues from St George's Hospital in London concluded that while the risks of cardiac surgery "above 70 years of age, and certainly above 80 years of age, are appreciably higher... they are not prohibitive" (Unsworth-White *et al.*, 1993), and, in common with the Washington unit, about a quarter of their cardiac patients were aged 70 and over. In the last 10 years, there have been several hundred publications on cardiac surgery in old age, and in many areas, particularly North America, it is becoming almost routine. Alexander *et al.* (2000), from North Carolina, reviewed hospital outcome in 67 764 patients (4743 aged 80 years and over) undergoing cardiac surgery in 22 centers involved in the National Cardiovascular Network. The overall incidence of morbidity and mortality in the octogenarians was lower than that previously reported, but remained higher than the rates encountered in younger patients. However, in octogenarians without significant comorbidity, mortality rates approached those of younger patients.

While these results are encouraging, the elderly individual opting for open-heart surgery needs to be aware of the risks as well as the benefits. In an editorial giving a "cardiologist's perspective", Sprigings (1999) points out that the reported rate of postoperative stroke in some series of octogenarians undergoing aortic valve surgery is above 10%. As the nonsurgical treatment of severe aortic stenosis is unsatisfactory, Sprigings accepts that the decision to recommend surgery in those with severe symptoms and no other medical problems is not difficult, but there remain many other elderly cardiac patients in whom there is true uncertainty as to the right course of action. In all cardiac surgery, but particularly in conditions other than aortic stenosis, there is a widespread appreciation that the quality of life and the functional capacity as well as survival need to be taken into consideration, and cardiac surgery in old age can have major impact on the first two of these factors (Jaeger *et al.*, 1994; Walter and Mohan, 1995; Awad *et al.*, 1995; Olsson *et al.*, 1996).

Noncardiac Surgery

The major postoperative cardiac complications are myocardial infarction (MI) and acute heart failure. The former may be difficult to diagnose in the early postoperative period as pain can be masked by anesthesia and analgesia, and surgical trauma to muscles may make interpretation of cardiac enzyme changes difficult, although newer enzyme tests such as troponin-I and troponin-T offer the potential for enhanced specificity (Surveillance for perioperative MI, 2002). Using traditional clinical criteria, postoperative MI has been estimated to occur following 1–4% of general surgical operations in the over-65s and cardiac failure has been reported

in 4–10%, with the mortality rate associated with postoperative myocardial infarction being around 50% (Seymour *et al.*, 1992). The rate of postoperative cardiac complications in patients aged 75 and over is 2–3 times that of those aged 65–74 (Seymour *et al.*, 1992). Depending on the definitions and diagnostic tests used, much higher estimates of perioperative MI rates have been reported. Thus, Badner *et al.* (1998) in a group of 323 patients aged 50 or over undergoing noncardiac surgery reported a 5.3% incidence of postoperative MI when the criteria were based on autopsy data, new Q waves on ECG, and creatine kinase (CK-2) levels. However, when cardiac troponin-T levels greater than $0.2\,\mathrm{mcg\,l^{-1}}$ were incorporated into the diagnostic criteria, the estimated rate of perioperative MI rose to 11.2% and further relaxation of ECG criteria led to an estimate of 20.7%.

In day-to-day medical practice, the main need for preoperative cardiac assessment arises in the elderly patient who is undergoing *noncardiac* surgery. Thus, Mangano (1990) estimated that, for each patient undergoing cardiac surgery in the United States, there are up to 10 other "cardiac" patients (i.e. patients with known heart disease or two or more major cardiac risk factors) undergoing noncardiac surgery. Mangano estimates that a third of all patients aged 65 and over fall into this "cardiac" category, and a proportion of the remaining two-thirds will have occult ischemic heart disease which may reveal itself only during the perioperative period.

The "cardiac assessment of the noncardiac surgical patient" has accordingly become a major focus of research in recent years. The earliest reports in this field identified a number of individual risk factors which were correlated with an increase in adverse postoperative cardiac outcomes. These included previous myocardial infarction, congestive heart failure, angina, age, hypertension, diabetes, arrhythmias, peripheral vascular disease, valvular heart disease, smoking, and previous cardiac surgery (Badner *et al.*, 1998). Later, researchers attempted to construct multifactorial indices of cardiac risk from these individual risk factors (Goldman *et al.*, 1977; Detsky *et al.*, 1986), but, as recognized by their originators, there are limitations in applying these indices to individual patients (Mangano & Goldman, 1995; Mangano, 1995). A major milestone in this field was the appearance of the 1996 guidelines on perioperative cardiovascular evaluation for noncardiac surgery, issued jointly by the American College of Cardiology and the American Heart Association (AAC/AHA) (Eagle *et al.*, 1996). These were subsequently updated in 2002 taking account of 400 or so references that had appeared between 1995 and 2000 (Eagle *et al.*, 2002). The first point to make of both of the AAC/AHA reports is that they found relatively few randomized control trials (RCTs) on which to base their recommendations. Part of the problem is that most of the studies quantifying postoperative risks are necessarily of an observational or cohort design, although RCTs may be feasible at a later stage. Another problem with RCT studies in the field of perioperative risk reduction is that the interventions may be complex and consist of changes in practice and organization rather than simple drug interventions. However, as in most cases the field of cardiology lends itself to drug interventions, an important development between the 1996 and 2002 AAC/AHA reports was the appearance of trials showing short- and long-term cardiac benefits of β-blockade in surgical patients (see pages 32–35 of the 2002 report), with the two publications by Poldermans *et al.* (1999) and Boersma *et al.* (2001) being particularly influential. Other important additions to be found in the 2002 AAC/AHA update are discussions of renal insufficiency, better quantification of the predictive role of preoperative functional capacity, more detailed guidance on preoperative cardiac assessment, and an assessment of the role of percutaneous coronary intervention.

The fundamental three-part strategy of risk prediction used in the 1996 ACC/AHA report remained unchanged in the 2002 version. Indeed, a similar strategy is likely to be a suitable model for use in risk prediction outside the cardiovascular field. The three separate areas of risk considered are:

(a) major clinical predictors of risk
(b) functional capacity
(c) surgery-specific risk.

Within category (a), "major" clinical predictors are identified as *unstable coronary syndromes*, decompensated heart failure, congestive heart failure, significant arrhythmias, and severe valvular disease. In the "intermediate" clinical predictor group are found mild angina, previous myocardial infarction, compensated or stable congestive cardiac failure, diabetes, and renal insufficiency. The "minor" clinical predictors are advanced age, abnormal ECG, non-sinus rhythm, history of stroke, and uncontrolled hypertension.

In respect to category (b), specialists in geriatric medicine will readily identify with the concept that age by itself in the absence of disease is not a major predictor of an adverse outcome. Similarly, they will concur with the importance of functional capacity in determining the outcome. The 1996 ACC/AHA report introduced the concept of defining functional capacity in terms of metabolic equivalents (MET levels) and this approach deserves to be more widely known both in medicine and surgery. Perioperative cardiac problems are much increased when a patient is unable to meet a four MET level of activity: this is roughly equivalent to climbing a flight of stairs, walking up a hill or walking on level ground at a speed of 4 mph or 6.4 kmph. The 2002 report has continued to champion the MET concept, and was able to incorporate a publication by Reilly *et al.* (1999) relating self-reported exercise tolerance to the risk of serious perioperative complications.

Category (c), the third element of the ACC/AHA risk assessment, classifies surgical procedures into high, intermediate and low risk. Examples of "high" risk (cardiac risk often $>5\%$) include emergency major operations particularly in the elderly, aortic and other major vascular surgery, peripheral vascular surgery, and procedures likely to be associated with large fluid shifts or blood loss. "Intermediate" (cardiac risk generally $<5\%$) procedures include carotid endarterectomy, head and neck surgery, interperitoneal and intrathoracic

surgery, orthopedic surgery, and prostate surgery. "Low" risk procedures (cardiac risk generally <1%) include endoscopic procedures, superficial procedures, cataract surgery, and brain surgery.

The final part of the ACC/AHA risk assessment strategy is to weigh up the relative importance of categories (a), (b), and (c) in an individual patient, recognizing, for example, that adverse clinical predictors and functional impairment are much more to be feared in a patient undergoing intermediate or major surgery than they are in a patient undergoing minor surgery. As in 1996, an algorithm is provided for this purpose in the ACC/AHA 2002 report. The ACC/AHA guidelines will be reviewed annually from now on, and revisions will be published on the Internet (www.acc.org and www.americanheart.org). In addition, a recent paper by Mukherjee and Eagle (2003) provides a readily accessible summary of the current approach to perioperative cardiac assessment, illustrating the application of the ACC/AHA guidelines to a 68 year old patient with a cardiac history in whom elective surgery is being considered.

RESPIRATORY PROBLEMS (*see* Chapter 61, Respiratory Disease in the Elderly)

As Pulford and Connolly have pointed out (Pulford and Connolly, 1996), attempts to make a precise distinction between those changes in the lung that are caused by aging and those that are caused by accumulated damage from pollutants and lung disease are "doomed to failure". However in general, we can say that the aging lung undergoes (a) *structural changes*, with increased rigidity of the chest wall, reduced alveolar area, and increases in lung compliance, functional residual capacity and residual volume; and (b) *physiological changes*, with a reduction in exercise capacity and impaired control of ventilation (from a mixture of central and peripheral changes including reduced sensitivity to hypoxia). Pulford and Connolly identify an increase in closing volume (i.e. small airways collapse at higher lung volumes during expiration), as the single most clinically important result of all these changes in the aging lung, and increased closing volumes probably have a significant role in causing postoperative atelectasis.

Respiratory complications remain a significant cause of postoperative morbidity and potentially preventable postoperative mortality (Seymour and Vaz, 1989; Williams Russo *et al.*, 1992). In a recent review of factors influencing a range of postoperative complications in older people, Jin and Chung (2001) quote estimated incidences of 2–10% for postoperative respiratory complications in elderly people. They identify the site of surgery as being the best single predictor of postoperative respiratory complications, with incisions near the diaphragm having the highest rate of complications. Other clinical risk factors identified are duration and type of anesthesia, chronic obstructive lung disease, asthma, preoperative hypersecretion of mucus, chest deformation, and smoking within the month prior to surgery. Research into perioperative respiratory risk reduction has been less extensive than in the field of cardiac risk, but research themes have included the ability of preoperative symptoms, signs, and pulmonary function testing to predict postoperative outcome, and on the preventive methods, including physiotherapy, which can be applied in patients shown to be at risk (ACP, 1990; Zibrak *et al.*, 1990; Celli, 1993). A further important discovery has been the recognition that postoperative hypoxemia is common, and that it may occur several days after anesthesia.

A series of three publications from Lawrence (Lawrence *et al.*, 1995; Lawrence *et al.*, 1996; De Nino *et al.*, 1997) and his colleagues in Texas has reexamined the factors associated with perioperative respiratory complications and the efficacy of attempts to reduce respiratory morbidity and mortality. The first of these publications showed that, in terms of cost and morbidity, respiratory complications were as important as cardiac complications. The second publication found that postoperative respiratory complications were statistically associated with abnormal preoperative lung signs, abnormal chest radiology, overall morbidity, and the Goldman Cardiac index. However, when combined with these clinical predictors, spirometry did not improve risk prediction. A formal cost-effective analysis contained in the third publication led to the conclusion that, at the time of the study, preoperative spirometry in the United States was "blowing away" $8 million to $20 million Medicare dollars each year. An earlier systematic review of the role of preoperative spirometry in non-thoracic surgery had similarly found it difficult to demonstrate a clear-cut benefit of spirometry over and above that of preoperative clinical assessment (Thomas and McIntosh, 1994). A more recent report by Smetana (1999) has indicated that obesity and age may be less important predictors of respiratory risk than they were reported to be in earlier studies.

In the absence of definitive evidence in many areas, what should be our preoperative strategy in attempting to minimize postoperative respiratory complications in older patients? Many of the recommendations in this area are based on clinical experience or extrapolation from what is known about respiratory risk, rather than on randomized intervention trials. They include (Seymour, 1999) cessation of smoking 6 to 8 weeks before surgery, "pulmonary toilet" combined with physiotherapy for those at highest risk, care with the temperature and humidification of anesthetic gases, adequate analgesia, early removal of nasogastric tubes, and early mobilization.

How much technology should we use when assessing preoperative respiratory risk in older patients? Jin and Chung (2001) recommend obtaining a preoperative chest X ray in all patients aged 60 and over, but particularly in patients with respiratory symptoms, smoking, obesity, and cardiopulmonary disease. In those with an abnormal chest X ray, basic pulmonary function tests are recommended. If these are abnormal, they trigger pre- and postoperative prophylaxis in patients undergoing nonresective or upper

abdominal surgery. Patients in whom pulmonary resection is being considered require more intensive evaluation.

Postoperative Hypoxemia

A major discovery in the postoperative care of middle-aged and elderly patients in recent years has been that profound postoperative hypoxemia can occur many days after surgery (Catley *et al.*, 1985; Knill *et al.*, 1990). It used to be assumed that once the immediate sedative affects of general anesthesia had disappeared, that is, within a few hours of surgery, then the main risk period for hypoxemia had passed. However, with the discovery of pulse oximeters, which provided a noninvasive means of monitoring oxygen desaturation, it became clear that many patients were undergoing profound but clinically silent desaturations at night, sometimes up to a week after surgery. It is plausible that some of the arrhythmias and episodes of sudden death occurring several days after surgery which were previously attributed solely to cardiac causes were in fact the result of hypoxemia. However, while some authors claim that there is a close relationship between hypoxemia and cardiac disturbances such as ischemia or arrhythmias (Pateman and Hanning, 1989; Reeder *et al.*, 1991; Gill *et al.*, 1992; Stausholm *et al.*, 1995), others are not so convinced (Smith *et al.*, 1996).

The nocturnal desaturations can be reduced by giving continuous intranasal oxygen (McBrien and Sellers, 1995) for several days after surgery ("3 days and 5 nights" is a common regimen) and so these findings have considerable practical importance. Research efforts in the 1990s have been directed at explaining the mechanism of nocturnal desaturation in more detail, and trying to predict which patients are most at risk, so that this oxygen therapy can be better targeted. However, a final consensus has yet to emerge. If it is currently difficult to predict which elderly postoperative patients will develop postoperative hypoxemia, and if there is *prima facie* evidence that hypoxemia is harmful, it might appear logical to use oximetry to monitor the great majority of older people in the perioperative period, despite the costs in time, money, and inconvenience. However, scientific doubts about the efficacy of an "oximetry for all" approach have been raised by a large randomized study that was able to demonstrate that pulse oximetry reduced the *incidence* of postoperative hypoxemia, but which failed to demonstrate the expected *benefits* in postoperative complications (Moller *et al.*, 1993a; Moller *et al.*, 1993b).

Further, research is clearly warranted in this area. It seems likely that the final explanation of the variation in individual adverse effects of hypoxemia will be complex, and might, for instance, depend not only on the absolute level of oxygen, but also on the presence of hypocarbia, and/or the patient's previous level of hypoxemia. Research is also needed into the potential for hypoxemia to cause delirium and impair wound healing (Rosenberg, 1994).

RENAL FUNCTION AND FLUID STATUS

Postoperative Renal Failure and Renal Dysfunction

Deaths as the sole result of acute renal failure in the postoperative period are relatively rare after general surgery in older patients. Out of a total of 546 patients aged 65 years and over, undergoing general surgery in two prospective studies (Seymour and Vaz, 1989; Seymour and Pringle, 1982), the number of potentially preventable postoperative deaths was 26 but in only one was acute renal failure judged to be the *sole* cause of death. However, renal failure may also contribute to death in patients with multiple problems such as postoperative sepsis and cardiac failure.

Major vascular or cardiac operations are associated with an increased risk of renal failure when compared with general surgery. In a prospective study of 734 predominantly middle-aged cardiac surgery patients with normal preoperative renal function, Zanardo *et al.* (1994) recorded postoperative renal dysfunction in 11.4% and acute renal failure in 3.7%. Mortality rates were 0.8% for those with normal postoperative renal function, 9.5% for those with renal dysfunction, and 44.4% for those with acute renal failure.

Transient postoperative renal impairment is much more common than acute renal failure. Because the acute stress response results in difficulty in excreting a water load, it has been argued that a degree of postoperative oliguria is inevitable. However, careful fluid replacement, good analgesia, and controlled anesthesia can usually minimize this effect (Sweny, 1991; Burchardi and Kacmarczyk, 1994). Transient postoperative hyponatraemia is also a common phenomenon. Some episodes are related to difficulties in excreting a water load, but in urological practice the infusion of large amounts of hypotonic fluid into the bladder can also lead to significant retention of water and subsequent hyponatraemia. In the first few days following surgery or trauma, isotonic fluid sequestration in wound sites (the "third space") may also lead to subtle volume deficiencies (Van Zee and Lowry, 1995).

While anesthesia can have direct pharmacological effects on renal function and body fluid regulation, and while direct toxic effects have been reported with methoxyflurane, it appears that, in the majority of patients with postoperative renal impairment, nonanesthetic factors (such as volume impairment, sepsis, cardiovascular complications, the acute stress response, and the effects of mechanical ventilation) are more important (Sweny, 1991; Burchardi and Kacmarczyk, 1994)

Novis *et al.* (1994) have reviewed 28 studies of the preoperative risk factors associated with postoperative acute renal failure in patients undergoing general, biliary, vascular, and cardiac surgery. Preoperative renal impairment emerged as the most consistent predictor of postoperative impairment, and cardiac risk factors such as left ventricular dysfunction were better predictors than chronological age. In the search for potentially preventable risk factors for postoperative renal failure, patients with unrelieved obstructive jaundice deserve

particular mention, as up to 10% will develop postoperative renal failure, and they may require specific prophylactic measures (Parks *et al.*, 1994; Fogarty *et al.*, 1995; Green and Better, 1995).

Assessment and Treatment of Fluid–electrolyte Imbalance (*see* Chapter 117, Water and Electrolyte Balance in Health and Disease)

Because the aging kidney and cardiovascular system often have limited homeostatic ability (Phillips *et al.*, 1993), particular care needs to be taken not to deplete or overload the older patient with fluids during the perioperative period. Preoperative water and/or salt depletion are particularly likely in patients with vomiting, diarrhea, pyrexia, or anorexia. Volume deficits may not be apparent in a patient who is lying quietly in bed and may only be revealed at the time of anesthetic induction, when blunting of the normal regulatory mechanisms may result in profound hypotension in a patient who has a deficiency of water and/or salt.

A careful preoperative assessment of elderly patients looking for evidence of water or salt depletion is, therefore important, although such an assessment is more difficult in the older patient than it is in the younger adult for a number of reasons (Gross *et al.*, 1992). For instance, skin turgor is often reduced in normal elderly people, especially on sun-exposed areas. Longitudinal tongue furrows are probably a better indicator of cell shrinkage (Gross *et al.*, 1992) but are difficult to quantify. A dry tongue may be a sign of water loss, but is more commonly associated with mouth breathing. Absence of sweating in the axillae has also been suggested as a sign of water loss, with a reported sensitivity of 50%, a specificity of 82%, a positive predictive value of 45%, and a negative predictive value of 84% in a group of elderly medical patients (Eaton *et al.*, 1994).

In trying to assess the individual patient, it is important to realize that the clinical and pathological effects of water depletion on the one hand and salt depletion on the other are quite different (Van Zee & Lowry, 1995). Levinsky (1994) has argued that the word "dehydration" should strictly be applied to pure water depletion, but the term is often used more generally to encompass combined deficits of salt and water (Weinberg and Minaker, 1995).

Water depletion tends to have its initial effect on the intracellular rather than the extracellular space. The early physical *signs* of pure water depletion are subtle and include drowsiness, mental confusion, and a low-grade fever (Van Zee and Lowry, 1995). The major *symptom* associated with water depletion is thirst. However, patients with serious surgical or medical illnesses may be too ill or too sedated to experience this otherwise powerful sensation, or there may be preexisting communication difficulties such as dysphasia. In addition, in a proportion of older patients, the thirst mechanism seems to be impaired (Phillips *et al.*, 1993; Weinberg and Minaker, 1995).

As signs and symptoms are an unreliable way of diagnosing water depletion, it is fortunate that a high serum sodium can be used as a diagnostic aid. It has been estimated that 90% of cases of hypernatraemia encountered in elderly hospitalized patients are due to water depletion (Lye, 1984). In patients relying on nasogastric feeding, it is also very important to make sure that adequate amounts of water are given, as standard regimens may contain very little free water (Weinberg and Minaker, 1995).

In a retrospective series of adult hospital patients with serum sodium of over $150\,\text{mmol}\,l^{-1}$, mortality rates were over 54% (Long *et al.*, 1991), probably reflecting the severity of the underlying illness. However, care should be taken not to replace the deficit too quickly, as cerebral edema may result. Van Zee and Lowry (1995) recommend that only half of the calculated water deficit should be administered within the first 24 hours, with the remainder being replaced over the next 1–2 days. Water repletion can be achieved by 5% dextrose infusions intravenously or subcutaneously, or by providing water by mouth or through a nasogastric tube.

In the presence of hypernatraemia, the water deficit can be estimated as follows (Van Zee and Lowry, 1995)

1. Estimate the normal body water. The normal body water (liters) is usually estimated as being 60% of the body weight (kg) (*see* **Chapter 117, Water and Electrolyte Balance in Health and Disease**), but in older patients, a multiplication by 0.55 may be more accurate because of age changes in body composition.
2. Estimate the actual body water, using the formula:
   Actual total body water (l) = normal total body water (l)

$$\times \frac{\text{normal serum sodium(mmol } l^{-1})}{\text{actual serum sodium(mmol } l^{-1})}$$

3. Estimate the water deficit by subtracting (2) from (1).

Salt depletion (sometimes referred to as volume depletion, as salt loss is usually associated with a corresponding loss of water) can occur in the elderly preoperative patient through mechanisms such as vomiting and diarrhea. In addition, many elderly patients are on diuretics, often for dubious reasons. Whereas, water depletion tends to have its main impact intracellularly, salt depletion primarily causes shrinkage of the extracellular compartment. The extracellular compartment includes the intravascular space and so salt depletion tends to lead to hypotension (particularly postural hypotension) and tachycardia.

While salt depletion produces more definite physical signs than does water depletion, these signs may be less obvious in elderly people than in the young (Seymour *et al.*, 1992; Gross *et al.*, 1992). For example, if there is a preexisting degree of systolic hypertension, a subsequent fall in resting systolic blood pressure may go unnoticed. Standing the patient up will help to bring out postural hypotension, but postural hypotension may also be present in a quarter of apparently fit elderly people who are not volume depleted (Weinberg and

Minaker, 1995). The development of tachycardia in response to volume depletion is an autonomic reflex and such reflexes may be blunted in some elderly people and/or the ability of the heart to develop a tachycardia may be impaired in old age.

A bedside estimation of volume depletion which is underused in clinical practice is to look for a *low* jugular venous pressure by lying patients flat or even in a head-down position (Seymour *et al.*, 1992). In doubtful cases, a direct measurement of central venous pressure or even pulmonary artery pressure may be necessary, with or without a fluid challenge, but in the future noninvasive techniques should become available (McIntyre *et al.*, 1992; Vanoverschelde *et al.*, 1995). While a high serum sodium is an indicator of water depletion, the same is unfortunately not true of a low serum sodium as an indicator of salt depletion (Van Zee and Lowry, 1995).

In prescribing fluids in elderly patients over the perioperative period, there is unfortunately no magic formula that will allow an exact assessment of need to be made, and it is not possible to write prescriptions for days on end without further reference to the patient (Scottish Intercollegiate Guidelines Network, 2004). Some broad rules for quantifying the loss may be helpful, however.

1. A water loss of 2 kg or more is probably significant in an older patient (Lye, 1984).
2. In regard to younger adults, a saline loss of 4% of the body weight is "mild", 6–8% is "moderate", and 10% is "severe" (Shires and Canizaro, 1986). Because of their limited homeostatic reserve, elderly patients are likely to be even more at risk from a given percentage of saline loss.
3. In the younger surgical patient, Tweedle (1984) has estimated that 4 l of saline are lost before signs of depletion appear, and 4 l of saline are gained before edema develops. Again, the older patient is probably operating within narrower margins.

Some of the special problems in prescribing fluids in the elderly patient are discussed in Seymour *et al.* (1992). However, the basic approach, in surgical patients of all ages (Scottish Intercollegiate Guidelines Network, 2004; Van Zee and Lowry, 1995), is to assess the likely *preexisting* fluid losses, using a mixture of the clinical and biochemical methods already described, and to prescribe fluids that will both replace *preexisting* losses and keep up with *ongoing* losses as they occur. There is also a need to *adjust for baseline needs*, especially in patients who are taking nothing by mouth.

There are no simple guidelines on the rate of fluid administration. In young patients with a severe volume deficiency (as defined above), Shires and Canizaro 1986) recommend an initial infusion rate of $2\,l\,h^{-1}$, with a halving of this rate as soon as signs of improvement appear. When rates of infusion are above $1\,l\,h^{-1}$, however, they recommend that a physician be in constant attendance. For older patients, they point out that rapid repletion may be needed, but they advocate a more cautious approach, together with close monitoring via a central venous line or a pulmonary artery catheter.

Postoperative fluid, electrolyte and renal management of adults of all ages was an aspect of postoperative care that was considered by a recent SIGN Guideline (Scottish Intercollegiate Guidelines Network, 2004), but it was stated that there were very few relevant randomized controlled trials in the field, and that the recommendations relied heavily on clinical consensus.

NUTRITIONAL ASSESSMENT (*see* Chapter 24, Epidemiology of Nutrition and Aging; Chapter 25, Absorption of Nutrients)

Nutrition and Surgical Outcome

The two key questions in this area are, firstly, the degree to which under-nutrition affects surgical outcome and secondly, whether nutritional therapy is effective in reducing postoperative morbidity and mortality. The clinical assessment of malnutrition presents several problems, as recently discussed by Allison (2000). For example, there is no generally accepted definition of malnutrition to act as the basis for assessment, and even when a patient is severely underweight there is evidence that recent loss of weight is more important than the absolute level of weight achieved. Furthermore, while a low or falling body weight is reasonable evidence that energy intake is deficient (except perhaps in oedematous patients treated with large dose of diuretics), it is a poorer guide to protein deficiency and an even more indirect guide of micronutrient levels. The recent ESPEN (European Society for Parenteral and Enteral Nutrition) Guidelines for Nutrition Screening point out that different screening tools are required in different settings (community, hospital, and elderly) and propose a range of tools for further use in evaluation studies (Kondrup *et al.*, 2003).

A number of biochemical indicators have been identified as *metabolic markers of protein-calorie malnutrition* and may have a role in clinical assessment, but they can also be misleading. For instance, while a low albumin may be a marker of protein malnutrition, hypoalbuminaemia is also a common finding in chronic disease in old age or as an accompaniment of acute sepsis (Milne *et al.*, 2004; Avenell and Handoll, 2004). Patients with a low albumin from acute or chronic disease also tend to have a poorer postoperative outcome but it does not necessarily follow that the poor outcome arises directly from poor nutrition. More importantly, it does not follow that pre- and/or postoperative nutritional supplementation will reduce postoperative complications.

The assessment of malnutrition in elderly patients presents additional problems, and it is often difficult to tell whether a patient is "lean and fit" or "thin and frail". Measurement of Body Mass Index (BMI) classically depends on

knowing the patient's height, which may be difficult to measure in acutely ill bedfast patients and/or which may have been falsely decreased by osteoporosis, leading to an apparent improvement in the BMI. Some more recent nutritional assessments get over this by using an arm span, ulnar length or knee height instead of full height (Kondrup *et al.*, 2003). The presence of edema in patients with congestive cardiac failure may also be falsely reassuring in regard to the BMI. While recent weight loss is thought to be more important than the absolute weight, the former may be difficult to estimate in an older patient whose ability to give a history is reduced by coexistent dementia or acute delirium. In such cases, it may be necessary to consult old records, if they exist. A more general problem in the identification of undernutrition, at least in the United Kingdom, is that nutrition has had less attention in the undergraduate medical course than it deserves. Nutritional specialists have consistently commented on the poor level of nutritional knowledge of medical undergraduates and other health workers (Sizer *et al.*, 1996) and surveys on the nutritional status of hospital patients have consistently shown that malnutrition frequently goes unrecognized. Sometimes, however, these surveys have a paradoxical effect, as those who are not well disposed to nutritional assessment conclude that if the majority of hospital patients have evidence of malnutrition and if most old people get through surgery successfully, then nutrition cannot be very important. This attitude was not helped by some of the older studies, where the prevalence of malnutrition was probably overestimated because nonspecific nutritional markers such as a low albumin were used as a major part of the diagnosis.

It is clear that well-designed RCTs of nutrition supplementation in older surgical patients are needed to guide clinical management. Unfortunately, such studies are not as straightforward as they might seem at first. For example, on practical clinical grounds (not to mention economic grounds) supplementation that is given by mouth is to be preferred over nasogastric feeding if at all possible. However, the latter is much easier to quantify. There is the additional concern that if food supplements are given, habitual food intake will be reduced and so it is ideal to measure the total nutritional intake, even though this is notoriously difficult. Theoretical considerations lead to the conclusion that it might take 10–14 days for nutritional supplementation to have a beneficial effect, yet this would be practicable only in the case of elective surgery and with pressure on hospital beds would be difficult to deliver in a routine inpatient situation.

Despite these difficulties, several RCTs of nutritional therapy have been carried out, and three recent systematic reviews are of relevance to the older patient undergoing surgery. Thus, Milne *et al.* (2004) have looked at trials of protein and energy supplementation in elderly people at risk from malnutrition, Avenell and Handoll (2004) have looked at nutritional supplementation for hip fracture aftercare in the elderly and Howard and Ashley (2003) have reviewed nutrition in perioperative patients of all ages.

The review of Milne *et al.* (2004) was based on 31 trials, but only two of these (by Jensen and Hessov, 1997; MacFie *et al.*, 2000) were carried out on elderly surgical patients. The former study looked at dietary supplementation at home following surgery (N = 34) and the latter examined oral dietary supplements in 100 patients undergoing major elective gastrointestinal surgery. Neither study showed clinical benefit. In the wider review of which these two studies were only a small part, Milne *et al.*, (2004) concluded that protein and energy supplementation in older patients produced a small but consistent weight gain, together with a beneficial effect on mortality and a shorter length of hospital stay. However, the main conclusion was that larger studies were required, together with a specific consideration of the organizational and practical challenges involved in clinical nutritional supplementation. These conclusions would seem to have particular relevance in any future studies of older surgical patients.

The systematic review of Avenell and Handoll (2004) looked at patients with hip fracture, and so predominantly involved older people. However, the acute nature of hip fracture with the associated impracticability of prolonged preoperative nutrition means that the extrapolation to other elderly surgical patients needs to be made with care. 17 RCTs were judged of sufficient quality for inclusion in the review, but even then a number of defects in study design were identified, and the main recommendation was for further studies to be carried out. It was concluded that the strongest evidence for the effectiveness of nutritional supplementation existed for oral protein and energy feeds.

Howard and Ashley (2003) reviewed parenteral and enteral nutritional support in surgical patients of all ages in regard to (a) preoperative support, (b) postoperative nutrition support, and (c) cost of perioperative nutrition. They identified many unresolved issues and recommended:

1. More studies of the feasibility of preoperative enteral nutrition, with or without tube feeding, especially in the outpatient situation.
2. More studies to test whether the ability of postoperative enteral feeding to reduce postoperative complications and shorten length of stay can be further improved by the addition of "immune-enhancing" preparations.
3. The development of clinical methods for measuring bowel ischemia in patients with poor splanchnic perfusion.
4. A further exploration of the finding that preoperative parenteral nutrition appears to reduce noninfectious complications in severely malnourished patients by 10%, but that postoperative parenteral nutrition appears to increase complications by 10%. In particular, the hypothesis that postoperative parenteral nutrition increases infection rates by inducing hyperglycemia needs to be addressed.
5. As many of the studies of perioperative nutrition have involved patients who had some form of malignancy, it is often difficult to untangle the effects of undernutrition from hormonal changes because of direct tumor effect. These two mechanisms need to be examined separately, and there is a case for more nutritional studies in non-cancer surgical patients.

As the published evidence on the assessment and treatment of malnourished surgical patients is still incomplete, there is

still a need to incorporate clinical opinion when assessing nutritional function in an individual elderly surgical patient. Drawing on their considerable experience of nutritional assessment in the surgical situation, (Hill, 1988; Windsor and Hill, 1988; Windsor, 1993) have attempted to combine "clinical common sense" with readily available bedside methods. They suggest classifying patients into three groups:

1. Weight loss (in the last 3 months) less than 10% of body weight.
2. Weight loss of more than 10% of body weight, but with no impairment of function.
3. Weight loss of more than 10% of body weight, *and* with impairment of function.

The emphasis on "impairment of function" arises from the concept that it is the reduction in physical and mental function accompanying malnutrition that leads to adverse postoperative effects. A significant impairment in function is recorded when two or more of the following have coincided with the period of weight loss.

Reduction in activity level

Reduction in skeletal muscle function (such as hand grip strength)

Respiratory impairment (check effort and sound of coughing and dyspnea)

Impaired wound healing (unhealed wounds, sores or scratches, and/or skin sepsis)

Serum albumin less than $32\,g\,l^{-1}$

Impaired psychological status (impaired mood, alertness, and ability to concentrate; increased irritability).

As a statistically significant increase in postoperative pneumonia, septic complications, other major complications and hospital stay were seen only in group 3, Hill and Windsor suggest that nutritional support should be concentrated on this group (Windsor and Hill, 1988; Windsor, 1993).

Allison (2000), in his wide-ranging review of nutritional support in medical and surgical practice, draws attention to research evidence on patients and volunteers which indicates that it is much easier to maintain physical and mental function by early feeding than it is to regain function once it has been lost through significant malnutrition. His broad criteria for nutritional support are: (a) weight loss of more than 10% and continuing; (b) continuing inadequate oral intake; and (c) the presence of disease whose known natural history is associated with likely accelerated weight loss and poor intake for 10 days or more.

Preoperative obesity is another potential nutritional problem in the surgical patient and for a time received much more attention than undernutrition. It was expected that the obese patient would have more problems with postoperative respiratory infections and with complications associated with immobility. In addition, in young and middle-aged adults who are overweight the incidence of heart disease and diabetes tends to be higher, which, it was argued, would lead to a higher risk of postoperative complications. The risks of extreme obesity have been well documented but the disadvantages of moderate levels of obesity (of the order of up to 15% above recommended levels) have been less easy to demonstrate (Seymour *et al.*, 1992).

NEUROLOGICAL AND PSYCHOLOGICAL FUNCTION

Postoperative Stroke

In general surgical patients aged 65 and over, the incidence of postoperative stroke is around 1%, rising to around 3% in the over-80s (Seymour *et al.*, 1992). In the case of open-heart surgery in adults, the incidence of postoperative stroke is much higher than that for general surgery, particularly if minor and transient focal deficits are carefully sought (Mills, 1993; Sotaniemi, 1995). However, two studies of postoperative cardiac patients have concluded that the main risk of postoperative stroke occurs in a small subset of patients with preexisting cerebrovascular or carotid disease (Ricotta *et al.*, 1995; Redmond *et al.*, 1996). Targeting in such patients might have a role to play in the future, but carefully controlled trials will be required.

The risk of postoperative stroke following carotid endarterectomy needs special mention. The aim of the procedure is to reduce the risks of stroke in the medium and long term but, even under the best conditions, there is a small but significant risk of early postoperative stroke. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), have helped to identify the place of endarterectomy in patients with transient ischemic attacks and carotid stenoses of 70% or more, but the role of surgery in patients with asymptomatic stenoses is still disputed (Rothwell *et al.*, 1996a; Rothwell *et al.*, 1996b; Easton and Wilterdink, 1994) (*see* **Chapter 70, Management of Carotid Artery Stenosis**).

Postoperative Delirium

Postoperative delirium is a common occurrence after surgery, particularly in extreme old age and/or in patients who have underlying dementia. The exact incidence depends on the definition used and the type of postoperative assessment employed. However, 10–15% of older people having general surgery will have some evidence of postoperative delirium if it is looked for prospectively (Seymour and Vaz, 1989) and detailed psychological testing suggests that the true incidence may be over twice that level (Dyer *et al.*, 1995). The causes of postoperative delirium include the causes of delirium in nonoperative patients (Schor *et al.*, 1992). Thus infection, other acute physical illnesses, and reactions to drugs are all important. Hypoxemia is a potential cause of delirium in medical patients as well as in surgical patients, although in the latter there is the added problem of late postoperative episodic hypoxemia, as was mentioned above. Delirium due to withdrawal from drugs such as alcohol, tranquilizers or opiates is also seen in both medical and

surgical situations. However, withdrawal delirium tends to cause more diagnostic confusion in the latter situation, as a history of preoperative alcohol abuse or regular tranquilizer use may not have been elicited and so the occurrence of delirium in the first or second postoperative day may be falsely attributed to postoperative causes. Prospective studies of risk factors are difficult to carry out and so the large-scale investigation by Marcantonio and colleagues is particularly welcome (Marcantonio *et al.*, 1994). Independent correlates of postoperative delirium in this study included: age 70 or over; self-reported alcohol abuse; poor cognitive status; poor functional status; markedly abnormal preoperative sodium, potassium or glucose; noncardiac thoracic surgery; and aortic aneurysm surgery. In a large randomized controlled study of patients undergoing elective total knee replacement, Williams Russo *et al.* (1995) found no statistical difference between the incidence of postoperative delirium in patients following general anesthesia (12/128 or 9.4%) and that following epidural anesthesia (16/134 or 12%).

A useful general concept introduced by Inouye, and applicable to both medical and surgical patients, is that there should be an attempt to identify separate "predisposing" and "precipitating" factors for delirium (Inouye and Charpentier, 1996; Inouye, 1999). These two factors interact: for example, patients with a large number of predisposing factors require only a small precipitant to tip them into a delirious state. While there have been advances in multivariate risk scores to predict the risk of delirium both in surgical and medical situations (Marcantonio *et al.*, 1994; Inouye *et al.*, 1993), perhaps the biggest practical development has been the concept of adopting a series of preventative measures in *all* patients undergoing medical and surgical treatment to minimize the risk of delirium developing. These appear to be able to reduce delirium in the short-term in medical (Inouye *et al.*, 1999; Rizzo *et al.*, 2001) and surgical patients (Marcantonio *et al.*, 2001), although long-term benefits still need to be proven (Bogardus *et al.*, 2003).

As in acute delirium in nonsurgical situations, the postoperative patient who is delirious needs an urgent physical diagnosis (Scottish Intercollegiate Guidelines Network, 2004) as the delirium is usually due to treatable but potentially serious medical problems.

Postoperative Dementia

Can dementia appear for the first time purely as the result of a general anesthetic? In an often-quoted 5-year retrospective study, Bedford (1955) found 18 people in the Oxfordshire area in whom there was reasonable evidence that dementia had occurred for the first time after an apparently uneventful anesthetic, but in a subsequent prospective study of 678 elderly surgical patients (Simpson *et al.*, 1961) only one such patient was found. These two reports stimulated many more studies of long-term cognitive function after surgery. Some of these studies have randomized elective orthopedic patients to regional and general anesthetic treatment and have compared values on psychometric tests 3–6 months after surgery with preoperative values. Williams Russo *et al.* (1995) confirmed the results of previous studies in finding no long-term difference in mental functioning between elderly patients undergoing elective orthopedic surgery under regional anesthesia and those undergoing a general anesthetic. However, while there was no difference between the two types of anesthetic group, the cognitive function of 12 out of the 231 (7/114 epidural and 5/117 general anesthesia) patients examined at 6 months was worse than it had been preoperatively. The authors point out that this decline might have occurred in a similar elderly group of patients not having surgery, but long-term follow-ups of nonoperative patients using the same cognitive assessment protocol were not carried out as part of that study.

The study by Jones *et al.* (1990) also failed to find any objective differences in cognitive and functional competence between general and regional anesthetic groups 3 months after elective knee or hip replacement. However, 11 out of 64 general anesthesia patients and 10 out of 65 regional anesthesia patients considered that their memory and concentration were worse than they were preoperatively. Jones *et al.* commented that these subjective changes might have been too subtle to pickup on formal testing, or might represent mild depression or the state of postoperative fatigue that has also been reported in younger patients. Their overall conclusion, however, was that "modern anesthesia, either general or regional, seemed to have no significant long-term effects on mental function in elderly patients".

A potential criticism of all the earlier studies was that pre- and postoperative cognitive state was not measured in a standardized way. Because of this, the ISPOCD (International Study of Post Operative Cognitive Dysfunction) investigators set out to perform a definitive study of cognitive impairment after general surgery in older patients. They used a standardized battery of cognitive tests before and after elective surgery and looked at changes 1 week and 3 months after the surgery took place. In addition, a range of predictive factors including hypoxemia was investigated in the anticipation that these would be correlated with postoperative cognitive change. The main ISPOCD1 study was published in 1998 (Moller *et al.*, 1998) but unfortunately did not provide the reassurance for older people that had been anticipated. Perioperative hypoxemia and hypotension appear to have no relationship to postoperative cognitive dysfunction, but nevertheless, in around 16% of patients, careful psychological testing revealed cognitive deficits at 3 months which had not been present prior to elective surgery. Statistically, the only risk factor which was correlated with an adverse cognitive outcome, despite a series of multivariable analyses, was age.

The ISPOCD investigators have therefore embarked on a series of investigations under the broad heading of ISPOCD2 to examine further hypotheses about the causes of postoperative cognitive impairment. In addition, a sample of the original ISPOCD1 patients has now been followed for two years postoperatively (Abildstrom *et al.*, 2000). The cognitive performance of these ISPOCD1 patients at two years was compared with that of patients of similar age who had not undergone surgery and it appeared that the prevalence of cognitive dysfunction was similar in both populations. In other

words, the events around surgery and anesthesia appeared to have led to a degree of cognitive loss which lasted at least 3 months (i.e. was more prolonged than simple postoperative delirium), but by 2 years the nonoperated population had "caught up".

PROPHYLAXIS AGAINST THROMBOEMBOLISM

The concept underlying the commonest form of prophylaxis against thromboembolism is that doses of heparin that would be insufficient to *treat* thromboembolism are often sufficient to *prevent* venous thrombosis, provided that they are given prior to surgery. The decision whether to give prophylaxis or not, and whether to use heparin and/or another approach such as graded pressure stockings, depends on patient factors (e.g. age, malignancy, obesity, immobility, and many other factors increase the risk of thromboembolism) and the nature of the surgical procedure (e.g. prolonged operations involving the hip or pelvis provide a greater thrombotic stimulus than shorter operations involving the periphery)(Seymour *et al.*, 1992). There is also need to balance the risks of bleeding against the risks of thromboembolism, and some of the newer forms of heparin may be used in selected conditions such as total hip replacement. Published guidelines of preoperative protocols for prophylaxis against thromboembolism are widely available (see, for example, SIGN Guideline 62, 2002), but in practice it is best to harmonize procedures with local guidelines.

PROPHYLAXIS AGAINST SEPSIS

Using antibiotics for prophylaxis against postoperative sepsis should not be confused with the use of full therapeutic courses of antibiotics once sepsis has occurred. In the former situation, the aim is to achieve high blood levels of an antibiotic at the time of the initial surgical incision and during the surgical procedure. Typically, this is achieved by giving an intravenous cephalosporin 30 minutes before surgery, followed by up to two further doses if the operative procedure is prolonged. While general reviews can set the scene (Scottish Intercollegiate Guidelines Network, 2000), local guidelines need to be followed, particularly as the sensitivity of bacteria to antibiotics varies from area to area. Guidelines also deal with the selection of patients for prophylaxis against sepsis. For instance, surgery on the gut has a much higher rate of postoperative sepsis than does a more peripheral procedure. However, risks and benefits also need to be balanced. For example, in elective joint surgery the risk of infection is low, but the consequences of infection are very serious and so there is a lower threshold for giving prophylactic antibiotics. Different preventive strategies need to be adopted when a patient has a preexisting heart valve lesion. Here, a surgical operation, a surgical procedure such as cystoscopy, or even a diagnostic procedure such as a barium enema, has the potential to provide a bacteremia that may lead to subsequent endocarditis.

CONCLUDING REMARKS

This chapter has been able to give only a brief introduction to the care of the elderly surgical patient, a subject on which whole textbooks are now being written. It is hoped that the conceptual framework of the chapter will allow the reader to pursue individual aspects of the subject in more detail, by reading some of the references, but more importantly by carrying out specific literature searches in response to the problems of individual elderly surgical patients. The optimal care of an elderly surgical patient requires an interdisciplinary approach from surgeons, anesthetists, physicians, nurses, and professions allied to medicine and many others and, for this reason, interdisciplinary organizations are now starting to emerge. These include the Age Anaesthesia Association founded several years ago by members of the Association of Anaesthetists of Great Britain and Ireland, but which also includes members from within surgical and medical specialties.

KEY POINTS

- The absolute and relative rates of surgery in old age are increasing year by year, but referral rates for elective surgery in very elderly patients may still be suboptimal.
- The major part of the statistical association between age and adverse postoperative outcome arises not as a result of aging itself, but through a secondary association with age-association disease.
- There is a growing body of evidence relating to the assessment, monitoring, and treatment of preoperative comorbidity and postoperative complications, but further targeted research work is needed in these areas.
- The American College of Cardiology/American Heart Association guidelines on perioperative evaluation for noncardiac surgery are of relevance in the cardiovascular assessment of older patients.
- In caring for older surgical patients in hospital, in addition to careful preoperative assessment, there is need for close scrutiny in the early postoperative period, particularly at the time when the older patient is transferred back to the general ward.

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Anesthesia in Older People

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INTRODUCTION

Elderly surgical patients present a specific challenge to anesthesiologists and may be at greater risk of an adverse outcome (Kazmers *et al.*, 1998). This is accounted for by a reduced ability to maintain or restore physiological homeostasis in the face of surgical and medical disease (Miller, 1998). This is exacerbated further by the presence of medical comorbidity such as cardiac or pulmonary disease or diabetes mellitus (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery, 1996). The statistical likelihood of having a coincident medical pathology increases with advancing years. The elderly have a higher rate of mortality associated with anesthesia and surgery than their younger counterparts. Postoperative adverse events on the cardiac, pulmonary, renal, and cerebral systems are the main concerns for older surgical patients at high risk. The very fact that the patient requires hospital admission for their surgery exposes them to risk, with familiar hazards including nosocomial infection, administration of the wrong drug, and side effects of certain procedures and investigations. Elderly patients are more likely to experience an adverse event during their hospital stay.

The elderly, and in particular those older than 85 years, are the fastest growing segment of the European and North American populations (Hall, 1997). Accordingly, overall life expectancy and active life expectancy have increased (General Office for Statistics, 1995). The number of older patients presenting for surgery and anesthesia is increasing and should not be a bar to surgery (Crosby *et al.*, 1992). The complexity of surgical procedures is also expanding. In 2001, The Association of Anaesthetists of Great Britain and Ireland called for this expansion to be recognized and incorporated into service provision. They also called for greater availability of 24-hour recovery facilities, High Dependency Unit (HDU), and Intensive Therapy Unit (ITU) bed for these patients. The National Confidential Enquiry into Perioperative Deaths (NCEPOD, 1999) has highlighted the importance of availability of high dependency and intensive care facilities for the safe care of older patients: "the decision to operate includes the commitment to provide appropriate supportive care".

This chapter elaborates on some of the risks to the elderly patient during the perioperative period and how they may be managed in order to minimize postoperative morbidity and mortality in this vulnerable patient group.

THE OUTCOME OF SURGERY AND ANESTHESIA IN THE ELDERLY

Mortality after surgery and anesthesia is defined as the death rate within 30 days (NCEPOD, 1999). The outcome of older patients from surgery, in general terms, has been studied by several authors in the past two decades (Chelluri *et al.*, 1992; Hosking *et al.*, 1989; Djokovic and Hedley-Whyte, 1979), suggesting that health-care practitioners have anecdotally identified areas for potential clinical improvement for many years. However, there are no recent surgical outcome studies for older patients. These early studies suggest that older patients have acceptable rates of perioperative mortality. There have been many advances in surgery and anesthesia, such as laparoscopic surgery, ultrashort-acting anesthetic medications, and regional pain management over the past two decades, reducing mortality rates (Table 1, Figure 1). Higher mortality rates are associated with higher American Association of Anesthesiologists (ASA) grade of physical status grade and emergency procedures (ASA, 1963). ASA is an independent predictor of mortality (Table 2). The highest risk surgical procedure in older patients is an exploratory laparotomy, because of the high risk of bowel infarction and disseminated carcinomatosis. The presence of preoperative renal, liver, and central nervous system impairment were predictors of poorer outcome.

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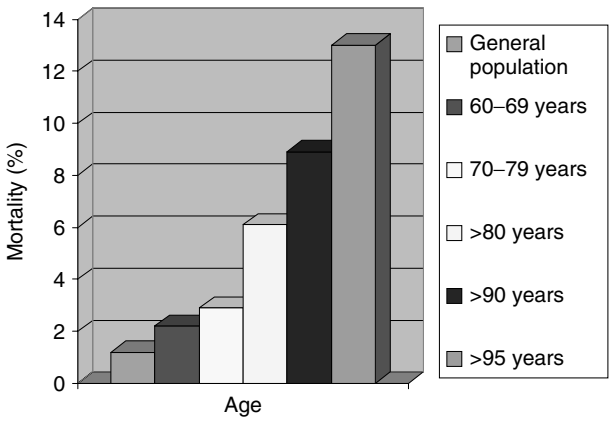

Figure 1 Mortality associated with surgery and anesthesia

Table 1 Mortality associated with surgery and anesthesia

Age (years)	Mortality rate
General population	1.2% (Pedersen *et al.*, 1990)
60–69	2.2% (Pedersen *et al.*, 1990)
70–79	2.9% (Pedersen *et al.*, 1990)
>80	5.8–6.2% (Djokovic and Hedley-Whyte, 1979)
>90	8.4% (Hosking *et al.*, 1989)
>95	13% (Djokovic and Hedley-Whyte, 1979)

Table 2 ASA grading of physical status (American Society of Anesthesiologists 1963)

Grade	
I	Normal healthy patient
II	Patient with mild systemic disease
III	Patient with severe systemic disease
IV	Patient with severe systemic disease which presents a constant threat to life
V	Moribund patient not expected to survive without operation

Source: Reproduced by permission of American Society of Anesthesiologists, Inc.

CARDIOVASCULAR MORBIDITY ASSOCIATED WITH SURGERY AND ANESTHESIA

The age-related changes that occur within the cardiovascular system are responsible for the higher incidence of perioperative myocardial infarction, cardiac failure, and arrhythmias in this age-group. There is a reduction in the sensitivity of the parasympathetic system to changes in baroreceptor stretch, blood pressure, and heart rate. The sensitivity of the sympathetic system also declines. This diminishes the body's ability to compensate for sudden change. There is a progressive stiffening of both the arterial and venous vessels, again reducing capacity for vasoconstriction or dilatation in the face of loss of intravascular volume. Stiffening of the myocardium occurs also, affecting diastolic relaxation and filling pressures. This may lead onto diastolic dysfunction with an increase in left atrial pressure and pulmonary congestion. Superimposed on physiological change, anesthetic agents cause peripheral vasodilatation, with a decrease in systemic vascular resistance. As many elderly patients have a contracted intravascular volume secondary to diuretic therapy, this can mean a sudden fall in tissue perfusion pressure. Anesthetic agents are myocardial depressants, particularly in higher doses, and have the capacity to adversely affect cardiac output.

Preoperative assessment is focused on identifying those risk factors that have been identified in studies as being predictive of adverse postoperative outcome (Table 3) (Goldman *et al.*, 1977; Eagle *et al.*, 1996). Following the initial interview, the patient's baseline level of function is assessed. If there are no significant predictors in the history, evaluation may be safely confined to detailed physical examination and a 12-lead electrocardiogram (ECG). ECG will identify patients with left ventricular hypertrophy or ST segment depression. These patients may require further investigation with an exercise ECG, depending on the surgical procedure planned. Patients who cannot exercise because of claudication or arthritis may be assessed with a dobutamine stress echocardiograph. Coronary angiography is reserved for patients with angina at rest or unstable angina. On the basis of the results, preoperative revascularization may be warranted. Clinically detected cardiac murmurs and features of congestive cardiac failure are further evaluated using echocardiography. Preoperative valve replacement is indicated for patients with severe disease. Less severe valve lesions or those following valve surgery require prophylactic antibiotic administration.

Arrhythmia detected at rest or during exercise should be treated if possible before surgery. If sinus rhythm is not achieved, rate control with anticoagulation is acceptable. Type II or type III heart block requires insertion of a temporary or permanent pacemaker.

Using the information gained from the history, examination, and further investigations, the anesthetic management is aimed at maximizing myocardial perfusion through maintenance of tissue perfusion pressure and oxygenation throughout the intraoperative and postoperative period. Postoperative admission to the HDU or intensive care unit should be anticipated for elderly patients with significant cardiac symptoms, especially those undergoing abdominal or thoracic procedures. Invasive monitoring of blood pressure and central venous pressure is commenced early and continued throughout the perioperative period. Regional anesthesia provides superior analgesia postoperatively and may reduce the

Table 3 Predictive factors for postoperative cardiovascular morbidity

Myocardial infarction within previous 3 months
Decompensated congestive cardiac failure
Arrhythmia (except premature atrial contractions)
Unstable angina or angina at rest (New York Heart Association Grade IV)
Uncontrolled hypertension
Severe valvular disease
Poor general medical condition
Poor exercise capacity
Diabetes mellitus
History of stroke

incidence of adverse cardiac events in certain patients, such as vascular and abdominal surgery. The institution of perioperative β-receptor blockade has been shown to reduce the risk of myocardial ischemia and is generally well tolerated by older patients (Poldermans *et al.*, 1999). β-blockade is thought to increase the time spent in diastole, increasing filling, and increasing time for coronary artery perfusion.

A combination of intravenous fluid infusion and vasopressor agents are used to maintain mean arterial blood pressure within 20% of the patient's baseline, awake blood pressure. Episodes of hypotension must be managed promptly and oxygenation increased during the period of reduced flow.

Postoperatively, the patient requires a similar level of care and monitoring. Supplemental oxygen therapy, optimum analgesia, rate control, and judicious blood transfusion will assist in maximizing myocardial oxygen supply.

Particular attention should focus on the first 3 days, when myocardial infarction is most likely to occur. Many episodes of ischemia in this age-group may be silent and may not be associated with the development of Q waves on the ECG. A low index of suspicion, the presence of new ST changes, in combination with serial estimations of serum troponin T and I concentrations will assist in early diagnosis.

RESPIRATORY MORBIDITY ASSOCIATED WITH SURGERY AND ANESTHESIA

The physiological changes associated with aging predispose the older patient to respiratory complications after surgery and anesthesia. A mixed obstructive/restrictive pattern develops from the decrease in total lung capacity, elastic recoil of the thorax, pulmonary parenchymal compliance, and vital capacity. Decreased compliance and muscle power mean a fall in forced expiration and reduced capacity to cough and clear secretions. Closing capacity, dead space, and residual volume increase so that the lungs of the supine patient become atelectatic. These changes do not occur in a uniform manner throughout the lungs, resulting in areas of good ventilation in combination with underventilated segments. A decrease in pulmonary blood flow combined with progressive loss of alveolar surface area diminishes the resting arterial oxygen tension from 95 ± 2 mmHg at age 20 to 73 ± 5 mmHg at 75 years. Occurring in tandem, there is an age-associated loss of central nervous system sensitivity to changes in arterial oxygen and carbon dioxide tensions. The physiological and structural changes cause an increase in ventilation/perfusion mismatch. This is exacerbated by the effect of anesthesia, in particular, general anesthesia. In addition, general anesthesia reduces reflex pulmonary hypoxic vasoconstriction. Regional anesthesia impacts less on the respiratory system as it does not necessitate intubation of the trachea, avoids the effect of intermittent positive pressure ventilation, and provides highly effective postoperative pain relief.

Preoperative preparation of the patient involves a detailed history and examination in combination with functional assessment. Taking the patient for a walk, including two flights of stairs, during the preoperative visit provides a useful measure of the patient's baseline physiological status. Smoking cessation for at least 8 weeks is to be recommended (Smetana, 1999). Chest physiotherapy in the 24 hours preceding surgery provides some physical benefit and facilitates instruction for deep breathing and coughing postoperatively. Patients with active pulmonary infection require more postponement of surgery and more aggressive medical treatment.

The anesthetic technique should employ regional analgesia/anesthesia where possible. Short-agents such as propofol, remifentanil, sevoflurane, and atracurium are most suitable for general anesthesia. Muscle relaxants should always be reversed at the end of the procedure. Invasive monitoring may be used to advantage to guide fluid therapy as the older patient will tolerate rapid expansion of intravascular and extravascular volumes poorly due to the changes in pulmonary compliance, perfusion, and renal function. This may be continued into the postoperative period in the context of intensive care or HDU admission. Postoperatively, oxygen supplementation and chest physiotherapy should be continued for a minimum of 5 days as this is the greatest period of risk of nocturnal hypoxia and the onset of pneumonia.

CENTRAL NERVOUS SYSTEM MORBIDITY ASSOCIATED WITH SURGERY AND ANESTHESIA

Elderly patients are at risk of serious central nervous system morbidity and mortality due to neuronal loss associated with aging, the presence of coincident pathology such as cerebrovascular atherosclerosis, and a reduction in neurotransmitter concentrations. This makes them less able to adapt successfully to the challenges imposed by surgery and anesthesia. The morbidity associated with anesthesia and surgery in the older patient most commonly takes the form of postoperative confusion (POC) or stroke.

Postoperative Confusion

The risk factors for the development of POC are listed in Table 4. POC is associated with an increased rate of morbidity, delayed return to baseline function, and delayed discharge home from hospital. To date, there is little evidence for an overall strategy to reduce the incidence in surgical patients, but some general recommendations may be made. Consideration should be given to admitting the patient as a daycase, as elderly patients become less disorientated when in familiar surroundings with familiar carers. The preoperative assessment should highlight particular issues that could be modified or preempted, such as alcohol withdrawal depression. Hearing aids and spectacles should be left with the patient until induction of anesthesia and returned to the patient a soon as possible. Medications listed

Table 4 Risk factors for the development of postoperative confusion

Preoperative factors
Older age
Depression/Anxiety
Dementia
Preoperative sensory deficit in hearing or vision
Alcohol withdrawal/Sedative withdrawal
Preoperative use of multiple medications
Intraoperative factors
Hypoxia
Hypocarbia
Hypotension
Postoperative factors
Inadequate analgesia
Perioperative factors
Sepsis
Surgical procedure
Cardiac surgery
Orthopedic surgery especially joint replacement
Perioperative medications
Anticholinergics: Atropine, scopolamine. Glycopyrrolate to a lesser extent
Barbiturates
Benzodiazepines
Antihistamines

in Table 3 should be avoided. Intraoperative monitoring of blood pressure, ventilation, and oxygenation requires a meticulous approach. Regional analgesic techniques should be employed where possible to reduce the use of sedating narcotics in the postoperative period. There is no difference in the incidence of POC between the intraoperative use of general anesthesia and spinal or epidural anesthesia (Chung *et al.*, 1997). Postoperatively, if the patient is confused, they should be nursed in a quiet, dark room. Organic causes should be treated promptly. Haloperidol 0.25–2 mg orally at night may be useful. Low doses of diazepam or chlorpromazine may be used as adjuncts if the patient does not respond to simple measures. Physical restraints usually serve to antagonize the patient further and should not be used. Referral to the occupational therapy and social work departments will be necessary to assist with cognitive assessment, follow-up, and discharge planning.

Long-term cognitive impairment has been documented by the International Study of Postoperative Cognitive Dysfunction (ISPOCD) (Moller *et al.*, 1998). Ten per cent of patients were found to have cognitive deficits 3 months after surgery, with age as the only significant predictive factor.

Postoperative Stroke

There have been few studies to determine the incidence of stroke occurring after surgery and anesthesia. The incidence from small retrospective studies would seem to suggest that the incidence is low–; in the order of 0.25% when a patient is undergoing noncarotid vascular surgery (Larsen *et al.*, 1988; Sultana *et al.*, 1997). Stroke most commonly occurs between the 5th and 26th day postoperatively. Risk factors for postoperative stroke are in Table 5 (Jin and Chung, 2001).

Table 5 Risk factors for postoperative stroke in the elderly

Preoperative factors:	Preexisting cerebrovascular disease
	Ischemic cardiac disease
	Atherosclerosis
	Carotid occlusion
	Preoperative vascular disease
	Hypertension
	Diabetes mellitus
	Physical inactivity
Intraoperative and postoperative factors:	Hemodynamic instability
	Hypoxemia

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Patients with poorly controlled preoperative hypertension should have their surgery postponed to allow time to institute adequate pharmacological control. Patients with clinically detected carotid bruits should have further investigations and, if necessary, referral to a vascular surgeon before their intended procedure. The severity of the neurological deficit and the potential for rehabilitation after perioperative stroke varies enormously, and therapy must be directed at the individual patient.

RENAL MORBIDITY ASSOCIATED WITH SURGERY AND ANESTHESIA

Renal function is known to deteriorate with age, and, therefore, greater care will be needed to maintain renal function perioperatively. Decline in numbers of the functional unit, the glomerulus with age, means that glomerular filtration rate falls from 125 ml minute^{-1} in the young adult to 80 ml minute^{-1} in the older individual. As this fall in glomerular filtration rate (GFR) is usually accompanied by a decrease in muscle mass, there is rarely an increase in serum creatinine. During the perioperative period, the kidney will be exposed to many challenges: rapid fluid shifts in the intravascular and extravascular compartments, numerous medications administered simultaneously, electrolyte changes, and acid–base abnormalities (Epstein, 1996). In the face of these challenges, the underlying loss of function becomes exposed, leading to the development of postoperative renal failure. Atherosclerosis of the vascular supply of the kidney and coincident disease due to diabetes mellitus or hypertension further complicates the situation. In addition, the elderly patient tends to be taking a greater number of prescribed medications that have the potential to interact with anesthetic agents and conditions arising during surgery, such as hypotension.

Anesthetic drugs have little direct effect on renal function. Anesthetic agents reduce cardiac output with subsequent renal vasoconstriction, which may cause a fall in renal perfusion. Enflurane and isoflurane produce fluoride when metabolized, which may cause renal injury if the anesthesia is very prolonged. Sevoflurane produces a substance known as *compound A* at low fresh gas flows, which is nephrotoxic

if not removed by effective scavenging of waste anesthetic gases (Conzen *et al.*, 2002). It is unusual for either of these chemical entities to present a problem in the clinical context.

Management of the patient starts with a high index of suspicion. Following a detailed preoperative review, fluid and electrolyte status should be closely monitored in the pre-, intra- and postoperative periods. Nephrotoxic medications should be stopped preoperatively if possible. Medications that deplete the intravascular volume and lead to electrolyte loss should be reviewed in the context of the patient's state of hydration and the planned surgical procedure. For example, a patient taking a loop diuretic scheduled for elective inguinal hernia repair should probably continue taking the medication, while a patient with low urinary output scheduled for emergency laparotomy for bowel obstruction should have the loop diuretic reviewed by the anesthesiologist. The dosing intervals of medications excreted by the kidney such as aminoglycosides may need to change and doses titrated to plasma levels. The development of perioperative renal failure increases the requirement for renal replacement, intensive care admission, and mortality. Acute tubular necrosis accounts for the majority of cases of renal failure. Prevention is based on optimizing the circulation preoperatively, close hemodynamic monitoring perioperatively, and maintenance of adequate perfusion pressures, including the judicious use of inotropes. Intraoperative low-dose dopamine infusion promoting renal vasodilatation and the use of mannitol as a free radical scavenger have been advocated (Kellum and Decker, 2001; Lameire *et al.*, 2003).

PERIOPERATIVE HYPOTHERMIA

Elderly patients are at a greater risk of developing perioperative hypothermia than younger patients owing to a number of factors. They have a reduced muscle mass, with a lower basal metabolic rate. This is often accompanied by reduced fat stores secondary to malnutrition. The shivering mechanism occurs later in response to cooling. In young patients, shivering begins peripherally at 1 °C less the normal core temperature of 36.5 °C. As patients age, this may not occur until their core temperature has fallen by 2 °C. Shivering increases cellular oxygen demands by 20–30%, increasing myocardial oxygen consumption, which may be deleterious for the older patient with cardiovascular pathology. Less vasoconstriction occurs in the older patient for a given fall in temperature, meaning that more heat is lost to the environment.

Surgery and anesthesia have a detrimental effect on thermoregulation. Anesthetic agents cause peripheral vasodilatation with abolition of the shivering mechanism so that patients lose the ability to compensate for cooling. The opening of major cavities such as the abdomen and thorax increases the amount of heat lost to the environment. The effect of perioperative hypothermia are listed in Table 6.

Prevention of hypothermia is more efficient and cost effective than warming the patient postoperatively. Patients should be kept in a warm room with blankets during their admission to the operating department. Induction of anesthesia should take place in a similar environment. Anesthetic gases should be warmed and humidified. Intravenous fluids should be warmed. Sterile preparation of the operative site should take place using warmed sterile solutions. A warm ambient temperature of the operating room should be maintained until the patient is draped. Forced air warming blankets may be placed under the drapes. At the end of the procedure, warm blankets should be placed over the patient during their transfer to the postanesthetic care unit.

Table 6 The effect of perioperative hypothermia

- Increased cardiac morbidity
- Increased incidence of cardiac arrhythmias
- Altered platelet function
- Increased blood loss
- Increased blood viscosity – combined with vasoconstriction may cause higher incidence of deep venous thrombosis
- Shift of oxygen dissociation curve to left with less oxygen released by hemoglobin to the tissues
- Inhalation of cold gases causes reduction in protective reflexes in respiratory tract through effects on cilia motility
- Increased incidence of postoperative wound infection
- Increased incidence of postoperative decubitus ulcers
- Decreased drug metabolism, resulting in longer recovery times
- Prolonged hospitalization

PREOPERATIVE ASSESSMENT

When carrying out a preoperative assessment of the older patient, it is important to place the function of the cardiovascular and respiratory systems into the context of the whole patient. It must be remembered that patients may have mild cognitive impairment affecting their memory, or they may be embarrassed and unwilling to admit disability. Answers may be slow as information is recalled. The history may be extensive and complicated and so sufficient time should be allotted to the interview. The clinical presentation of disease may differ greatly from that in younger patients. Conditions such as hyper and hypothyroidism are notoriously difficult to diagnose in the older patient. It is best if the assessment takes place several days before the planned surgery to allow enough time for further investigations if necessary. Attendance at a preanesthetic outpatient clinic will mean the patient can meet all of the multidisciplinary team members together, providing enhanced perioperative and discharge planning.

Following the interview, the anesthesiologist must review the patient's medical chart and carry out a comprehensive physical examination. Keeping in mind the demands and implications of each surgical procedure, the anesthetic plan will then be made and discussed with the patient. The anesthesiologist should expect much variation between each elderly patient. Routine investigations based on age alone are not warranted and should be directed by the clinical evaluation (Fleisher, 2001).

Particular issues to be addressed over the course of the assessment are:

1. The planned surgery. The surgical procedures most frequently carried out in the elderly are listed in Table 7.
2. The cognitive status of the patient. Does the patient answer questions in a coherent manner? Will they be suitable for ambulatory admission or a regional anesthetic technique?
3. The baseline function of the patient. Can they dress themselves; do the shopping, walk up a short flight of stairs?
4. Does the patient have symptoms suggestive of cardiac disease? Remember, patients may not report symptoms because of reduced mobility.
5. Does the patient have signs or symptoms of respiratory disease? Shortness of breath at rest is an important prognostic sign.
6. What are the patient's current medications and their compliance with them?
7. Previous anesthetic experiences.
8. Vital signs on examination especially blood pressure, pulse rate, and rhythm.

Meticulous attention to detail when planning the perioperative care of the patient can reduce the incidence of minor morbidity. Reduction of minor incidents may prevent escalation into life-threatening events.

Table 7 Pharmacological analgesic options

Agent	Advantages	Side effects
Acetaminophen (Paracetamol)	Oral and rectal route Opioid sparing	Hepatotoxicity, do not exceed 4 g/24 hours
NSAID	Oral, rectal, and parenteral route Opioid sparing	Gastric irritation Renal toxicity Antiplatelet effects
COX-II Inhibitors	Oral and parenteral route Opioid sparing Less severe gastric irritation and renal toxicity than NSAIDs	Gastric irritation Renal toxicity
Opioids	Oral, rectal, parenteral, spinal, epidural route Profound analgesia available as short-acting and long-acting preparations	Sedation/Confusion/ Dysphoria Respiratory depression Metabolites may be toxic, for example, normeperidine Nausea/Vomiting Ileus Pruritus Urinary retention when administered into CSF/epidural space Bradycardia Hypotension especially if patient is dehydrated

NSAID, Non-steroidal Anti-Inflammatory; COX-II, Cyclo-oxygenase-II.

PAIN ASSESSMENT AND MANAGEMENT IN THE ELDERLY

Pain Assessment

Effective pain management in the elderly is subject to all of the usual barriers to pain management, such as fear of addiction. With the older surgical patient, there are additional problems to be overcome.

The assessment of pain forms the basis of successful pain relief. It is necessary to obtain a baseline measure of pain before instituting pharmacological measures to reduce that pain. Assessment allows the treatment to be evaluated and the need for further pain relief established (Katz and Melzack, 1999).

The needs of the older patient in assessing pain have not yet been fully met (Cook *et al.*, 1999). Conventional pain scores such as the visual analogue score (VAS) have limited application in this age-group due to the prevalence of mild/moderate cognitive impairment, hearing difficulties, and poor eyesight. The older patient may differ significantly in their cultural interpretation of pain and pain relief (Severn and Dodds, 1997).

Reporting of pain may be altered in this age-group because of the misperception among older patients that it is necessary for pain to follow surgery and that staff are doing all that they can to relieve it. They may also fear reporting that they have pain in case this means something has gone wrong, or that they may be seen as being "difficult". Health-care staff may mistake patients who do not report pain for patients who do not *have* pain. Attempts have been made to validate other scores such as the Faces Pain Score in older adults, but at present, there is no single system suitable for all elderly patients (Wong and Baker, 1988; Herr *et al.*, 1998). The accuracy of pain assessments may be increased by making the assessment more frequently, particularly following the administration of each analgesic dose.

Another hurdle to achieving adequate pain relief is the assumption that elderly patients do not experience pain to the same extent as younger patients. There is very little evidence for this misperception (Oberle *et al.*, 1990).

The Effect of Pain in Older Surgical Patients

The consequences of pain in surgical patients include (Ballantyne *et al.*, 1998; Rodgers *et al.*, 2000):

- sympathetic hyperactivity, producing tachycardia, myocardial ischemia, hypertension via the adrenal hormonal axis;
- decreased pulmonary function with atelectasis and hypoxemia, as a result of poor cough and reduced mobility;
- increased risk of deep venous thrombosis (DVT), as a result of reduced mobility;
- potential development of a chronic pain state through sensitization of pain pathways;

- postoperative delirium. This is particularly the case in patients who have predisposing risk factors for delirium such as visual, hearing, or cognitive deficit;
- increased length of stay.

Adequate pain relief in all patients may reduce postoperative morbidity (Ballantyne *et al.*, 1998).

The preoperative assessment visit should be used as an opportunity to discuss with the patient the postoperative analgesia pertinent for their procedure, particularly when regional analgesic techniques are planned. Education and reassurance may be provided to the patient and their family, diminishing their concerns regarding addiction and side effects. Instruction may be given on the use of equipment for patient controlled analgesia (PCA), which may be reinforced later by a visit from the acute pain team.

Pharmacological Management of Pain

A continuous, multimodal approach to postoperative pain management is indicated for elderly patients because it minimizes potential adverse effects from high doses of any single agent. Changes in drug absorption, distribution, metabolism, and elimination may affect the eventual plasma level and effect of a given analgesic drug. Increased gastric pH and decreased gastric motility reduce or delay drug absorption. The volume of distribution of drugs changes because of an increase in total body fat and a decrease in body water. Water-soluble opiates such as morphine have a smaller volume of distribution and therefore can produce higher plasma levels. Lipid-soluble drugs, such as fentanyl, have a larger volume of distribution and can produce a prolonged duration of action in older patients (Dodds, 1995). Reduced serum albumin concentrations and other plasma proteins from chronic illness or poor nutrition will reduce drug distribution, increasing the potential for adverse affects. Concurrent medical conditions, for example, renal impairment, may reduce excretion of the drug from the body. Liver disease may reduce drug metabolism and lead to accumulation of active drug and active drug metabolites. Reduced muscle mass leads to unpredictable absorption of drugs administered by the intramuscular route (Dodds, 1995).

The pharmacological analgesic options available are listed in Table 7. The key to effective pain management in patients of all ages is regular and appropriate assessment, combined with regular administration of multimodal analgesic agents.

The Role of Regional Analgesia

The intraoperative use of regional anesthetic techniques either in combination with general anesthesia or alone has been shown to reduce short- and long-term cardiac and mortality in the elderly following total hip arthroplasty, vascular surgery, and abdominal surgery. It is thought to do this by sympatholysis, attenuating the stress response and improving myocardial oxygenation. Regional analgesia continued into the postoperative phase provides more profound analgesia with lower doses of narcotics than intravenous opioid administration, thus minimizing the potential for sedation, respiratory depression, and ileus. It decreases the incidence of respiratory complications in patients undergoing abdominal and thoracic procedures and decreases admission rates to the intensive care unit and overall length of stay (Rodgers *et al.*, 2000). Regional analgesia decreases the rate of postoperative deep venous thrombosis due to relative vasodilatation of the venous plexus in the lower limbs and by decreasing the time to mobilization. Continuous epidural analgesia postoperatively can cause hypotension and lower extremity motor and sensory deficits. For this reason, nursing and medical staff require training on the recognition and management of potential complications of regional analgesic techniques.

The Role of Patient Controlled Analgesia (PCA) in the Elderly

Intravenous PCA has been shown to be safe in elderly patients (Egbert *et al.*, 1990), but health-care staff frequently hesitate to prescribe it because of the concern that it may cause confusion or inadequate analgesia in the older patient. Older patients should not be automatically excluded from using PCA, either via the intravenous or the epidural route. The cognitive state and physical abilities of each patient should be assessed on an individual basis.

ETHICAL CONSIDERATIONS FOR PERIOPERATIVE CARE OF THE ELDERLY

Decisions regarding surgery and anesthesia become more complicated in the older patient particularly when their ability to make a competent decision is compromised through cognitive impairment or illness. *Paternalism* on the part of the physician does not respect the patient's fundamental right to autonomy. Patients must be provided with the information they require, in a suitable format, to empower them with decision-making capacity. Informed consent leading to the choice of a treatment option or informed refusal of a treatment option must be respected by all professionals. If there is concern regarding the older patient's ability to assimilate information and decide, then further advice should be taken before deeming the patient "incompetent". Formal assessment of mental state may be necessary. If legal incompetence is concluded, decisions about the cessation or instigation of treatment may be taken by a proxy. This is often a family member. However, it may not be valid to assume that the proxy knows the wishes of a patient as they may never have discussed issues such as withdrawal of treatment. The proxy may be appointed on a formal basis through enduring power of attorney, or the patient may

make their wishes known through an advanced directive. The legal standing of advanced directives varies across legal jurisdictions. If there is no proxy available, doctors may make decisions about care "in the best interests" of the patient. Efforts should be made early in the patient's admission to anticipate important decisions about medical care so that the patient may be involved as much as possible and proxy decision making is avoided. The patient's current and potential quality of life may impact on the decision to proceed to surgery or not.

Previously made decisions concerning resuscitation, often referred to as do-not-resuscitate (DNR) orders, should be revised before a patient is admitted to the operating department for surgery. The outcome of cardiac arrest differs greatly from that on the general ward, with 60% of patients surviving to hospital discharge compared with 7–17% of patients who sustain cardiopulmonary arrest on the ward (Martin *et al.*, 1991). This because cardiac arrest in the operating theater is monitored and witnessed, whereas a patient may be arrested on the ward for a variable length of time before resuscitation efforts begin. In addition, cardiac arrest in the operating theater is often due to reversible causes such as arrhythmia, medication administration or hypovolemia, which when promptly managed, restore adequate circulation to the patient. In the light of this, a patient with a terminal process such as pancreatic cancer, with a DNR order on the ward, may have this decision reversed during the period he is in the operating theater for palliative ileostomy, if that is what the patient wishes following informed consent.

Table 8 Summary of the anesthetic management of elderly patients

Preoperative assessment for identifying high-risk patients
Careful history
Physical examination
Twelve-lead ECG
Functional status assessment
Nutrition assessment
Preoperative preparation
Effective control of coexisting disease
Stopped smoking for 8 weeks
Training in cough and lung expansion techniques
Chest physiotherapy for elderly at risk of pulmonary complications
Correction of malnutrition
Routine precautions for major surgery
Temperature monitor and control
Ripple mattress
DVT prophylaxis
Intra-arterial pressure monitoring
Hemodynamic stability
Combination of anesthetic and vasopressor, β-blockers and vasodilatation
Avoid fluid overload
Quick recovery from anesthesia
Use short-acting anesthetic agents
Combine epidural anesthesia with GA for major abdominal and thoracic surgery
Antagonize neuromuscular blocking drugs
Postoperative period
Prevent hypoxemia: supplemental oxygen, reversal of neuromuscular drugs
Prevent hypothermia: keep warm perioperatively
Effective postoperative pain control: regular multimodal analgesia

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STRATEGY TO REDUCE POSTOPERATIVE MORBIDITY AND MORTALITY IN THE ELDERLY

Reduction in anesthesia- and surgery-related morbidity and mortality involves a strategy that encompasses both individual organ systems and a wider view of the perioperative process (Table 8).

Preoperative Nutritional Supplementation

Up to 40% of older patients admitted to hospital are malnourished (McWhirter and Pennington, 1994).

Elderly patients with malnutrition are poor candidates for surgery and anesthesia, as it places them at particular risk from hypothermia, decubitus ulcers, drug overdose, local and systemic infection, anemia, and wound breakdown. The most common form of malnutrition in this age-group is protein-calorie malnutrition (Bonjour *et al.*, 1996). Low protein intake is associated with low intakes of calcium and vitamin D, both of which are necessary in the formation of callus after fracture. Loss of muscle secondary to malnutrition increases fatigability, decreases strength, and reduces the ability to maintain adequate ventilation.

The evidence from recent studies, including a Cochrane review, suggests that nutritional supplementation should be confined to those patients who are malnourished, in order to achieve an acceptable risk-benefit ratio, where side effects to the patient are balanced against a demonstrable clinical effect (Avenell and Handoll, 2000). The evidence to date suggests that simple oral supplements are the optimum method of supplementation as oral supplementation is more cost effective, more tolerable, and psychologically more acceptable to patients than nasogastric or parenteral nutrition. It has not been extensively studied however.

Simple qualitative assessment of nutritional status on admission to hospital may be carried out as part of the routine nursing assessment (Allison, 1995). Because of the prevalence of poor nutrition in older patients presenting for surgery, prompt preoperative referral to a dietician of all patients who are deemed malnourished on nursing assessment should take place. This will facilitate early institution of simple oral supplementation in the postoperative phase, with nasogastric supplementation in patients who are severely malnourished. The emphasis should be on restoring function and decreasing perioperative morbidity rather than rapid weight gain.

Prevention of Perioperative Decubitus Ulcers

The older surgical patient presents a unique challenge to the perioperative care team in the prevention of pressure ulcers. It is suggested that 25% of pressure ulcers are acquired

intraoperatively (Aronovitch, 1999). For many patients, pressure ulcers mean increased pain, longer hospital stays, and reduced quality of life. A pressure ulcer can be defined as an area of localized damage to the skin and underlying tissue, caused by a disruption in the blood supply, preventing oxygen and vital nutrients from reaching the cells (EPUAP, 1998). Schultz *et al.* (1999) suggested that a pressure sore beginning in the operating theater develops initially in muscle and the subcutaneous tissues before progressing outwards to the dermis and epidermis. This causes an erythematous area, which may be mistaken for a burn. This may go on to become an established pressure sore. Pressure sores occurring in surgical patients are often not attributed to their time spent in theater, as the initial damage may not be apparent until several hours or days have passed (Vermillion, 1990).

The development of a pressure ulcer is considered to be largely preventable with the implementation of an effective preventive strategy (EPUAP, 1998), and the occurrence of pressure ulcers has been used as a proxy measurement of quality care.

Anesthetized patients are subjected to prolonged pressure on dependent body parts as neither the position or duration of surgery can be altered. Duration of surgery is a major risk factor in pressure ulcer formation, in conjunction with the patient's level of tissue tolerance and the support surface. Other risk factors for pressure ulcer formation have been well established (Table 9). A constellation of these features is frequently found in the older patient presenting for surgery.

On the basis of the literature to date, prevention of decubitus ulcers in the perioperative period should concentrate on the following points:

Table 9 Risk factors for the development of perioperative decubitus ulcers

Extrinsic
Pressure
Shear
Friction
Moisture
Intrinsic
Age (>40 years)
Nutritional status
Body mass index
Comorbidity
Core temperature
Low diastolic pressure
Low serum albumin
Immobility prior to surgery
Operating room factors
Duration of surgery
Surgical position
Type of mattress
Positioning devices
Warming devices
Epidural anesthesia/analgesia
Anesthetic agents
Type of surgery
Extracorporeal circulation
Inappropriate manual handling

- early assessment of risk factors, combined with full history and clinical examination;
- meticulous attention during manual handling, particularly after the patient has been anesthetized;
- caution during positioning for surgery;
- specialized table mattresses such as alternating air devices or gel overlays should be used for patients at particular risk;
- maintain normothermia;
- maintain diastolic blood pressure above 35 mmHg;
- low-dose local anesthetic infusions for regional analgesic techniques;
- frequent reevaluation.

The Role of Daycase Admission

There is no upper age limit for daycase admission, and older patients may benefit cognitively from reduced disruption to their daily environment and routine. Prior consultation at the preoperative assessment clinic should screen patients for suitability. Patients should be medically stable and able to understand simple instructions with regard to medications and fasting. A reminder telephone call the evening before surgery is useful in encouraging compliance. Patients require a responsible companion to accompany them home and to stay overnight. It is this issue that most often causes difficulty. Community services and follow-up need to be in place before the patient leaves the hospital.

Choice of Surgical Approach

The appropriateness of the surgery may need to be reviewed in older patients who, because of their preoperative baseline, are at particular risk of a poor outcome. Unnecessary surgery that exposes the patient to a high risk/low benefit ratio should not be undertaken without expert opinion and full informed consent from the patient. If possible, a less invasive surgical approach may be utilized, for example, thoracoscopic evacuation of hemothorax or laparoscopic-assisted colonic resection. These techniques result in less pain, a quicker recovery, and a shorter hospital stay.

Perioperative Audit

There is an important role for perioperative audit in the care of the older surgical patient. Attendance at preoperative assessment clinics, proportion of patients cancelled for medical reasons on the morning of surgery, unplanned admission to the intensive care unit, incidence of postoperative myocardial infarction, patient satisfaction, and 30-day mortality are just a few examples of outcome measures that may provide scope for audit and implementation of change in individual surgical units.

CONCLUSIONS

Good anesthetic care of the older person involves an assiduous approach to both minor and major elements of the perioperative process. The preparation of the patient begins early and is best carried out in a multidisciplinary unit that is focused on the needs of the elderly. Most information required to plan the anesthetic may be gained from a detailed history and clinical examination of the patient. Occasionally, special investigations or preparatory procedures are required.

Short-acting agents and/or regional anesthesia are recommended, providing there are no special indications for general anesthesia or contraindications to regional techniques. Provision of adequate pain relief with regular assessment and formal charting of pain scores should be adopted as routine practice. Fluid and electrolyte management should not be left to the most junior member of the team – consideration of the fluid, electrolyte, and nutritional needs of the patient should be a priority throughout the perioperative course. Oxygen supplementation should be continued routinely to reduce the incidence of hypoxemia preoperatively and postoperatively.

KEY POINTS

- Advanced age is not a barrier to anesthesia and surgery.
- Anesthesia should be carried out, or closely supervised, by an anesthesiologist with sufficient experience of anesthesia in elderly patients.
- Adequate time must be allocated for a detailed preoperative assessment.
- Invasive monitoring and regional anesthesia should be utilized liberally.
- The intraoperative anesthesia care should be viewed as part of a continuum, with therapy such as oxygen supplementation, analgesia, and fluid management continued into the postoperative period.

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Health Issues in the Aging Female

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CANCER

Cancer is one of the leading causes of death in women (Levi *et al.*, 2001). The aging female is at risk for endometrial, ovarian, breast, cervical, vulvar, and vaginal cancer. Since there is risk with increasing age, reviewing the risk factors are important to help promote a good quality of life. Proper screening, early detection, treatment, and management of comorbidities are essential.

Endometrial Cancer

Endometrial cancer is the fourth most common malignancy in women after breast, colorectal, and lung cancer. Peak incidence occurs in women between 50 and 60 years of age, and the incidence appears to be climbing. The 5-year survival rate for all stages of endometrial cancer has been estimated at 65%.

Risk factors include nulliparity, obesity, and prolonged use of unopposed exogenous estrogen. The most common symptom is postmenopausal vaginal bleeding.

Besides a physical examination and pap smear, a pelvic ultrasonography and either a endometrial biopsy or dilation and curettage is required for diagnosis or exclusion of diagnosis of endometrial cancer. (A positive Pap test for endometrial cancer will only show in 35–50% of the cases and should not be the only determinant in diagnosis.) Optimal treatment is a hysterectomy with bilateral oophorectomy, and dissection of the retroperitoneal lymph nodes in the pelvic and para-aortic region (Geisler and Geisler, 2001). Additional treatment, such as chemotherapy, radiation or both may also be indicated for advanced stages of cancer and discussion is needed with the patient's oncologist and geriatrician to weigh the risks with the benefits.

Ovarian Cancer

After endometrial cancer, ovarian cancer is the second most common gynecological malignancy. Peak incidence occurs in women aged between 50 and 60. Risk factors include uninterrupted ovulation (nulliparity or contraceptive usage) and inherited genetic mutations.

Symptoms usually are nonspecific. Abdominal pain, abdominal distention, and gastrointestinal disturbances are complaints sometimes voiced from women with ovarian cancers, but symptoms may not develop until late in the disease process. Screening, except for high-risk patients, may include ultrasonography and tumor markers; however, it is thought to be of limited value.

Ovaries are generally small and not palpable in the postmenopausal woman and if, upon physical exam, an ovary is able to be palpated, immediate evaluation is warranted since it is suggestive of ovarian cancer. Initial treatment involves surgical removal of the tumor. Chemotherapy may be considered depending on the tumor stage, the patient's comorbidities, and benefits versus risks. Since most ovarian cancers are detected when the tumor is advanced, long-term prognosis is usually poor.

Breast Cancer

Approximately 50% of all new breast cancer cases occur in women over the age of 65. The incidence of breast cancer increases up to the age of 80, levels out between the ages of 80 and 85, and then is thought to decline. It is difficult to evaluate those over 85 years owing to limited data.

Risk factors for developing breast cancer may include personal or family history of breast cancer and/or colon or endometrial cancer in first-degree relatives, nulliparity or late first pregnancy at 31 years of age or older, late menopause, early menarche, abdominal obesity, estrogen replacement therapy, history of atypical hyperplasia on biopsy for benign breast disease (Chlebowski *et al.*, 2003).

Screening for breast cancer in a postmenopausal woman includes monthly self–breast examinations, an annual physical exam by a physician or other health-care provider, and a yearly, or every 2 years, mammogram. Research has shown that screening for breast cancer in women aged 50 to 70

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has improved survival by early detection. There are many doctors that feel that mortality could be reduced 25–30% if all women received proper mammographic screening. There is limited data on breast screening in woman over 70 years, but it is thought that mammography is of benefit. Since 10–20% of all breast cancers are not picked up on mammography, physical examination is also important.

Less than 50% of all women 65 years or older have ever had a mammogram, and those who have had a mammogram, have obtained one on a routine basis. There has been argument among physicians against instituting routine screening for breast cancer in the elderly woman, stating that disability and shorter life expectancy may have a direct effect on the desirability and cost-effectiveness of screening. On the other hand, the life expectancy of a healthy woman in her mid-to-late 70s is approximately 10 more years, and for a healthy woman aged 85, 7 more years. Thus, screening appears to be warranted.

The clinical characteristics of breast cancer are the same, despite the age of the individual. Cancer is generally suspected when breast lesions palpated feel firm or abnormalities are detected on mammography. A palpable breast mass in a postmenopausal woman requires immediate attention since most palpable masses are malignant. All breast masses in this age-group should have a biopsy whether the mass was palpated and/or detected on mammography.

Prognosis is determined by the stage of the disease. Owing to lack of clinical studies, it is unclear if women over the age of 65 have the same clinical course as compared to that of younger women. The course of treatment is prompted by the stage of the disease. Until recently, many elderly women with breast cancer were not aggressively treated; however, today many older women with breast cancer are working with their oncologists and geriatricians discussing various treatment options.

Cervical Cancer

Cervical cancer occurs in women of all ages but its incidence peaks in women aged 40 to 50 years (Benedet *et al.*, 2001). Symptoms vary and hinge on the stage of the tumor. Some women may be asymptomatic, while others may show clinical signs of postmenopausal or postcoital bleeding. Routine Pap testing is the best method of screening. If the Pap test results are positive, colposcopy-directed biopsies and endocervical curettage are used to establish diagnosis.

Radical hysterectomy is the recommended treatment for cervical cancer. Adjuvant radiation or chemotherapy may also be used. The combined cure rate for all cervical cancers is 50–60%.

Vulvar Cancer

Vulvar cancer accounts for approximately 3–4% of all gynecological malignancies in the United States (Beller *et al.*, 2001a). The average age at diagnosis is 70 years, and the incidence increases with age. The most common symptoms exhibited in vulvar cancer are vulvar pruritus, pain, and a palpable vulvar lesion; however, many women are asymptomatic (Hyde *et al.*, 2002). A discharge may be present. Histology generally reveals squamous cell carcinoma. Biopsy may be indicated for diagnosis. Treatment is generally surgical and for extensive lesions, a radical vulvectomy with unilateral or bilateral inguinal lymphadenectomy is recommended. Radiation and chemotherapy may also be considered adjuvant therapy. Prognosis for early-staged lesion are generally favorable. The 5-year survival rate is 80–90% if there is no metastasis to the lymph node and 16–30% if lymph node metastasis is present.

Vaginal Cancer

Vaginal cancer is relatively rare (Beller *et al.*, 2001b). The average age at diagnosis is 60 to 65 years. It is estimated that 95% of these lesions are squamous cell carcinomas. Vaginal bleeding or discharge is an early symptom. Pain or postcoital bleeding may be exhibited in sexually active women. Where the tumor involves the anterior vaginal wall, it may cause dysfunction with voiding, since the vaginal wall may invade into the urethra. Biopsy is indicated for diagnosis. Radiation therapy is the main choice of treatment; however, surgery and chemotherapy may be utilized in specific cases. Prognosis is dependant upon the size and location of the tumor. The 5-year survival rate for all types is estimated to be from 25–48%.

MENOPAUSE

Menopause is the permanent cessation of menses as a result of ovarian aging. It is clinically diagnosed after 12 months of amenorrhea. The perimenopausal transition is defined as the time prior to the permanent cessation of menses and is identified with irregular menstrual cycles. Transitional time has been shown to vary in length from 2 to 8 years.

The average age, in the United States, at which menopause occurs is 51.

Early symptoms of menopause include irregular menstrual cycles, headache, fatigue, changes in mood and cognition, insomnia, and hot flashes (Table 1). Some women may experience vertigo, heart palpitations, and tachycardia. A later clinical presentation may include urinary incontinence, dry skin, breast changes, genital atrophy with dyspareunia, vaginitis, and cystitis.

Early symptoms of menopause is often irregular menstrual periods. They may vary in frequency, duration, and blood flow amount. Menstrual bleeding that is unusually heavy, lasts more than 10 days, or that occurs more often than once every 3 weeks should be clinically evaluated for possible neoplasms.

Another early symptom of menopause is hot flashes. About 80% of perimenopausal women report hot flashes

Table 1 Signs and symptoms of menopause

Irregular menstrual cycle
Insomnia
Hot flashes
Mood swings
Cognitive changes
Skin changes
Genitourinary atrophy
Headache
Fatigue
Vertigo
Heart palpitations/tachycardia

and up to 50% of these women may continue to have symptoms for up to 5 years. Hot flashes may also occur after surgical menopause. Research shows that short-term use of hormone replacement therapy (HRT) will help relieve severe vasomotor symptoms, but will not abolish symptoms.

Women who have had bilateral salpingo oophorectomy are at high risk for cardiovascular disease. This is especially true if HRT was not initiated. Early natural menopause is also at high risk.

Diagnosing menopause may be determined by elevated serum levels of follicle-stimulating hormone. Estrogen replacement therapy is the best treatment for symptoms of menopause. Duration of estrogen replacement therapy is controversial and each case should be reviewed for risk versus benefit.

Postmenopausal Vaginal Bleeding

About 20–30% of postmenopausal vaginal bleeding is due to atypical adenomatous endometrial hyperplasia or endometrial cancer. It may also be caused by the use of estrogen or progesterone or by genital atrophy resulting from low estrogen levels.

History taking should include past and present gynecological problems. A drug history should indicate whether any exogenous estrogens were used. A pelvic and bimanual exam should be performed to rule out any trauma, tumors, or bleeding from atrophic sites. A Pap test should also be performed to aid in diagnosis. Transvaginal ultrasonography may be useful for diagnosis. If the endometrial thickness is less than 5 mm, cancer or endometrial hyperplasia is doubtful. Endometrial thickness over 5 mm is suspicious for malignancy and further work-up is promptly warranted. Endometrial biopsy may then be indicated as well as a full fractional dilatation and curettage (D & C).

If postmenopausal bleeding is found to be cancerous, then treatment should be tumor specific. If cancer is nondetected, estrogen is initiated because it may be secondary to atrophy. For those women taking exogenous hormones, the estrogen dosage may need to be decreased and progesterone increased. If bleeding continues, a more aggressive work-up is needed.

Postmenopausal Hormone Replacement Therapy

Approximately 6 million women in the United States are taking HRT. The use of estrogen ranges from relief of postmenopausal symptoms to what was assumed, until recently, long-term health benefits. Until recently, it was felt that estrogen replacement had a protective effect against cardiovascular disease. From the data collected by the Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II) trial and other recent secondary prevention studies, the new recommendations are against initiating or continuing its use for the primary prevention of cardiovascular disease. The Women's Health Initiative (WHI) study stated that estrogen and progestin therapy should not be initiated or continued for the primary prevention of coronary heart disease and was suggestive that it may stimulate breast cancer growth and hinder breast cancer diagnosis. This combination of hormone replacement also showed an increase in pulmonary embolus.

Sexual Dysfunction in the Menopausal Woman

Many women have experienced a lack of interest (decreased libido) or arousal in sexual activity (sexual arousal disorder), achieving orgasm (female orgasmic disorder), or have had pain prior or during sexual activity (dyspareunia) (Gutmann, 2005; Kingsburg, 2004). When one or more of these symptoms occur, causing anguish and interference with interpersonal relationships, it is diagnosed as female sexual dysfunction (FSD). The exact prevalence is unknown; however, one survey found that more than 40% of women aged 18 to 59 alluded to having sexual dysfunction. It has also been suggested that the prevalence of FSD increases while women are going through menopause transition.

Perimenopausal and postmenopausal women have repeatedly reported that they have lost an interest in sex and do not find sex "pleasurable". Studies have shown that there is a decline in sexual functioning from early to late perimenopause. In late perimenopausal to postmenopausal women, studies reveal that there is a decrease in libido and sexual responsitivity, an increase in dyspareunia, and a decline in sexual activity. Screening questions that are useful for FSD are given in Table 2.

The causes of FSD are multifactorial. Hormonal, physical, and psychosocial changes are key components of FSD.

Table 2 Screening questions for female sexual dysfunction

1. Are you currently involved in a sexual relationship? With men? With women? Both? Multiple partners?
2. How often do you engage in sexual activity? Intercourse? Masturbation?
3. Do you feel that your sex drive has changed? Less? Same? Increased?
4. Do you have difficulty in obtaining an orgasm? Inability? Pain with?
5. Are you satisfied with your current sexual relations?
6. Do you have any sexual concerns that you would like to discuss?

Hormonal Changes

There is a decline of circulating androgens during the late reproductive years. Androgen deficiency is associated with a decline in libido, decline in sensitivity to sexual stimulation, and arousability.

Estrogen deficiency can cause changes in the genitourinary system. Estrogen therapy, both topical and systemic, has been shown to improve vaginal atrophy, increase blood flow to the vagina and increase lubrication.

Physical Changes

In addition to the hormonal changes that occur in the genitourinary system, other conditions can contribute to FDS. Limited movement or pain from arthritis may be a factor. Recent pelvic surgery or trauma is another. Some medications, such as, antihistamines, antidepressants, and blood pressure medication can lead to a decreased libido and inability to achieve orgasm.

Psychosocial Changes

A woman may have concerns over the well being of her sexual partner. If she or her sexual partner is ill, or have a debilitating disease, it can have a direct impact on sexual function. Women, who live longer than men, often are without a sex partner. Not having a partner does not mean they are no longer in need of nurturing, affection, and physical contact. Depression and anxiety can contribute to FDS.

Research has shown that only 14% of Americans aged 40 to 80 have been asked by their doctor if they had any sexual problems within the past 3 years. Since this number is relatively small, the physician or health-care provider needs to remember to inquire about the patient's sexual health along with the history taking during physical exam.

Data from a large survey has indicated that 68% of men and women thought their physician would be uncomfortable talking about sex, and 71% thought that if sexual problems were disclosed, nothing would be done about the problem. Only 14% out of 1384 women ever reported sexual problems to their health-care provider in a study conducted by the American Association of Retired Persons. Of those women discussing sexual problems, most confer with their gynecologist rather than their private medical doctor (PCP). It is felt that physicians do not talk about sex because of a lack of education, comfort and confidence, and lack of time and treatment options (Table 2).

OSTEOPOROSIS

Osteoporosis is a major risk factor for fractures in the older population and is estimated to account for approximately 1.5 million low trauma fractures yearly (Ribeiro *et al.*, 2000). The lifetime risk of sustaining a fracture to the spine (symptomatic), hip or distal radius in white women is approximately 40% (while only 13% in white men) aged 50 years and older. The 6-month mortality rate from a hip fracture is approximately 10–20%. Of the survivors, about 25% will require assisted or nursing home care and approximately 50% will require an assistive device to aid in their ambulation. Osteoporotic fractures are associated with annual costs in the United States ranging between 7 and 20 billion dollars. One to one-and-a-half percent of all hospital beds in Europe are occupied by patients with osteoporosis. This European figure is expected to more than double in the next 50 years. In the United States, the estimated prevalence of osteoporosis is 8 million in women and 2 million in men and the estimated related health costs exceed 14 billion dollars annually. Primary osteoporosis occurs mainly in older people aged 51 to 75 years, and can be arranged in two groups: postmenopausal osteoporosis and age-related bone loss (senescence). The incidence of primary osteoporosis is six times more common in women than in men. Women are at higher risk because they have a lower peak bone mass compared to men and have an acceleration of bone loss during menopause.

Primary osteoporosis is thought to be atypical in premenopausal women, while secondary osteoporosis composes only a small amount of elderly women. (Elderly women may have a combination of both primary and secondary osteoporosis.)

Age-related bone loss is complex and multifactorial. As one ages, changes occur in cortical bone, trabecular bone, and bone marrow. Studies show that there is a decline in bone mineral density after the third decade of life and continues to decline at a rate of approximately 0.5% per year. During menopause, women, however, have an accelerated bone mineral density loss at an estimated rate of 3–5%.

Hormonal changes of vitamin D and reduction of calcium absorption also have an impact on aging bone. Vitamin D levels decrease with age and vitamin D deficiency in elderly people is common. Absorption rates also decline by 40%. Aging changes in skin reduce the amount of 7-dehydrocholesterol, the precursor and rate of conversion of vitamin D_3. Declining renal function leads to a drop of activity of 1-α-hydroxylase, which is responsible for the activation of vitamin D_3. Lower calcium levels then occur from these changes causing activation of the calcium sensor receptor in the parathyroid gland. Parathyroid hormone is secreted, stimulating osteoclast activity, which keeps serum calcium levels in homeostasis at the price of bone mineralization. Secondary osteoporosis may also have many other conditions causing bone loss such as various endocrine and neoplastic abnormalities, gastrointestinal disease, and drug usage (Table 3).

Osteoporosis has no symptoms; therefore, a thorough evaluation is critical for detection of osteoporosis. Assessment begins with a complete history alluding to its risk factors as stated in Table 4. Major risk factors for osteoporosis

Table 3 Secondary causes of osteoporosis

Endocrine
Hyperthyroidism
Cushing's syndrome
Osteomalacia
Paget's disease
Primary hyperparathyroidism
Gastrointestinal
Malabsorption syndromes
Alcoholism
Neoplastic states
Bone Metastases
Multiple myeloma
Medication
Glucocorticoids
Anticonvulsants
Excessive thyroid hormone replacement

Table 4 Risk factors for osteoporosis

Advanced age
Female gender
Race (more prevalent among white, Asian, and Hispanic decent)
Heredity (approximately 50–80% of peak bone mass is genetically determined)
Small body size/weight (<127 pounds)
Smoking
Alcoholism
Sedentary lifestyle/immobility
Low dietary calcium/vitamin D intake
History of previous fractures/falls
Decrease long life exposure to estrogen
Certain medication (anticonvulsants, gluccocorticoids, thyroid hormone, barbiturates)
Caffeine use
Early menopause or oophorectomy

are increased age, female, ethnicity, and thin body habitus. History of previous fracture(s) needs further assessment, focusing on whether the fracture occurred with only minimal trauma (suggestive of low bone density). Physical examination for osteoporosis should look for secondary causes. For example, an ill, cachectic woman may need assessment for malnutrition, malignancy, or malabsorption syndrome. A loss of body height may indicate vertebral compression fracture(s), or dorsal kyphosis from osteoporosis may be seen on clinical exam.

Laboratory evaluation should reflect clinical findings. All women with osteoporosis should receive a chemistry profile including electrolytes, kidney and liver function, glucose, calcium, phosphorus, and albumin. They should also have a complete blood count to rule out anemia and malignancy. Thyroid function should be assessed in women over 50 years. Other lab tests should be ordered as individually warranted such as 25(OH)-vitamin D and parathyroid hormone for those with low serum calcium to look for vitamin D deficiency and secondary hyperparathyroidism.

The combination of history taking, physical examination, and lab tests will help in diagnosing osteoporosis or other secondary causes.

Bone densitometry is the only test which confirms diagnosis of osteoporosis in the absence of fracture. To confirm diagnosis of primary osteoporosis, one needs to rule out secondary osteoporosis, malignancy, and osteomalacia. Although many women have some type of knowledge about osteoporosis, health-care providers need to educate the general population about the importance of taking certain steps to aid in its prevention. Treatment includes providing calcium and vitamin D supplementation, which can reduce the risk of fracture up to 30%. Estrogen therapy can prevent bone loss in menopausal women and is the treatment of choice in postmenopausal women. The second best choice in the treatment of osteoporosis is the use of biphosphonates. This group of drugs increases bone mass, thus decreasing the risk for fractures. Other medications used include selective estrogen receptor modulators and calcitonin. Other treatment modalities include exercise with a focus on muscle strengthening, weight bearing, and balance. Direct effects on bone may be relatively small but will aid in decreasing the incidence of falls which may lead to fractures (Messinger-Rapport and Thacker, 2002).

KEY POINTS

- The Women's Health Initiative has decreased the enthusiasm for hormone replacement therapy in older women.
- Screening for cancer remains important in older women.
- Female sexual dysfunction is a relatively common problem in older women.
- Osteoporotic fractures are a major cause of disability and mortality in older women.

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Antiaging

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INTRODUCTION: WHAT IS ANTIAGING MEDICINE AND WHY IS IT APPEALING?

Antiaging medicine involves the use of treatments specifically designed to slow, prevent, or reverse the effects of aging on people, which is in contrast to medical treatments that prevent or treat specific diseases. While proponents describe this approach as "the future of medicine", in fact, the search for the "fountain of youth" is hardly a new endeavor (Gammack and Morley, 2004). For example, stories about specific plants or bodies of water that convey eternal youth are common in ancient mythology, and the Bible contains references to a River of Immortality that flowed from the Garden of Eden. More recently in the thirteenth century, Roger Bacon suggested that a balanced diet, exercise, rest, and the "breath of a virgin" would extend life span. Ponce de Leon, the colonial governor of Puerto Rico, discovered Florida while searching for Bimini, where the Fountain of Youth was reportedly located. Even Nobel laureates were not immune to the seduction of antiaging therapies. Elie Metchnikoff believed aging was due to toxins released by the gut, and ate yogurt in an attempt to ward off the effects of these toxins. Linus Pauling took mega doses of vitamin C as an antiaging treatment. While many of these early stories are amusing, the rapid increase in knowledge about the biologic mechanisms involved in aging and the physiologic changes associated with aging have made the quest for antiaging therapies more rational, and due to the establishment of companies dedicated to developing antiaging therapies, more serious than ever.

The current plausibility of antiaging therapies combined with two other powerful social forces has fueled the explosion in interest and spending on antiaging therapies. These two forces are the growth of the Internet and the graying of many Western countries. First, the Internet now provides anyone the opportunity to exchange information or opinion about any topic on websites with little to no supervision. As health is an important topic to most people, an internet search on any health related topic will literally yield thousands to hundreds of thousands of "hits", each linked to a unique website. Some websites provide accurate and helpful information while others provide incorrect information and yet others provide information intended to sell a product that is also available on the same website. Along with being a source of information, the Internet has also developed into a virtual shopping mall for thousands of small businesses to sell wares around the globe. Second, the populations of the United States, Western Europe, and Japan are aging with a significant increase in the numbers of individuals older than 50 years. This "newly old" population is in better physical health than prior generations and often has had the experience of watching their parents age and cope with the consequences. Consequently, there has been a rise in interest in holistic approaches and disease prevention. These two forces have created a ready marketplace of interested consumers who are interested in and willing to purchase antiaging treatments.

The growth of the antiaging medicine movement and the progress of biogerontologists in unraveling basic mechanisms involved in aging have also had impacts upon the geriatrics community. Some in the geriatrics community have been drawn into the battle between antiaging medicine providers and biogerontologists about the relative lack of safety or effectiveness data for any of the currently touted antiaging therapies (Olshansky *et al.*, 2002). Antiaging medicine providers have also attacked the field of geriatrics as being unnecessary because of the dramatic effects that antiaging treatments will have on human aging. Often it seems that the discussion of antiaging treatments has become so overtaken with hyperbole that rational discussion has fallen by the wayside (Turner, 2004). This has left many in the geriatrics community skeptical about the claims of either antiaging medicine providers or biogerontologists, while at the same time uneasy about the social and health effects of success emanating from either camp.

This chapter will explore the topic of antiaging therapies on multiple levels. First, the idea of an antiaging treatment will be defined and the rationale for thinking why such a treatment could ever be developed will be discussed.

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Second, some currently touted antiaging therapies along with the data, or the lack of data, supporting their use will be presented. Finally, the ethical issues behind the development and the use of antiaging treatments and the potential effects of a successful treatment in the field of geriatrics will be discussed.

WHAT IS AN ANTIAGING THERAPY?

Aging has multiple effects on people. The aging phenotype involves cosmetic changes like gray hair and wrinkles, physiologic changes like decreases in cardiovascular or pulmonary function and physiologic reserves, psychological changes like declines in short-term memory, and medical changes such as a marked increase in susceptibility to a large number of diseases as well as an increased risk for functional decline. An antiaging therapy could similarly act in one or more ways to counteract the aging process or its direct effects (Fisher and Hill, 2004). Specifically, an antiaging treatment could modify the biochemical and molecular events involved in aging and hence directly address the aging process. Alternately, an antiaging therapy could act more indirectly to either lessen the susceptibility to age-associated diseases or to correct physiologic changes associated with aging that result in aspects of the aging phenotype. Obviously, an intervention could work in multiple ways as exercise, for example, both corrects physiologic changes associated with aging by correcting declines in physical strength and stamina in part due to sarcopenia and also decreases the susceptibility to disease by raising HDL (high-density lipoprotein) cholesterol and preventing osteoporosis. Interestingly, therapies that act to lessen the susceptibility to age-associated disease are already commonly used in conventional medicine practice as preventive care practices, such as mammography, immunizations, colonoscopy, hypertension treatment, and cholesterol screening, and have as an expressed goal the prevention of diseases that increase in prevalence along with age. While these preventative care practices would never have been considered antiaging therapies, their goals do overlap with those of antiaging medicine. Consistent with this, most guidelines for preventive care include recommended ages for when to start screening and treatment. As preventive medicine is well known among physicians and discussed in detail both in the other chapters of this text and elsewhere, this chapter will instead focus on "antiaging" therapies that are intended to directly modify the aging process or its direct consequences.

The terms "antiaging medicine" or "antiaging therapy" are applied rather broadly in popular culture. Often, magazine articles or television programs will refer to cosmetic procedures like face-lifts, the use of botulinum toxin (Botox) to minimize wrinkles, or teeth whitening as "antiaging medicine". However, these treatments do not have any real effect on the aging process or its direct effects on individual health and functioning, and hence for the purposes of this chapter do not represent "antiaging" therapies. Furthermore, the providers of plastic surgery, Botox, or teeth whitening neither intend or claim to alter the effects of aging at a biochemical level or to improve the health or functioning of any organ systems. Instead, these procedures simply represent temporary measures to address specific cosmetic aspects of the aging phenotype.

Consequently, an antiaging therapy should have three features: (1) the medication or treatment acts by modifying the aging process or its direct effects; (2) it should promote continued good health or reduce disability; and (3) it should not simply be targeted to symptoms associated with normal aging (Fisher and Hill, 2004). First, an antiaging medicine or therapy by definition should act to address either the aging process or its direct effects on molecules, cells, tissues, or organs. An antiaging therapy needs to alter causal mechanisms related to aging such as oxidative stress, unfolded proteins, cell senescence, or hormone changes. Prolonging life by itself is not a true measure of a therapy, as immunization, proper sanitation, use of seat belts, and specific disease treatments, such as the use of aspirin in patients with coronary artery disease, can all produce increased longevity without being an antiaging therapy. A therapy can either act in a specific tissue or can act systemically.

Second, the use of an antiaging therapy should promote continued good health or reduce disability. An important goal of antiaging medicine is to address two major failings of treatments focused on specific diseases, which are the decline of overall patient health and functioning over time due to aging, and the related increase in disability. An antiaging therapy should address the causative role that aging plays in future disease and disability. A true failure, both from the societal and individual perspective, would be a treatment that simply results in the prolongation of poor health and functional disability, such as prolonging time in a nursing home.

Third, an antiaging therapy should not simply target symptoms associated with the aging phenotype, like gray hair, wrinkled skin, or normal short-term memory loss, without having some effect on the underlying aging process and altering its role in health and disease. Symptomatic treatment is an important part of geriatric medical care, and it is common in geriatrics to use treatments that mask symptoms, such as the use of pain control medications, or to minimize the functional effects of symptoms, for example, through the prescription of adaptive devices. Furthermore, cosmetics, hair dye, aesthetic dentistry, or cosmetic surgery procedures can be a useful way for patients to cope with aging. However, none of these treatments can rightly be thought of as providing benefit beyond altering temporarily the experience of aging.

ARE PATIENTS USING ANTIAGING THERAPIES?

While there is little information about the exact number of antiaging medicine providers, the number of patients using treatments, and the amount of money spent yearly

on antiaging treatments, the use of antiaging treatments clearly do contribute to the $4 billion spent annually on alternative and complementary treatments (Butler, 2000). The American Academy of Anti-Aging Medicine ("A4M") reports having 12 500 members on their official website (http://www.worldhealth.net/, accessed June 30, 2004). Furthermore, the Internet contains literally millions of websites dedicated to providing information on, and selling, antiaging therapies as a Yahoo search done on June 30, 2004 with the search term "antiaging" yielded 3 490 000 hits. Additionally, a Harris Interactive poll conducted in October 2002 found that while the majority of those surveyed were skeptical of antiaging therapies and providers, 7% of those surveyed had either personally used or knew someone who used an antiaging therapy (Harris Interactive Inc., 2003). Over half of this group felt that the therapy was either very beneficial or somewhat beneficial while only 27% felt it was harmful. Hence, while the number of antiaging treatment users is small at this time, there are enough current users to support a fairly significant number of providers and vendors of products. These antiaging medicine users seem to be satisfied overall with the products and services and probably have become loyal repeat patients.

IS THERE A SCIENTIFIC BASIS FOR ANTIAGING THERAPIES? (*see* Chapter 2, A Biological Perspective on Aging)

During the last 10–15 years, knowledge about the aging process in humans and lower animals has greatly expanded. Both genetic and drug interventions have produced significant increases in longevity in model animals and have helped elucidate biologic mechanisms involved in the normal aging of these animal species (Guarente and Kenyon, 2000). While a complete understanding of the aging process is still far off, some basic principles about aging have emerged. Though no current product has been conclusively shown to alter one of these mechanisms and alter human aging, it is reasonable to assume that future drugs will be designed and tested, with a few, perhaps, being effective. The next section will briefly discuss some of the biologic mechanisms involved in aging in lower animals and presumably in humans, which represent potential targets for current and future aging therapies.

OXIDATIVE STRESS

As early as the 1950s, aging was proposed to be, at least in part, due to the collective damage to proteins, lipids, and nucleic acids from oxidative stress (Harman, 2003). The generation of chemical energy by mitochondria, destruction of pathogens by immune cells, and many other catabolic and anabolic biochemical reactions produce reactive oxygen or reactive nitrogen species. These species can then chemically modify and consequently damage proteins, DNA, or lipids either in cells or in tissues (Table 1). With sufficient damage to cellular proteins and DNA, cell and organ dysfunction could occur and result in aging of the animal. Study of aged model animals has shown the accumulation of oxidative damage with markers of oxidative damage being elevated two to three fold between reproductive maturity and death.

Consistent with the hypothesis, the scavenging of reactive oxygen species either by antioxidants or proteins with antioxidant actions results in increased longevity of experimental animals (Table 1). Additionally, many of the genetic

Table 1 Antiaging therapies

Aging mechanism	Effects	Treatment strategy	Treatment	Evidence of benefit from human studies
Oxidative stress	Damage to lipids, proteins, and DNA	Antioxidants	Vitamin A	−−¶
			β-carotene	+/−
			Vitamin C	+/−¶
			Vitamin E	+/−¶
			α-Lipoic acid	+/−
Hormone changes	(1) Production of symptoms associated with aging through reductions in hormone levels from young adulthood.	(1) Hormone replacement	(1) Growth hormone	−−
			Estrogen	−−
			Testosterone	+/−
			DHEA	+/−
	(2) Regulation of organismal aging by hormones	(2) Hormone Manipulation or Inhibition.	(2) ? IGF-1 Antagonists	?
Cell senescence	Loss of dividing cells and possible effects of dysfunctional senescent cells	? Inhibition of cell senescence, destruction of senescent cells	?	?
Caloric restriction	Increases lifespan by 30–50%, slows morphologic changes, and delays development of age-related disease	? Activation of *sir2* proteins	Resveratrol	+ (Observational studies of red wine consumption)

Improvements in scientific understanding of the biology of aging has allowed the rational development of antiaging therapies designed to address specific mechanisms. While no treatment has been tested in clinical studies for specific effects on aging, clinical studies of age-related diseases have allowed examination of potential benefits and side effects of treatments. Key to symbols: ?, unknown; ++, clear evidence of benefit; +, evidence of benefit; +/−, inconsistent evidence of benefit; −, lack of benefit; −−, evidence of harm that outweighs benefit; ¶, evidence of harm for specific subsets of patients (see text for details).

mutations identified, which extend lifespan have as one of their actions the induction of antioxidant proteins, for example, the *daf-2* gene in the worm, *Caenorhabditis elegans*, which doubles the worm lifespan, acts in part through the induction of catalase and superoxide dismutase through a downstream signaling cascade. So, far the effects of long-term treatment of humans with antioxidants on aging are not known. A diet favoring the intake of fruits and vegetables rich in antioxidants appears to protect against several age-related diseases, but whether this ultimately translates into retarded aging or increased longevity is unknown (Thomas, 2004). Furthermore, it is not clear if the dietary benefits are due to antioxidants, as multiple clinical trials studying the effects of antioxidant vitamin supplements on specific age-related diseases have yielded largely negative results.

MODULATION OF AGING BY HORMONES

There has been great interest in the role of hormones in causing or preventing aging (Table 1). In humans, it is clear that many hormones, such as growth hormone, dehydroepiandrosterone (DHEA), and sex hormones among others, change during aging, with this change usually representing a significant decline in hormone levels by old age (Horani and Morley, 2004). For some of these hormones, deficiency in younger people produces some of the symptoms felt to be associated with aging in older persons, such as fatigue, muscular weakness, decline in lean body mass, difficulty concentrating, and decrease in the sense of well-being (Morley, 2004). With regard to geriatric patients, these symptoms often reflect more of a caricature of aging than the reality of day-to-day life, are largely nonspecific with regard to any single hormone, and have a multitude of potential causes beyond hormone deficiencies. However, these observations have led to significant interest in the role that single or multiple relative hormone deficiencies may play in the aging phenotype. Effects of hormone supplements on geriatric patients will be discussed in a later section.

Interestingly, genetic experiments in lower animals have demonstrated hormones as also being important modulators of the aging process (Guarente and Kenyon, 2000). In these animals, the levels of these hormones in early to mid-adulthood can have dramatic effects on the rate of aging during adulthood and the ultimate lifespan of the animal (Table 1). For example, in the worm, *C. elegans*, the *daf-2* gene encodes a receptor in the insulin/insulin-like growth factor-1 (IGF-1) family. Ordinarily, *daf-2* signals in early adulthood to curtail maximal longevity. Animals lacking this receptor are unable to receive the signal and age at a much slower rate than normal animals. Many of the target genes induced in the absence of the *daf-2* have recently been described and include multiple heat shock proteins, catalase, superoxide dismutase, and proteins involved in immune defense, like antimicrobial peptides. Interestingly, no single target gene mediates all of the lifespan increases, but instead, each gene has a relatively small but additive effect.

Genes analogous to *daf-2* have been identified in other animals including mice and humans (Tatar *et al.*, 2003). In mammals, *daf-2* is felt to be more homologous to the IGF-1 receptor than the insulin receptor. IGF-1 is made by the liver and muscles in response to growth hormone. Work with mouse mutants have suggested that signaling by growth hormone and IGF-1 shortens lifespan in the same way as in the worm. Two types of mouse mutants, Ames and Snell dwarf mice, lack the somatotropes in the pituitary gland responsible for making growth hormone and are dwarves and long-lived. Laron dwarf mice lack the growth-hormone receptor and are also long-lived. Knockout mice lacking the IGF-1 receptor have been generated. These mice are normal in size, but are also long-lived. Additionally, in mice, as in humans, the levels of growth hormone decline with age. If adult mice are given exogenous growth hormone to increase the serum levels, these mice demonstrate accelerated aging. Together, this suggests that the *daf-2*/IGF-1 signaling pathways play a conserved role in lifespan determination.

If hormones can regulate aging, then why are the levels not set to maximize lifespan? The answer is that most of these hormones have multiple physiologic roles beyond the control of aging. The levels of hormones that maximize lifespan often have negative consequences too, such as impacts on fertility or survival when food is limiting. For example, competition experiments have found that *daf-2* mutant worms quickly disappear from a mixed population under lab conditions designed to mimic the worm's harsh native environment. These hormones act to manage the trade-offs needed for growth, survival, and reproduction. Since energy is usually a limited resource, energy spent on reproduction, growth, or daily activity is not being spent on the self-maintenance needed to minimize the impacts of aging. As environmental conditions are variable, the levels of these hormones can be adjusted to maximize the ability to cope with the conditions. These findings suggest that hormonal manipulation could have dramatic effects on aging though important trade-offs may be involved (Table 1).

CELL SENESCENCE

Leonard Hayflick noted in the 1960s that primary cell lines divided a limited number of times before cell senescence or cell death results. It is thought that the Hayflick limit reflects the loss of telomeres and activation of p53 (Campisi, 2003). Telomeres are repetitive sequences found at the end of chromosomes that are needed to prevent shortening of chromosomes during DNA replication. An enzyme known as *telomerase* is able to maintain telomeres after cell division by synthesizing and adding these repeats to the end of the chromosome. Mice express telomerase in all tissues, but in humans, the expression is much more limited, with expression in germ cells and a limited number of stem cells.

One function of telomeres is to protect the ends of chromosomes through the recruitment of telomere-binding proteins that prevent the end from triggering the double strand break–repair mechanism, producing the activation of p53 and break–repair enzymes. p53 either halts cell division to allow repair before DNA replication or can result in cell death via apoptosis. In cells that have lost telomeres due to multiple rounds of DNA replication without repair by telomerase, the chromosomal ends now behave as a bare DNA end and activate p53. In contrast to double strand DNA breaks, the chromosome end without telomeres cannot be repaired. Hence, p53 activation becomes permanent and results in permanent cell senescence or in some cases in cell death. In older people, it is likely that in tissues, like skin, that have frequent cell division but no telomerase, some of the cells have lost enough telomeres to become senescent (Table 1). Besides being unable to divide, senescent cells often show changes in gene expression resulting in alterations in the secretion of growth factors and synthesis of extracellular matrix, which can have harmful effects on other nonsenescent cells in a tissue.

Finding ways to prevent or reverse cell senescence could be an attractive target for antiaging therapies (Table 1). For example, the activation of telomerase in tissue culture cells that usually lack the enzyme has been shown to prevent cellular senescence. However, cancer cells also activate telomerase during oncogenesis, and telomerase inhibitors are being studied as an anticancer therapy (Campisi, 2003). Hence, alterations in cellular senescence pathways would have to be carried out selectively as the senescence pathways also represent cellular mechanisms to prevent the development of cancer.

CALORIC RESTRICTION

Caloric restriction is an almost uniformly effective means of increasing lifespan of animal species (Koubova and Guarente, 2003). This manipulation involves decreasing the calorie intake by 40–60% compared with *ad lib* fed animals while providing adequate calories and nutrients to prevent malnutrition (Table 1). Animals treated with caloric restriction show an average increase in lifespan of 30–40% compared with control animals and a slowing of the phenotypic changes of aging. Additionally, restricted animals develop age-associated disease and disability at later ages relative to *ad lib* fed animals. The presumed effectiveness and simplicity of caloric restriction make it an attractive antiaging approach for humans. However, caloric restriction also likely results in significant feelings of hunger, which ultimately limits the applicability and desirability of this approach. Consequently, there is intense interest in understanding the mechanisms underlying the caloric restriction response as a means to develop ways to uncouple caloric restriction from the beneficial effects.

While the exact mechanism of action of caloric restriction is unknown, there is evidence to support the presence of several mechanisms (Koubova and Guarente, 2003). It is also definitely possible that the currently identified mechanisms are all secondary to an unknown process. Animals undergoing caloric restriction show changes in metabolism resulting in declines in the production of reactive oxygen species. This decline along with increases in protein turnover results in decreases in the levels of proteins showing oxidative damage. Additionally, changes in metabolism accompany a change in energy utilization from glucose to fatty acid-derived ketone bodies. Several prominent hormonal changes that accompany this switch in mammals are significant reductions in insulin, growth hormone, and IGF-1 production. Prolonged caloric restriction also produces a reduction in fat mass due to the consumption of fat calories. The reduced fat mass probably also causes a dramatic change in the production of a variety of known and unknown fat-derived hormones. Future experiments with lower animals should help determine whether the hormonal and metabolic changes accompanying caloric restriction play a cause or effect role.

An important clue in the study of caloric restriction came from work with the *sir2* gene in yeast (Koubova and Guarente, 2003). This gene was originally identified as a mutation that increases the reproductive lifespan of yeast. The *sir2* gene encodes a (nicotinamide adenosine dinucleotide) NAD-dependent histone and protein de-acetylase, which is able to remove acetyl groups from specific lysine residues in the presence of the co-factor NAD+. At least in yeast, *sir2* appears to play a role in mediating the antiaging effects of caloric restriction. Caloric restriction results in the induction of enzymes that convert nicotinamide to NAD. Nicotinamide is generated by the de-acetylation reaction when the acetyl group is transferred from lysine to NAD. Nicotinamide is also a potent noncompetitive inhibitor of *sir2*. Hence, the conversion of nicotinamide to NAD removes an inhibitor of *sir2* and increases the available substrate for the reaction. Interestingly, resveratrol, which is a plant polyphenol found in red wine, was identified as a potent *in vitro* activator of *sir2*, and was subsequently shown to greatly increase the yeast lifespan (Howitz *et al.*, 2003). For yeast, resveratrol is able to mediate these effects independent of caloric restriction, suggesting that it acts like a caloric restriction mimetic (Table 1). It will be interesting to determine if *sir2* homologs in people and mammals play similar roles in the responses to caloric restriction. If so, there is the exciting possibility that the effects of red wine in people, like the prevention of cardiovascular and neurologic disease or cancer prevention, are due to caloric restriction mimetic effects mediated through mammalian *sir2* proteins.

DATA FOR CURRENT THERAPIES

No current antiaging therapy has been shown to either slow aging or reverse the effects of aging in people (Olshansky *et al.*, 2002). However, even this statement has some significant limitations as none of the currently touted antiaging

therapies have been tested in clinical studies, such as a randomized controlled trial, specifically designed to address whether these drugs act as antiaging therapies. These conclusions have been largely based upon the lack of effectiveness of antiaging therapies in trials often designed for purposes only peripherally related to antiaging. For example, antioxidant vitamins have been tested in large long-term studies designed to address whether these vitamins can be used to prevent diseases such as cardiovascular disease or specific types of cancer (Thomas, 2004). While both cardiovascular disease and cancer are both aging-associated diseases, neither of these diseases is synonymous with aging, as some people will live an entire life without developing either disease. Growth hormone comes closest to being studied in human clinical trials designed to test its effect on aging (Vance, 2003). Several trials have given growth hormone to older subjects to assess the effects of the drug on strength, stamina, and body composition. These studies have been limited by small study sizes and a short duration of treatment. Plus, questions can be asked about whether assessing strength, stamina, and body composition are appropriate or the best measures of the aging phenotype.

This discussion illustrates a major stumbling block that scientists, physicians, antiaging medicine practitioners, and pharmaceutical companies interested in developing antiaging therapies will need to contend with, which is the lack of a convenient and widely accepted means of testing candidate therapies. It is unrealistic to expect that candidate therapies will undergo the long-term trials lasting for several decades to definitively prove effects on aging or its direct effects on people. These trials need large sample sizes, likely needing to be multicenter to exclude geographic and lifestyle effects, and extended trial times to conclusively show differences between control and treated groups. However, the cost of starting such a trial would likely be prohibitive, and the danger is that sufficient patients would drop out, relocate, or develop medical conditions violating inclusion criteria so that in the end the data could be useless. An important research goal in the near future is to develop widely accepted surrogate markers for aging that would allow the testing of antiaging therapies in a more rapid fashion, looking for changes in surrogate markers as opposed to long-term effects on aging (Baker and Sprott, 1988). While this means of testing would be less satisfying, it would ultimately be much more practical.

The remainder of this section will review the data for several types of currently touted antiaging therapies: antioxidants, growth hormone, and several types of steroid hormones such as testosterone and DHEA.

ANTIOXIDANTS

As discussed earlier, there is significant evidence from experimental animals that oxidative stress contributes to organismal aging (Harman, 2003). Besides aging, there is evidence that oxidative damage is involved in age-associated diseases such as atherosclerosis, cancer, Parkinson's disease, and Alzheimer's disease (Harman, 2003). Observational studies have consistently shown that increased dietary consumption of fruits and vegetables rich in antioxidant compounds protect against the development of these age-associated diseases (Lawlor *et al.*, 2004; Thomas, 2004). However, observational studies suffer from the potential bias that changes in consumption of specific fruits and vegetables could represent a marker for an unmeasured variable that actually accounts for the observed differences (Lawlor *et al.*, 2004). Consequently, prospective clinical studies have been conducted to test whether the use of antioxidants alone alter the development or progression of specific age-related diseases (Table 1). On the basis of wide availability, low cost, and safety concerns, human studies have used pharmacologic doses of antioxidant vitamins, specifically vitamin A, the vitamin A precursor β-carotene, vitamin C, and vitamin E. An important caution is that the observational (National Health and Nutrition Examination Survey) NHANES studies have failed to demonstrate any major increase in lifespan in persons taking vitamin supplements compared to nonusers.

VITAMIN E (*see* Chapter 29, Vitamins and Minerals in the Elderly)

Vitamin E is a lipid-soluble vitamin, which is thought to act biologically as an antioxidant (Table 1). Vitamin E is most commonly given as α-tocopherol, though three other tocopherols and four tocotrienols are chemically related but have lesser biologic activity (Thomas, 2004). The dosages of vitamin E used in clinical studies have ranged from 150 IU per day to 2000 IU per day. Vitamin E is the safest of the lipid-soluble vitamins, and with high doses of vitamin E, nausea, flatulence, and diarrhea have been commonly reported. Vitamin E also raises the vitamin K requirement and can cause bleeding in patients on oral anticoagulants. The only other side effects noted have been an increase in falls in a study using demented patients and an increase in hemorrhagic stroke in older male smokers.

Prospective observational studies have found that the use of vitamin E supplements for two or more years is associated with a reduction in the risk of coronary artery disease by 20–40% in patients without preexisting coronary artery disease. However, subsequent randomized studies have produced largely negative results (Eidelman *et al.*, 2004). The Primary Prevention project, which studied patients with cardiovascular risk factors, but no history of cardiovascular disease, found no effect of vitamin E during 3.6 years of follow-up, though a beneficial effect of low-dose aspirin was seen in a separate treatment arm. Also, the α-tocopherol and β-carotene Cancer Prevention Study (ATBC), which studied male smokers in southwestern Finland, showed little to no effect of vitamin E in patients without coronary artery disease either in the development of angina or myocardial infarction. With regard to secondary prevention in patients with coronary artery disease, a subgroup

analysis of the ATBC study, the Heart Outcomes Prevention Evaluation study, the HDL-Atherosclerosis Treatment study, the MRC/BHF Heart Protection Study, the Women's Angiographic Vitamin and Estrogen Study (WAVES), and the Italian GISSI study showed no effect of vitamin E supplementation on cardiac outcomes. In contrast, the smaller Cambridge Heart Antioxidant Study showed a roughly 50% reduction in recurrent myocardial infarction. Also, patients on chronic hemodialysis are felt to be exposed to additional oxidative stress due to dialysis, and the Secondary Prevention with Antioxidants of Cardiovascular Disease in End-stage Renal Disease (SPACE) study, which included a majority of patients with coronary artery disease, showed a roughly 50% reduction in all cardiovascular endpoints and a greater reduction in myocardial infarction. A smaller number of studies have evaluated the effects of vitamin E on atherosclerosis at other sites and with most finding no evidence for benefit. Two studies evaluating the progression of carotid atherosclerosis via ultrasound over 3 to 4.5 years found no effect of vitamin E on intimal thickening, though the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study found a reduction in thickening in men treated with a combination of vitamin E and vitamin C. Subgroup analyses from the ATBC study found no protective benefit for vitamin E on the development of abdominal aortic aneurysm or peripheral vascular disease. Finally, results from the HDL-Atherosclerosis study suggests that the use of an antioxidant cocktail including vitamin E could be harmful in patients with normal low-density lipoprotein (LDL) and low HDL levels treated with niacin and simvastatin, as the use of the antioxidants blunted the effects of niacin and simvastatin on raising HDL, reducing progression of atherosclerosis, and reducing cardiovascular events (Brown *et al.*, 2001). Similarly, the Women's Angiographic Vitamin and Estrogen study found that the use of vitamin E and C supplements had no effect on the progression of coronary artery narrowing, but significantly increased the chances of death from cardiovascular causes. In summary, there is little evidence for a benefit of vitamin E in the primary or secondary prevention of cardiovascular disease (Eidelman *et al.*, 2004). However, on the basis of current evidence, it may be reasonable to use vitamin E in patients receiving chronic hemodialysis.

Vitamin E has also been studied with regard to stroke, cancer, Alzheimer's disease, cataracts, and age-related macular degeneration. The effects of vitamin E supplementation on stroke were studied using data from the ATBC study. While vitamin E was associated with an overall higher risk of hemorrhagic stroke, both hypertensive patients and hypertensive patients with diabetes had a decreased risk of cerebral infarction. However, the hypertensive patients without diabetes had an elevated risk of subarachnoid hemorrhage that was not seen in diabetic patients. It is not clear at this time if these data represent a protective effect of vitamin E for hypertensive and diabetic patients. Several studies have examined the effects of vitamin E on the development of cancer with largely negative results. In smokers, the ATBC study found no effect on the development of lung cancer, an increase in the incidence of stomach cancer, and fewer cases of prostate and colorectal cancer (The α-Tocopherol β-Carotene Cancer Prevention Study Group, 1994). Follow-up studies of vitamin E in the prevention of colorectal cancer have produced mixed results. One study found no effect of vitamin E on the development of bladder cancer. One study has found no effect of vitamin E on the development of breast cancer. The decrease in prostate cancer seen in the ATBC study has been suggested to be due in part to lowered serum androgen levels as patients receiving vitamin E had significantly lower serum levels of testosterone and androstenedione. There is weak data supporting the use of vitamin E for delaying the progression of Alzheimer's disease as one study evaluated the effectiveness of vitamin E in patients with Alzheimer's disease of moderate severity (Sano *et al.*, 1997). The raw data showed no benefit from the use of vitamin E; however, the placebo group scored significantly higher on the entry mini-mental state examination (MMSE), making comparison difficult. When the baseline MMSE score was used as a covariate in interpreting the data, a significant delay was observed in the composite end point of time to death, institutionalization, loss of ability to perform two of three basic activities of daily living (ADL's), or development of severe dementia (670 days versus 440 days). Treatment of smokers as part of the ATBC trial with vitamin E for 6 years had no effect on the incidence of age-related macular degeneration at the end of the study. However, the Age-related Eye Disease study found that treatment of patients with preexisting age-related macular degeneration, with a combination of antioxidants including vitamin E resulted in a decrease in the progression to advanced macular degeneration (AREDSRG, 2001). However, another study found no effect on the progression of age-related macular degeneration with the use of a vitamin E supplement alone. With regard to cataract formation, one study found no effect of an antioxidant regimen including vitamin E, and another study found no effect of vitamin E alone on the development of cataracts. The Roche European American Cataract Trial, which used an antioxidant mixture including vitamin E, found a small decrease in the growth rate of cataracts, though this was more pronounced with patients enrolled at the US site and not with patients enrolled at the UK site. In conclusion, there is little evidence that the use of vitamin E has a protective effect in the development of cancer and little evidence that vitamin E is useful in slowing the progression of Alzheimer's disease. The use of vitamin E as part of a combination of antioxidants appears promising for slowing the progression of age-related macular degeneration, but not for the prevention of cataract.

The effect of vitamin E on respiratory infections has also been investigated. In a post-hoc analysis of the ATBC study, the use of vitamin E was found to have no effect on the development of pneumonia requiring hospitalization. A small study found that the use of a multivitamin supplement including vitamin E might improve the response to influenza vaccination. However, in a community-based study, the use of a vitamin E supplement had no effect on the incidence of upper respiratory tract infections (URI) and actually seemed to increase the severity and duration of symptoms during a URI (Graat *et al.*, 2002).

VITAMIN A (*see* Chapter 29, Vitamins and Minerals in the Elderly)

Vitamin A belongs to a group of over 600 naturally occurring compounds known as *carotenoids*. All of the carotenoids have antioxidant activity (Table 1), but only around 50 of the carotenoids have provitamin A activity, which means that they can be converted in the body to vitamin A (Thomas, 2004). The main dietary carotenoids are β-carotene, which is a vitamin A precursor, and lycopene, which has potent antioxidant properties but does not have provitamin A activity. Vitamin A also has additional biologic roles. Specifically, vitamin A is metabolized to retinol and plays a key role in vision as part of the rhodopsin protein that converts light to electrical signals in photoreceptor cells. Additionally, several vitamin A metabolites act as hormones and play important roles in the development as well as the regulation of cell growth and differentiation. These metabolites, known as *retinoids,* act as hormones via interactions with several retinoic acid receptors, which bind DNA and alter gene expression in response to hormone binding in a manner similar to thyroid hormone receptors.

The recommended daily allowance (RDA) for vitamin A is 5000 IU (1.5 mg) per day, with an intake of 10 000 IU per day that was felt to be safe. Several recent studies have raised concerns that chronic vitamin A consumption in the 10 000 IU range per day can worsen osteoporosis and result in an elevated risk of hip fracture in postmenopausal women (Feskanich *et al.*, 2002). This may be due in part to an increased production of parathyroid hormone (PTH) with resultant hypercalcemia. In addition to concerns about the effects on osteoporosis, it is seen that vitamin A is the most toxic of the lipid-soluble vitamins with both acute toxicity and chronic toxicity. Acute toxicity requires the ingestion of more than 200 000 IU per day as could be seen in a drug overdose. Chronic toxicity occurs following the ingestion of 50 000 IU per day for over 3 months. Symptoms of chronic toxicity include hair loss, mouth sores, nausea and vomiting, dry skin, hepatomegaly, and increased intracranial pressure, which can result in headaches and altered mental status. In contrast, since the conversion of β-carotene is highly regulated, the consumption of the provitamin β-carotene is felt to be safe with the main adverse event being yellowing of the skin. As a result of these safety issues, most studies use β-carotene instead of vitamin A.

Observational studies showed that a higher intake of fruits and vegetables containing both β-carotene and other carotenoids is associated with lower risks of cancer and cardiovascular disease with risk reductions of up to 30% being observed (Thomas, 2004). However, randomized studies designed to test for protective effects of supplements containing β-carotene with respect to cancer and cardiovascular disease have been very disappointing.

With regard to cancer, the ATBC study found that a group of Finnish male smokers treated with β-carotene had no decrease in cancer at the major sites and instead showed increases in the incidence of lung, prostate, and stomach cancer (The α-Tocopherol β-carotene Cancer Prevention Study Group, 1994). Additionally, the β-carotene and Retinol Efficacy trial (CARET), which treated smokers, former smokers, and workers exposed to asbestosis with vitamin A and β-carotene for 4 years, was stopped prematurely partly because of a 59% increase in lung cancer mortality in the treatment arm (Omenn *et al.*, 1996). The CARET study additionally found no change in the incidence of cancer at other sites. It is especially concerning that a later study using the CARET data found that the use of the β-carotene and vitamin A supplement actually blocked the protective effects of dietary carotenoids. The Physician's Health study found no impact of β-carotene on the incidence of cancer including lung cancer during 12 years of treatment. However, this study, in contrast to ATBC and CARET, had few smokers and former smokers. Women treated with β-carotene in the Women's Health study for roughly 2 years, then followed for 2 years more, demonstrated no change in the incidence of cancer.

The effects of β-carotene supplements on cardiovascular disease have also been tested in clinical trials with the ATBC study, the Physician's Health study, the MRC/BHF Heart Protection study, the CARET study, and the Women's Health study showing no positive effect of β-carotene on cardiovascular outcomes such as myocardial infarction or stoke (Hasnain and Mooradian, 2004). Additionally, two studies using the ATBC cohort looked at the effect of β-carotene on the risk of abdominal aortic aneurysm (AAA) formation and the progression of intermittent claudication due to peripheral vascular disease and did not see benefit from supplement use. Also, results from the HDL-Atherosclerosis study suggests that the use of an antioxidant cocktail including β-carotene could be harmful in patients with normal LDL and low HDL levels treated with niacin and simvastatin, as the use of the antioxidants blunted the effects of niacin and simvastatin on raising the HDL, reducing progression of atherosclerosis, and reducing cardiovascular events (Brown *et al.*, 2001). The ATBC study also examined the effect of β-carotene use on the development of both cataracts and age-related macular degeneration and failed to find evidence of benefit. In contrast, the Age-Related Eye Disease study has found that the use of β-carotene as part of an antioxidant mixture reduced the development of advanced age-related macular degeneration in patients with preexisting disease (AREDSRG, 2001).

Hence, despite benefits seen in observational studies of a diet rich in carotenoids, there is no evidence from randomized studies for the benefits of vitamin A or β-carotene supplements with regard to cancer, cardiovascular disease, or eye disease. Additionally, there is significant evidence for potential harm with the use of supplements for smokers and former smokers with regard to lung cancer and for postmenopausal women with regard to osteoporosis.

VITAMIN C (*see* Chapter 29, Vitamins and Minerals in the Elderly)

Vitamin C is a water-soluble vitamin that is found in citrus fruits, melons, strawberries, tomatoes, peppers, leafy

vegetables, and broccoli (Thomas, 2004). In the body, vitamin C is involved in multiple oxidation-reduction reactions including the cross-linking between protein strands involved in the synthesis of collagen. Vitamin C also has antioxidant properties, and the use of vitamin C as an antiaging therapy, among other uses, was actively promoted by Nobel laureate Linus Pauling (Table 1). The RDA for vitamin C is 90 mg per day for men and 75 mg per day for women. Oral supplementation beyond these levels has progressively less effect upon the serum vitamin C levels as both the absorption from the GI tract and excretion via the urine is tightly regulated. Vitamin C has low toxicity even in large doses with the most common side effects consisting of GI upset, flatulence, and diarrhea. As vitamin C is metabolized to oxalate, there is also the possibility that high-dose supplementation could lead to oxalate kidney stones. Vitamin C supplementation, along with vitamin E supplements, may reduce the rate of *Helicobacter pylori* eradication in patients being treated with lansoprazole-amoxicillin-metronidazole triple treatment. Additionally, the use of vitamin C supplements can also be problematic in patients with diabetes, as vitamin C impairs tests measuring glucose in blood and urine. There is also a theoretical concern that supplementation with 500 mg per day of vitamin C could lead to oxidative damage to DNA as levels of 8-oxoadenine, a form of adenine produced by oxidative damage, are increased in patients taking vitamin C daily for 6 weeks (Podmore *et al.*, 1998).

Compared with vitamin A and vitamin E, few studies have evaluated vitamin C alone on the incidence of cardiovascular disease or cancer. Both the MRC/BHF Heart Protection Study and the WAVE study showed no benefit in cardiovascular outcomes with the use of an antioxidant supplement containing vitamin C (Hasnain and Mooradian, 2004). In addition, similar to vitamin E and vitamin A, the HDL-Atherosclerosis study suggested that the use of an antioxidant cocktail including vitamin C could be harmful in patients with normal LDL and low HDL levels, who are treated with niacin and simvastatin (Brown *et al.*, 2001). Preclinical studies have suggested that vitamin C supplementation may have a positive effect on vascular endothelial function and vascular tone. Hence, three studies have examined the effects of vitamin C supplementation on hypertension in patients with mixed results. A 1-month trial of vitamin C in diabetic patients showed a significant decrease in blood pressure, but an 8-month study in nondiabetic elderly patients saw a significant decline in blood pressure with supplementation only for the first month with nonsignificant effects for the remainder of the study. Additionally, a 5-year study found no effect of vitamin C on blood pressure. However, the ASAP study found that the use of a vitamin E and vitamin C supplement decreased the progression of atherosclerosis in patients with elevated serum cholesterol. Also in post-hoc analysis, a study treating patients with a multivitamin containing vitamin C found that elevation of plasma vitamin C levels correlated with reduction in C-reactive protein levels. There is little benefit observed for vitamin C in the prevention of cancer. One exception is stomach cancer where patients with preexisting precancerous lesions of the stomach had a significantly decreased rate of progression to stomach cancer when given vitamin C. Vitamin C has also been tested for age-related macular degeneration, as part of an antioxidant mixture, and shown to decrease the rate of progression to advanced macular degeneration. The Roche European American Cataract Trial, which used an antioxidant mixture including vitamin E, found a small decrease in the growth rate of cataracts, though this was more pronounced with patients enrolled at the US site and not with patients enrolled at the UK site. Vitamin C has recently been tried as a topical therapy in patients with photodamage with positive results in terms of appearance and the synthesis of new collagen. Also, the oral use of an antioxidant mixture including vitamin C may help prevent the development of photodamage. In conclusion, vitamin C has potential benefits in patients at high risk for stomach cancer, in patients with early age-related macular degeneration, and in patients with photodamage when given topically. Otherwise, there is no evidence of benefit and concerns about use related to DNA damage, kidney stones, and inhibition of lipid modifying therapy.

α-LIPOIC ACID

α-Lipoic acid is considered to be one of the most potent antioxidants, as it is able to reduce and hence regenerate other antioxidants such as vitamin E and glutathione (Table 1). Clinical studies testing α-lipoic acid are rather limited. Small studies have suggested that it may be helpful in treating diabetic neuropathy, improving diabetic control, treating photodamage of the facial skin, and retarding the progression of neurodegenerative diseases, but there is a need for further studies before this agent can be recommended.

WHAT DO THE NEGATIVE RESULTS IN CLINICAL TRIALS OF ANTIOXIDANTS MEAN?

How should the largely negative results of randomized studies of the antioxidant vitamins be interpreted? Some have suggested that these data draw into question the oxidative damage theory of aging and age-related disease while others have pointed out that the negative results could be due to reasons other than oxidative damage not being involved (Shishehbor and Hazen, 2004). For example, no dose finding studies have been carried out to determine the optimal dosages of antioxidants in people. Also, the levels of these antioxidant vitamins are regulated both in plasma and in tissues via regulation of absorption, excretion, transport, and metabolism. Hence, studies may have used inadequate doses of antioxidants, or more importantly the antioxidants studied may be unable to reach adequate levels in the proper anatomic or cellular locations. For example, a study of carotid endarterectomy patients found that use of vitamin E supplements lead to increased plasma vitamin E levels, but no increases in levels in the atheroma. An additional limitation of the current

studies is that the effectiveness of the antioxidant supplements in actually lowering markers of oxidative stress was not demonstrated. Moreover, the antioxidant vitamins chosen on the basis of dietary epidemiologic studies may not represent the antioxidants responsible for the clinical effect and in fact may not even act in patients as antioxidants. For example, a study examining the effects of vitamin E supplements on serum vitamin E levels and oxidative stress found increased serum levels of serum vitamin E in patients taking increasing doses of the vitamin, but that the increased serum levels did not translate into changes in measures of lipid peroxidation as a measure of membrane oxidative damage (Meagher *et al.*, 2001). This study calls into question both the dosages of vitamin E used in existing studies and the appropriateness of using vitamin E as an antioxidant in patients eating a standard American diet. There are also concerns about the duration of therapy, as it is unclear when antioxidants would be most effective. Most animal studies treated animals for their entire lives, whereas clinical studies have started much later, treating adult patients, often for secondary prevention. Interest in newer antioxidants, such as the catalase/superoxide dismutase mimetics, will hopefully lead to future studies designed to address both clinical concerns as well as these more practical concerns.

HORMONES AS ANTIAGING THERAPIES

As discussed earlier, it is clear that many hormones, such as growth hormone, DHEA, and sex hormones among others, change during aging, with this change usually representing a significant decline in hormone levels by old age. For some of these hormones, deficiency in younger people produces some of the symptoms felt to be associated with aging in older persons, which has lead to significant interest in the role that single or multiple relative hormone deficiencies may play in the aging phenotype (Horani and Morley, 2004).

Clinical studies have examined the effects of growth hormone, testosterone, DHEA, and estrogen/progesterone supplementation on patients (Table 1). However, many of these studies have been of short duration and used clinical end points, such as change in lean body mass instead of physical strength, gait, or ADL function, which may have questionable relevance (Horani and Morley, 2004). Furthermore, none of the hormone-replacement therapies have undergone the long-term clinical testing needed to determine if they do represent an antiaging therapy that can slow, reverse, or ameliorate the effects of aging.

GROWTH HORMONE (*see* Chapter 118, Endocrinology of Aging)

Growth hormone is a polypeptide hormone that is made by the pituitary gland and acts primarily on liver and muscle to result in the production of IGF-1, which then acts on the ultimate target tissues (Horani and Morley, 2004). Growth-hormone secretion reaches its maximum during the growth spurt accompanying puberty before beginning a steady decline of approximately 14% per decade in both men and women. Much of this decline is due to a selective reduction in the nocturnal pulsatile secretion of growth hormone, with declines in both pulse height and pulse frequency seen. Some of the changes associated with aging are reminiscent of those seen in adult patients with frank growth-hormone deficiency, such as reduction in lean body mass, increase in body fat especially abdominal obesity, decrease in muscular strength, and difficulty with cognitive functioning. These observations led Dr Daniel Rudman to suggest in the mid-1980s that during aging a growth-hormone somatopause occurs, which may contribute to the aging phenotype (Rudman, 1985). In support of this hypothesis, Rudman observed a decrease in IGF-1 levels between healthy older patients in the community and frail patients living in a nursing home setting. However, other studies have failed to find a correlation between IGF-1 levels and physical or cognitive functioning.

There has been much interest in testing the effects of supplementing growth hormone in the elderly (Table 1). Trials with patients have shown that responses to growth hormone or growth hormone secretagogues, as measured by serum IGF-1 levels, persist in the elderly. Most studies have enrolled relatively healthy patients with low baseline IGF-1 levels and have treated the patients with doses of growth hormone adjusted to produce IGF levels in patients that fall in the low to mid-normal range seen in young adults. Few long-term growth-hormone trials have been conducted with most trials ending after a few months. Treatment with growth hormone has shown increases in lean body mass, increases in skin thickness, and decreases in fat mass (Rudman *et al.*, 1990). These changes were more pronounced in elderly men than in postmenopausal women. Interestingly, the increases in muscle mass have not been accompanied by significant increases in physical strength or stamina. A recent study conducted at the national institute of health (NIH) demonstrated that there are small but synergistic increases in strength and stamina when growth hormone was combined with testosterone in men (Blackman *et al.*, 2002). Effects of growth hormone on cognition and memory have not been well studied but so far the results are mixed. Growth-hormone treatment has been shown in several studies to improve bone mineral density both with respect to total body and to the lumbar spine, but whether these increases impact on fracture risk is not known.

Growth hormone has also been tested for benefits in patients with specific acute or chronic diseases due to its anabolic actions (Ruokonen and Takala, 2002). Trials with growth hormone have suggested that it might be beneficial in burn and postoperative patients to reverse catabolism. However, trials in intensive care unit (ICU) patients have shown mixed results with a large multicenter study demonstrating a dramatic increase in mortality among treated patients. A small study suggested that treatment of patients with dilated cardiomyopathy with growth hormone lowers circulating levels of inflammatory cytokines and

improves left ventricular contractile function. This result is promising but will need to be replicated in a larger study and be linked to improvements in cardiac outcomes like functional class, hospitalization, and mortality.

Growth-hormone treatment has shown side effects of lower extremity edema, gynecomastia, carpal tunnel syndrome, arthralgias, and headache (Horani and Morley, 2004). These side effects are common and reversible with lowering of the growth-hormone dose by 25–50%. More concerning is the increase in glucose intolerance and frank diabetes seen in clinical trials with growth-hormone treatment which is due to decreases in peripheral uptake of glucose (Blackman *et al.*, 2002). Given the strong associations between insulin resistance and diabetes and cardiovascular disease, this finding may make long-term growth hormone use risky.

Growth hormone also carries two potential risks, which are: a possible increase in cancer risk given the cell growth stimulant properties of IGF-1, and a possible acceleration of aging caused by growth-hormone supplementation. With regard to cancer, several epidemiologic studies have found associations between IGF-1 levels and the risk of colon, breast, lung, and prostate cancer (Horani and Morley, 2004). With regard to aging, studies in mice suggest that increases in growth hormone and IGF-1 signaling may lead to lifespan shortening instead of prolongation. Mice deficient in growth hormone live longer than those with normal growth-hormone levels (Tatar *et al.*, 2003). Additionally, treatment of mice with supplemental growth hormone in adulthood is also associated with premature aging.

At this time, the modest benefits of growth hormone, high cost, and potential long-term risks weigh against the use of growth hormone in the elderly. Longer-term studies of growth hormone are needed to determine if the increases in muscle mass prevent decline or improve function long term, to determine the possible dangers associated with long-term use, and to compare growth hormone with less costly interventions.

TESTOSTERONE (*see* Chapter 118, Endocrinology of Aging; Chapter 121, Ovarian and Testicular Function)

Testosterone replacement for men has been advocated by some endocrinologists as well as by many in the antiaging field (Table 1). In men, testosterone levels peak during late adolescence, then decrease at a rate of roughly $100\,\mathrm{ng\,dL^{-1}}$ per decade afterwards because of decreases in testosterone production (Horani and Morley, 2004; Yialamas and Hayes, 2003). Additionally, most circulating testosterone is not bioavailable as it is bound by sex hormone-binding globulin, and the levels of sex hormone-binding globulin also increase with age. Hence, depending upon whether total or bioavailable testosterone is measured and the specific definition of hypogonadism, 10–49% of men in their fifties to sixties, 30 to 70% of men in their seventies, and 35–70% of men in their eighties have hypogonadism. Along with declines in testosterone levels, aging men experience decreases in muscle mass and strength, decreases in bone mass, increases in fat mass, decreases in sexual interest and potency, and decreases in cognitive function, which mimic similar symptoms seen in younger hypogonadal men (Horani and Morley, 2004).

Several studies have studied the supplementation of testosterone in men with low testosterone levels either via injections or via a scrotal patch, but no long-term studies have been conducted (Horani and Morley, 2004; Yialamas and Hayes, 2003). Most studies have treated older men with low testosterone levels and have shown an increase in lean body mass accompanied by a decrease in fat mass. The increase in muscle mass has usually not been accompanied by an increase in strength with the possible exception of men with very low testosterone levels, that is, less than $200\,\mathrm{ng\,dL^{-1}}$. Additionally, the increases in muscle mass have not led to improvements in frailty or functioning. Testosterone has also been found to have positive effects on markers of bone turnover, though this has not consistently led to increases in bone mineral density. This may be due to the effects of testosterone on bone being predominantly mediated through aromatization to estradiol. Sexual function has shown mixed results with supplementation, with men with lower initial testosterone levels tending to have the most significant improvements. With respect to sexual function, testosterone supplementation has shown benefit for improving libido, while for potency, conflicting results have been seen. The effects of testosterone supplementation on memory and cognitive function have also been tested with mixed results. Additionally, testosterone supplementation has not been beneficial in patients with mild cognitive impairment. There is data to suggest that testosterone replacement can improve mood, sense of well-being, and concentration, but testosterone does not improve symptoms of major depression.

Concerns have been raised regarding potential effects of supplementation on prostate and cardiovascular disease (Rhoden and Morgentaler, 2004). Studies have consistently found no connection between supplementation and the development of benign prostate hyperplasia (BPH) symptoms. A few studies have found small increases in prostate specific antigen (PSA) in elderly men receiving exogenous testosterone, though these studies have not lasted long enough and enrolled sufficient numbers to determine if this translates to an increased risk of prostate cancer. While hormone ablation has proven to be a successful treatment for prostate cancer, epidemiologic studies have not found a relationship between testosterone levels and the subsequent development of prostate cancer (Horani and Morley, 2004; Yialamas and Hayes, 2003). However, given the theoretical concern for increased development of prostate cancer or increased growth of subclinical tumors with supplementation, most advocate digital rectal examination and PSA testing prior to beginning testosterone treatment, with follow-up every 6 months (Rhoden and Morgentaler, 2004). At follow-up testing, an increase in PSA of $2\,\mathrm{ng\,ml^{-1}}$ over baseline or an increase of $0.75\,\mathrm{ng\,ml^{-1}\,year^{-1}}$ or greater should trigger the stopping of testosterone and prostate biopsy to exclude cancer. With

regard to cardiovascular disease, most studies have found that administration of testosterone leads to no change or slight decreases in the HDL cholesterol which are counterbalanced with no change or slight decreases in total cholesterol and LDL cholesterol. Additionally, testosterone causes coronary artery dilatation and has been shown to decrease angina in patients with symptomatic coronary artery disease. Other side effects include worsening of sleep apnea and erythrocytosis, which can be seen in up to 25% of patients receiving treatment. This can be easily managed either by decreasing the dose of testosterone given or by using phlebotomy or blood donation.

Despite the lack of long-term trials showing safety and effectiveness, several professional societies have recommended that men with testosterone deficiency, diagnosed by free or total testosterone, and symptoms of androgen deficiency be offered testosterone replacement after initial prostate cancer screening (Rhoden and Morgentaler, 2004). While testosterone may address some of the symptoms of aging in men, the data to support the claims made for testosterone replacement, especially for non-deficient men by some in the antiaging field, appears to be lacking.

ESTROGEN (*see* Chapter 118, Endocrinology of Aging; Chapter 121, Ovarian and Testicular Function)

The hormonal changes accompanying menopause are among the most pronounced hormone changes during aging and are frequently accompanied by prominent symptoms (Horani and Morley, 2004). Consequently, estrogen or estrogen/progesterone hormone-replacement therapy (HRT) has been available for sometime. Observational studies consistently indicated benefits for HRT beyond the treatment of menopause with a possible role in the prevention of cardiovascular disease, colorectal cancer, dementia, and osteoporosis. As a result, most physicians advocated the use of HRT, and many women opted for it, which resulted in 38% of postmenopausal women in the United States using HRT as of just a few years ago. However, the results of randomized studies did not show evidence of benefits, and in contrast, demonstrated evidence of harm with the use of HRT (Table 1). Consequently, HRT is no longer recommended for use other than for short-term treatment of menopausal symptoms, and the number of HRT users has plummeted (Grady, 2003).

Clinical studies have shown HRT to be beneficial for treating the symptoms of menopause, including hot flashes, night sweats, insomnia, vaginal dryness, and mood swings, and preventing osteoporosis (Grady, 2003). The symptoms of menopause can be treated in other ways, such as using clonidine or selective-serotonin reuptake inhibitors, but these approaches are not as effective as HRT. Osteoporosis is also effectively treated with HRT with increases in bone mineral density and decreases in fractures observed. However, osteoporosis can also be treated with either bisphosphonates or raloxifene, which is a selective modulator of estrogen receptors, with roughly equivalent effectiveness. Hence, the clearest indication for HRT would be to manage menopausal symptoms.

Much of the interest in HRT was generated by benefits with regard to the prevention of cardiovascular disease, colorectal cancer, and dementia seen in earlier observational trials. However, the randomized Heart and Estrogen/Progestin Replacement Study (HERS) and Women's Health Initiative (WHI) study have failed to demonstrate these benefits. The only possible exception is colorectal cancer, where the WHI did show a slight decrease in cases of colorectal cancer suggesting a possible benefit. In contrast, for cardiovascular disease data from HERS, WHI, the Estrogen Replacement and Atherosclerosis trial, and HERS II demonstrated that HRT could be harmful in both women with preexisting coronary artery disease and even in women without a history of cardiovascular disease, as increases in myocardial infarctions were seen during the early study years. Initially, it appeared that the increase in cardiovascular events seen in the first 1–2 years of use would be then offset by a subsequent decrease in cardiovascular events. However, data from the HERS follow-up study, HERS II, demonstrated that there was no decrease in cardiovascular events with continued use (Grady *et al.*, 2002). For dementia, the randomized Women's Health Initiative Memory Study (WHIMS) showed an increased risk of dementia with HRT use during almost 5 years of follow-up (Shumaker *et al.*, 2003). This increase in dementia could perhaps be due to an increase in vascular dementia, given the increase in stroke observed. The impact of HRT on the quality of life and mental health was also explored by using the HERS cohort. This study found that the use of HRT had no impact upon physical function, depressive symptoms, overall mental health, or measures of energy or fatigue. Only women with flushing related to menopause at the start of the study showed any improvement in mental health and depressive symptoms from the use of HRT. Overall, the physical function, depressive symptoms, overall mental health, and measures of energy or fatigue were impacted more by co-morbid illnesses and disease severity than the use of HRT. As this study occurred as part of the HERS study, which enrolled only women with documented coronary artery disease, the results may not be easily generalized to other groups of patients.

HRT users have an increased risk of endometrial cancer, venous thromboembolism, breast cancer, and gallbladder disease (Manson and Martin, 2001). The risk of endometrial cancer is limited to women taking estrogen-only HRT, as women taking estrogen and progestin combination therapy have no increase in risk. Hence, women without a history of hysterectomy should only be given combination therapy. The risk of thromboembolism is elevated by a factor of roughly 2, but since thromboembolism is rare in otherwise healthy postmenopausal women, the absolute increase in risk is still rather small. For breast cancer, the overall risk appears to be increased by 35% compared to nonusers at 5 years, and the increase in risk increases with continued use. The use of HRT also appears to increase the risk of gallbladder disease by 40–50%.

DHEA (*see* Chapter 118, Endocrinology of Aging)

Dehydroepiandrosterone or DHEA appears to be used rather widely as an antiaging treatment especially since it is widely available over the counter as a non-FDA regulated nutritional supplement (Horani and Morley, 2004). DHEA and its sulfated derivative, DHEAS, are synthesized by the adrenal cortex and at the time of maximum production represent the most abundant steroids in the body. Levels of these hormones peak in the 20s then begin a 2% per year decline such that in 80-year-old patients the levels are only 10–20% of the earlier levels (Arlt, 2004; Horani and Morley, 2004). While the functions of DHEA and DHEAS are not completely understood, it appears that these steroids have functions in both peripheral tissues and the central nervous system (CNS). In peripheral tissues, DHEA serves as a precursor for sex steroid generation and is converted to androstenedione, testosterone, and estradiol. In contrast, in the CNS, DHEA appears to have direct effects on gamma-aminobutryic acid (GABA) and *N*-methyl-D-asparate (NMDA) receptors on neurons (Arlt, 2004).

Low levels of DHEA have been correlated with an increased risk of breast cancer in premenopausal women, an increase in cardiovascular disease and mortality in elderly men in several studies, a lower bone mineral density in perimenopausal women, and a higher likelihood of depressed mood in elderly women. DHEA levels have shown no consistent relationship with cognitive decline in either sex. Hence, there is significant interest in determining whether these observations represent a correlation with aging or, alternately, are caused by lower DHEA levels (Arlt, 2004; Horani and Morley, 2004).

Several studies have supplemented DHEA levels to those seen in young adults often with 50–100 mg doses per day (Table 1). Effects of DHEA supplementation on mood and sense of well-being have been assessed in several studies with mixed but generally positive results. However, some of the studies have used nonvalidated questionnaires for patient evaluation, making comparison difficult. The effects of DHEA on bone mineral density have also been assessed with mixed results, and additionally, a small study found no effect of DHEA on markers of bone turnover. DHEA has been found to have positive effects on skin thickness and indicators such as hydration, sebum production, and pigment, though there were sex differences observed. Women had more improvement in pigmentation and sebum production, while men had more improvement in hydration and thickness. Analysis of body composition with use has found mixed results, with some studies showing increases in muscle mass and decreases in fat mass and with other studies showing no effect. The observed increases in muscle mass did not seem to translate into increases in strength except in one study. In studies, adverse effects on lipid profile, except for small decreases in HDL levels, and glycemic control were generally not seen. In fact, one study suggested that DHEA could improve insulin sensitivity in postmenopausal women. A study treating women with adrenal insufficiency with DHEA saw hepatitis as an adverse effect, but this was reversible after DHEA was discontinued. Concerns have also been raised about the use of DHEA leading to prostate cancer in men or breast or ovarian cancer in women, though no clinical studies have demonstrated an increased risk of cancer with use. In conclusion, at least in the short-term, DHEA supplementation appears safe but there is little evidence that supplementation is beneficial in older patients (Arlt, 2004; Horani and Morley, 2004). Long-term studies to establish the benefits of supplementation, assess safety, and determine the durability of benefits will be needed before routine supplementation can be recommended. Also, patients and practitioners should be aware that many of the DHEA products on the market do not contain bioavailable DHEA.

IS MANIPULATING AGING A GOOD THING TO DO?

It is rather interesting to note the amount of debate surrounding this issue in the absence of any proven means to alter human aging. However, aging is ultimately a normal part of the human life cycle, so a major issue underlying the entire antiaging field is whether treating aging itself as opposed to illness or disability linked to aging is appropriate or desirable (Fisher and Hill, 2004; Miller, 2002; President's Council on Bioethics, 2003; Turner, 2004). Plus, there is likely to never be a treatment that postpones aging indefinitely, so unlike a cure for acquired immune deficiency syndrome (AIDS) or specific cancers that would end that illness for the rest of life, an antiaging treatment would likely be only temporary in effect. Despite this, the desire to escape aging and achieve enhanced longevity seems almost innate in people, given the frequency with which this theme has appeared in literature and history. While the personal value of retarding or reversing either aging or its effects is very individual, much of its value relates back to wanting to maintain hope for the future and prolong a life that is seen as active, full, and rewarding.

Proponents of antiaging medicine put forth several arguments as to why treatments should be aggressively developed (Miller, 2002; Turner, 2004). Some point to the multitude of health benefits experienced by experimental animals treated with caloric restriction or genetic manipulations, such as reductions in age-related diseases and disability. An effective antiaging therapy offers the promise of addressing geriatric syndromes like frailty, which have proven difficult to diagnose and manage via conventional medical treatment. Alternatively, treatment started in middle age could prevent the development of neurodegenerative diseases, such as Alzheimer's disease, that are a major source of anxiety. Furthermore, a treatment that could ensure the long, active, and healthy "golden years" that working adults daydream about would have tremendous individual value. Finally, actuarial estimates show that developing "cures" for all of the major causes of death would add only a few years to the current life expectancy (Fisher and Hill, 2004). Current disease-focused medical research and practice hence could involve significant

investments of time and resources with a smaller benefit than a modestly effective antiaging therapy.

Opponents of antiaging medicine also have strong arguments (President's Council on Bioethics, 2003). While many people would like a longer and healthier life, how will the additional time be spent? People envision this time to be spent in leisure activities funded by working adults through pensions or Social Security. However, this is not financially viable and for the vast majority of people would entail working years longer than prior generations. Will a treatment that provides more time for work instead of play still be as attractive? Others worry about the shift in resources from younger people to older people that would accompany the development and use of a successful antiaging therapy. Would education and children's health still be important? Will a world with a perpetually healthy, productive, and increasingly well-trained workforce still welcome children and have a place for them as they grow up? Additionally, during the last decade, concerns have been raised about the appropriate as opposed to inappropriate use of treatments such as cancer screening, automatic implantable cardiac defibrillators, and artificial nutrition in frail, older patients. Will an antiaging therapy be used appropriately or will it add to the treatment burden placed on patients at the end of life with the accompanying human and financial costs? Finally, in a world that is increasingly populated by humans, will there be sufficient space, water, and food for everyone?

It is difficult to reconcile the two sides at this point without more information about the antiaging treatment under debate. Consequently, much of the debate has focused on conceptions of what might exist in the future, sometimes with this conception being probably unrealistic, such as lifespan gains of hundreds of years (Turner, 2004). Being concerned about the social effects of a treatment that extends lifespan to 200 years or more is very reasonable, while a treatment that extends lifespan by 5–10 years but reduces the incidence of Alzheimer's disease by 75% carries fewer ethical concerns. Clearly, the future development of the antiaging medicine field needs to be shaped by public debate, but the current climate which is clouded by hyperbole and unrealistic expectations will make this difficult.

POSSIBLE IMPACTS OF ANTIAGING THERAPIES ON GERIATRIC PRACTICE

Many wonder about the future role of geriatrics, given patient interest in antiaging therapies and the scientific breakthroughs that offer the potential to fuel the development of effective treatments. Some in the antiaging medicine field have tried to paint a dim picture for the future of geriatrics by calling the specialty "dead" because of the gains in health and longevity they feel their therapies will offer. Some in the geriatrics field have joined with biogerontology scientists to attack the safety and effectiveness of currently touted antiaging therapies. Others in the geriatrics field have questioned the wisdom of developing antiaging therapies and worry whether this would become another expensive therapy forced upon frail seniors as being "standard of care". The aura of hyperbole that surrounds some claims for current antiaging therapies and scientific breakthroughs has only further escalated the war of words and has led some to fear for the future of society were an antiaging therapy to be developed.

Clearly, the development of an effective antiaging therapy would have a profound effect on society, the practice of medicine in general, and the specialty of geriatrics, in particular. However, it is unlikely that any antiaging therapy would end the practice of geriatrics. The chances of the development of a 100% effective antiaging therapy that completely halts aging, let alone reverses aging, is rather unlikely. Instead, the antiaging therapies that will emerge are likely to face many of the same issues as therapies for heart disease, stroke, cancer, and other chronic medical conditions, namely, that the treatment will be less than 100% effective, will require continuous use, and will involve trade-offs between benefits and side effects. For example, in many experimental animals there are distinct trade-offs between longevity and fertility. Additionally, since aging involves multiple mechanisms occurring simultaneously to varying degrees in all tissues and organs, probably the best that can be expected is an antiaging therapy that slows or reverses some but not all aspects of aging. Consistent with this, even experimental animals treated with combinations of powerful genetic or drug manipulations to slow aging fail to become immortal and instead eventually age and die. As a result, geriatric patients will still exist in a world with antiaging therapies, and apart from being perhaps older and having more tales to tell, may still face many of the medical, social, and functional problems of today's patients.

Instead of ending the field of geriatrics, the development of effective antiaging therapies might very well open new opportunities to intervene in the chronic medical problems and geriatric syndromes that plague many older patients. Potentially, the treatment of older people with an antiaging treatment could be very different in terms of the dosing, routes, indications, and goals of treatment. For example, an antiaging treatment that benefits middle-aged patients might have no benefit for an old patient in terms of longevity, but short-term intensive use might be an important adjunct during peri-operative care to prevent specific complications or to assist rehabilitation. Alternately, treatments such as hormonal manipulations may emerge, which offer the potential to maximize health and vitality today at the expense of future longevity. This would obviously be a treatment only for frail, older patients as a way to finish life's final tasks or opt for continued independence instead of prolonged dependence. Finally, decisions about selecting a treatment, whether to start a treatment, and when to stop therapy will almost certainly rely upon the key principles in geriatrics of focusing on maximizing function and elucidating a patient's goals of care to help patients choose treatments consistent with these goals.

KEY POINTS

- Patients are interested in antiaging treatments, but few are currently using them. New discoveries by researchers studying aging have made the development of an effective antiaging treatment in the future a reasonable possibility.
- There is little evidence from randomized controlled trials that antioxidant vitamins prevent age-related diseases such as cardiovascular disease or cancer.
- DHEA and testosterone might be beneficial for older patients but data from long-term clinical studies to prove benefits and safety are lacking.
- Clinical studies have shown postmenopausal HRT to only be beneficial for the treatment of menopausal symptoms and osteoporosis. However, the use of HRT carries many risks, such as increased risk of breast cancer, heart attack, and dementia, which outweigh these small benefits.
- The ethical debate about the development and use of antiaging treatments is still in its early phases. A major hurdle for this area is the currently vague ideas about what an antiaging therapy might realistically do.

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Ethical Issues

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INTRODUCTION

In the past, diseases that presented in old age were seen as part of the aging process. The advent of geriatric medicine changed this, and physicians began to understand the importance of identifying pathology in old age and of treating it. All students are now taught to look for multiple pathology when assessing elderly patients. Such is the enthusiasm for this approach that the impression is sometimes given that if all the elements giving rise to multiple pathology in an old person could be successfully treated, old age itself would disappear. Similarly, the obsession of modern society with maintaining youth through such measures as creams, vitamins, exercise, and surgery may also result in a denial of aging. In view of this, we begin this chapter with a philosophical reflection on old age. Moreover, an integral vision of old age can serve as a criterion for practical judgments. Old age is an authentic period of a person's life, not simply a process of decay. It is therefore necessary to establish the general grounds of this specific phase of human life to discover the ethical task that it poses before treating problems of applied ethics which present in old age.

OLD AGE AS AN AUTHENTIC PERIOD OF HUMAN LIFE

How can the process of aging be seen as a period of growth and fulfillment rather than a period of decay and degeneration? In many traditions from ancient China to Greece, in the Hebrew and Christian Bibles, to reach old age has been regarded as a divine blessing. In contrast to the high cultures of antiquity that were based on tradition, modern society, with its ever-increasing speed of change, does not show a similar veneration of old age. Yet, because of greater affluence and medical advances, the ancient wish for a long life has come to be true for the majority of the population in the industrialized countries. The average span of life has been lengthened by up to a third, and yet there is a lack of a definite place in the structures of society for the citizens who reach this phase. Is there a solution to this dilemma? What cultural wisdom needs to be redeveloped under the changed conditions of the modern world? In order to answer these questions, the intrinsic values of an age that has matured beyond the mid-life concerns of building a career and raising a family need to be identified. These values are based on the general traits that mark human existence (Auer, 1995a).

PRINCIPLES OF HUMAN PERSONHOOD

Human personhood can be characterized by three elements: autonomy, finitude, and historicity. While all three are present in each stage of human existence, they acquire a new edge in the final stage of life.

Autonomy

Autonomy can be defined as self-government by reason. It is closely linked to the "Categorical Imperative", which, in its humanistic formulation demands to "always treat humanity, whether in your own person or in the person of any other, never simply as a means, but always at the same time as an end" (Kant, 1964a). This principle underlines both the dignity of each person, and their mutual obligation to recognize the equal value of the other. Autonomy, according to Kant, is a mandate to direct oneself by the law of reason in one's life, not simply a "freedom to choose". It cannot be used to defend individualism free of obligations to others, and it includes duties toward oneself. (For a critical discussion of the difference between Kant's original concept of autonomy and current biomedical and consumerist understandings which owe more to JS Mill's emphasis on individuality that civil liberty has to protect against "the tyranny of the majority", (see O'Neill, 2002)). However,

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one problem remains with regard to the ethics of aging. If the unconditional recognition of the other is based on the dignity of each person's freedom, how can this prerequisite be verified? What about fellow human beings whose mental condition undermines their autonomy? It is important to examine the precise wording of Kant's foundation of dignity and understand its implications. (In the kingdom of ends, everything has either a price or a dignity. If it has a price, something else can be put in its place as an equivalent; if it is exalted above all price and so admits of no equivalent, then it has a dignity... that which constitutes the sole condition under which anything can be an end in itself has not merely a relative value – that is, a price – but has intrinsic value – that is, dignity (Kant 1964b)).

(1) It is a transcendental definition of dignity that refers to "conditions of the possibility", as opposed to an empirical one, such as being free of pain. But what is "that which constitutes the sole condition under which anything can be an end in itself"? It is not rationality as such, but in its moral orientation. "Morality is the only condition under which a rational being can be an end in himself... Therefore morality and humanity insofar as it is capable of morality, is the only ground of the dignity of human nature and of every rational nature". The decisive factor for being able to call human beings autonomous is their *capability* for morality, a faculty that can, but does not need to be actualized. It is crucial for the ethics of the end as well as of the beginning of human life that here, quite a different criterion for personhood is established than, for example, consciousness, agency, or the ability to have and voice interests. (2) Kant's understanding of dignity makes it clear that dignity is not at our disposal. Concretely, the specific difference between "having dignity" and "having a price" means that we cannot take stock of our own or anybody else's life. Kant's prohibition of suicide as irreconcilable with autonomy shows the distance between the concept he inaugurated and its current biomedical and cultural use. (3) It contradicts "teleological" arguments for which the empirical capacity to pursue the "goals and purposes of life" is the decisive criterion. Here, the gulf that separates Kant's arguments from some natural law positions becomes visible.

We will return to some practical consequences of Kant's ethics of dignity in the sections on euthanasia.

Finitude

It was the Danish religious philosopher Soren Kierkegaard who made the precarious position of human freedom the basis of his philosophical anthropology. In his *Sickness unto Death* (1849), the human self is portrayed as a "synthesis of the infinite and the finite, of the temporal and the eternal, of freedom and necessity" (Kierkegaard, 1968). The infinity of our intentions contrasts sharply with the finitude of our span of life which cuts short our ability to realize these intentions. Cultural tendencies toward maximizing instant gratification collude with the individual's desire to avoid the unwelcome perspective of death rather than take a reflective stance. The alternative then for a person who has reached this final phase of life lies between affirming and denying his or her own life history.

Historicity

Historicity is the third characteristic of human personhood. Humanity and each individual member spell out their essence only through the course of history and whilst the historical constellations are shared, a person's uniqueness can only be appraised through his response to these conditions. Each phase of life has its own criteria of fulfillment. The task posed for the older person by the historicity of human life is to welcome the opportunity to be accountable both to oneself and to younger generations by being a living link with the past.

THE ETHICAL TASK OF OLD AGE

The demand of choosing for oneself accompanies human existence in all the turns of a person's life. This task may be evaded in middle age by absorbing one's energies totally in a career or in other activities but in old age this cannot be done as easily. The choice at this age then is to either affirm or deny the way one's life has been shaped by oneself and others (Auer, 1995b). If this striving for the unity of one's life is accepted as the genuine task of old age, then the reminiscing of older people should not be discounted as merely a peculiar trait of the aged. Their challenge is to confront the choices they made and that were made for them and to appropriate them.

Attempts to concentrate solely on the present can even be seen as a move to escape from the task of integrating one's life, as one form of denial of a personal journey inevitably marked by disadvantages, wrong turns, and losses. It is a sign of mental health and moral courage to face up to these aspects of one's past and to be reconciled to them. Reconciliation and appropriation do not denote passive and resigned acceptance. They can refer to the ability or wisdom to sustain the tension of opposing poles in one's personality (Erikson *et al.*, 1986). The way in which a person meets the challenges of this phase is crucial for the fulfillment or failure of the whole of his or her life. Currently, many physicians in geriatric medicine see their role purely in terms of treating illness in old age. However, there is also a deeper role and this is the task of accompanying an aging person in a manner that allows him or her to accept and shape the final phase of life in a conscious and personal way (Schockenhoff, 1993).

AGEISM AND RESOURCE ALLOCATION

If one accepts that old age has its own task as outlined above, then one must reject philosophies which value only

that period of life when one can take advantage of what have been described as "the prime benefits of life" (Callahan, 1987). The American ethicist Daniel Callahan has been a particular advocate of the concept of a natural lifespan beyond which life-extending treatment would automatically be excluded (Callahan, 1987; Homet and Holstein, 1990). According to Callahan, the natural lifespan ends in most people by the late 70s or early 80s. This attitude of ascribing little or no value to the final years of life has been driven largely by a desire to ration health care resources in this age-group. Over the last decade, a great emphasis has been placed on the need to find morally acceptable criteria on which finite resources can be distributed in the face of infinite needs (Elford, 1987). However, it is a task that should apply to resources not just for the elderly but for all citizens. One of the more sophisticated approaches was developed by Daniels's application of Rawls's theory of justice to resource allocation for the elderly which argues for rationing on the basis of lifetime fair shares of health care (Daniels, 1985). The "prudential lifespan" argument allows for factors such as the redistribution of funds from life-extending measures to nursing home care and domiciliary support for disabled elderly persons. Although this model cannot be accused of ageism, neither can it be declared as just, as it does not address the larger frame of resource decisions made in the political system. In other words, any proposal on rationing can be just only if it forms part of an overall system that is just and when adequate resources are provided in the first place (Wicclair, 1993). The advantage of the Rawlsian approach is that it demands fair access for rich and poor alike to the basic goods of health care. However, in the absence of any just and fair scheme of resource distribution, steps must be taken to safeguard a certain level of resource for the needs of the elderly so that a generation in society that has contributed its share to the political economy will not be short changed.

The issue of resource allocation is not just one of finance. It is also a question of the social imagination being prepared to envisage structures which do justice to the fact that medicine is now more than ever dealing with an aging population. It is a challenge for modern society that is weak on prevention and strong on repair to redirect its health care structures toward a more community-based approach. If the ethical debate on resource allocation is constructed in terms of justified interests of different groups, the starting point is already biased (Mieth, 1993). What is needed is a step back from the financial constraints and a critical analysis of the prevailing priorities. The proper use of resources may then be achieved by adapting the health care system to take into account the needs of an aging society.

It could be argued that too much attention has been paid to the whole subject of rationing health care in the elderly, whereas the real debate should focus on the adequate provision of health care in this age-group. It is still the case that many elderly people who suffer from stroke are deprived of full access to multidisciplinary rehabilitation. In other instances, rehabilitation has to be truncated after an inadequate period because of pressure on resources. Older patients may have to opt for long-term institutional care as they never reach their full potential for recovery. The amount of waste and unnecessary spending in some areas of health is also a matter for ethical consideration, particularly when there is a question of further rationing in an already deprived area. The growth of evidence-based medicine and surgery should be of considerable assistance in addressing these very important issues.

Age has been described as a risk factor for inadequate treatment (Wetle, 1987). Greenfield *et al.* demonstrated that the elderly are more likely to be given inadequate therapy for breast cancer even when controlling for stage of disease, functional status, and comorbidity (Greenfield *et al.*, 1987). It cannot be ethical to make decisions on treatment purely on the basis of chronological age. Frequently, negative characteristics are attributed to older people and this stereotyping is allowed to cloud decisions on individual patients. Negative imagery is also often used when describing elderly patients in ethical debates. Overemphasis on the extremes of disability and incompetence in discussions on issues relating to the elderly can be prejudicial to the majority of elderly people when decisions are made on resource allocation and also prejudicial to the individual when decisions are being made on treatment options. The majority of the elderly reside at home, with only 5% in institutional care (National Council on Ageing & Older People, 2000) (*see* **Chapter 161, Health and Care for Older People in the United Kingdom**). Case histories often describe 75-year-olds with various problems as if this was the extreme of life. Yet, the average life expectancy of a woman of this age is now well over a decade – a very significant length of life at any age.

The physician has an ethical responsibility to defend the best interests of the patient at all times and to act as advocate when required. This may mean, for instance, resisting pressure to discharge patients prematurely because the length of stay has exceeded a figure dictated by the DRGs (diagnostic related groups), or some other system. It must be emphasized that DRG lengths of stay are only mean figures and that the needs of the individual patient must always be paramount. The ethic of patient advocacy is perceived to be under threat in Western society where physicians are increasingly expected to assume the role of a gatekeeper. Under these circumstances, and in view of the demographic shifts in Western societies to low birth rates and greater longevity, there is a real danger that an ethic of cost-effectiveness could assume an unhealthy dominance in many areas of medicine relating to older people (Jecker, 1994).

QUALITY OF LIFE

Clinical decisions in the older age-group are increasingly influenced by perceptions of the individual's quality of life (QoL) either before treatment or as anticipated after treatment. Yet assessments of QoL have been shown to be very subjective. The work of Pearlman *et al.* has demonstrated that physicians who decided to intubate and physicians who decided not to intubate the same hypothetical individual both

used assessment of the QoL as the major factor in making their decision (Pearlman *et al.*, 1982). The use of QoL assessment in decision making is ethically justifiable provided that the assessor does not inject a negative bias on the basis of the patient's age. QoL assessments interface with ethical considerations on many issues relating to the elderly and it has been the subject of substantial research. When physicians make judgments on the quality of life of their patients they do so usually on the basis of their qualifications as human beings rather than on their scientific knowledge. When they do make judgments from a professional perspective the criteria are often heavily influenced by a disease-related focus which concentrates on symptoms and limitations. Moreover, there are many papers in the literature which demonstrate major disagreements in many areas of medicine between assessments of patients, QoL provided by patients themselves and those provided by their doctors (Slevin *et al.*, 1988). Some more recently developed QoL measures seek to incorporate the individual perspective on QoL in the overall evaluation. For instance, in the Schedule for the Evaluation of Individual Quality of Life (SEIQoL), it is the individual him/herself who decides what QoL means, thus avoiding the problem of a professionally defined QoL (McGee, 1996).

EUTHANASIA

It is claimed that a natural consequence of the principle of autonomy, as outlined, is to be in control of the time and conditions of one's own death. It is up to the individuals concerned to decide on the value of their own existence to themselves. It can be argued that it is equally reprehensible to force a person who is willing to die to continue to live as it would be to condemn someone to die although he or she wants to live. Ethically, the question is whether these two options are as symmetrical as they are presented. The presupposition of this interpretation of the autonomy argument is that a person's life only needs to be protected as long as the individual deems it valuable. However, this position has been challenged on a number of grounds.

It is debatable whether the concept of autonomy can be stretched to include the ability to control one's own death. In its classical formulation, human finitude was the frame in which every act of autonomous self-determination was set. Both the beginning and the end of one's life were seen as a matter of contingency over which one had no choice. The question is which view is more in keeping with human freedom: to anticipate and "overtake" one's death by administering it oneself, or to accept one's death as one of the conditions of human freedom and make it one's own. The first view identifies the concept of human dignity with one's scope of power, whereas the second insists that dignity reaches beyond it since it also consists in taking a stance toward what happens to oneself. In the latter perspective, it is argued, the ultimate loss of power experienced in dying cannot negate dignity since this concept refers exactly to what is not at our disposal. A similar point is made when life itself is seen as something that has its own ethically relevant value quite apart from the value that the individual might ascribe to it. There is an ongoing debate on how its value relates to other values such as freedom, truth, or solidarity. The question as to whether there is true "symmetry" between forcing someone either to live or to die against his or her will has also been debated on temporal grounds. Even if forced, life is only for a definite period, whereas death is indefinite and irrevocable (Lamb, 1988).

In recent years, there has been much debate on the possible broader social consequences of legalizing voluntary euthanasia. Many fears have been articulated, including the fear that respect for human life in its ailing and dying forms will be eroded, and that the solidarity between generations, which is expressed in caring for the elderly, may be sacrificed for the demands of the healthy active members of society (*see* **Chapter 152, Carers and the Role of the Family**). It has also been suggested that the introduction of voluntary euthanasia may shift the burden of proof toward having to make a case for one's continuing interest in life in order to achieve medical treatment. It is claimed that an older person may feel obliged to calculate the value of his or her life against the costs to the family and to the state for maintaining it (Randall, 1993). In this latter situation, the decision to opt for euthanasia may not have been arrived at autonomously but be driven by the assumed expectations of others (Jecker, 1994).

Another controversial area relates to any implied obligation of medical personnel to assist patients who wish to die. It is argued that this would conflict with generally accepted statements of professional ethics and, in particular, with the principle of nonmaleficence. It is also claimed that making it legal for doctors to assist voluntary euthanasia could undermine the general attitude of trust the public has in their physicians who are expected to act in favor of life (Randall, 1993). The advocates of voluntary euthanasia see these fears as being greatly exaggerated by its opponents. However, others argue that even if the consequences are only feared their gravity is such that it should counsel against embarking on this course (Beauchamp and Childress, 1994). There are also reports in the literature of significant abuses of legal and professional standards regarding physician-assisted deaths in the Netherlands. These reports appear to substantiate the concerns of those physicians and ethicists who worry about the possibility of a "slippery slope" phenomenon if Western societies move to legalize physician-assisted death even under very restricted circumstances (Jecker, 1994; Pijnenborg *et al.*, 1993; Biggar, 2004).

Euthanasia has been legalized in the Netherlands and Belgium. The fear has been expressed that popular acclaim for euthanasia as a solution to suffering may divert attention from the development of palliative care services. According to surveys among oncologists, requests for euthanasia are very rare. They usually stem from poor pain control, and the patients almost invariably change their minds when their physical symptoms are controlled and when they are placed in a supportive environment (Cundiff, 1992). Heintz refutes assertions that adequate palliative care renders euthanasia

redundant and he suggests that requests for euthanasia reflect people's needs to maintain a sense of "intactness" and to retain control over events (Heintz, 1994).

NONVOLUNTARY EUTHANASIA

The ethical debate with regard to the extent of medical obligations toward incompetent patients has centered on people in a persistent vegetative state (PVS). Yet the positions formulated in this context on continuing or withholding treatment or care would also be relevant for old and terminally ill patients who are comatose or confused and cannot make their preferences known. Under these conditions decisions must be made for another person on the basis of his or her own best interests. It is therefore a paternalistic or vicarious decision. The person in question lacks the very attributes of autonomy, the abilities for self-reflection, rational decision making and communication. However, the concept of autonomy might inform the quality of life judgments of the person authorized to decide on behalf of the patient. The proxy might evaluate the other's quality of life as lacking the fundamental trait that gives it value, namely, freedom. It would be in keeping with some understandings of autonomy to restrict the obligations toward the reciprocal recognition of persons to free agents. Yet it is equally possible to encompass within the demand for recognition those fellow humans who do not yet or no longer share the rationality, consciousness, and reflexivity of the fully autonomous subject. With this anticipatory, asymmetric, innovative understanding of recognition, comatose and PVS patients would enjoy equal rights to care and treatment on the basis of their being members of the human species. This approach, which gives respect and protection to human life also in its incompetent stages, has been dismissed by some as "speciesism", whereas its advocates describe it as the highest ethical principle (Meilaender, 1987). A transcendental concept of dignity is the basis of this latter argument. (In her "Explanatory Memorandum" to the "Report on the Protection of the Human Rights and Dignity of the Terminally Ill or Dying" (Council of Europe), the Austrian Rapporteur Edeltraut Gatterer specifies: "(3)... Dignity is a consequence of being human. Thus, a condition of being can by no means afford a human being its dignity nor can it ever deprive him or her of it. (4)... Pain, suffering, or weakness do not deprive a human being of his or her dignity. (5)... One possesses dignity and its subsequent rights not due to the recognition of other human beings, but due to one's descent from them ... (6) An individual's dignity can be respected or violated, yet it can neither be granted nor lost. Respect for human dignity is independent of factual reciprocity. Respect for human dignity is also due where reciprocity is not, not yet, or no longer possible (i.e. toward patients in a coma). To believe that human dignity may be divided or limited to certain stages or conditions of life is a form of disregard for human dignity.")

The position espoused by Meilaender (1987) of unconditional respect and the continuance of care for the embodied other has been criticized as "vitalism" as it seems to accord the highest value to biological human life irrespective of its possibilities of expression. Critics of this approach offer an alternative one and that is to respect physical life as a condition for the values and goals of life such as communication that transcend the biological level. From this teleological view that derives the value of life from its ability to attain its purposes and ends, they would argue that hydration and nutrition for PVS patients who can no longer "pursue life's goals" can be withdrawn (Shannon and Walter, 1993). The best interests of the patient should be the only consideration taken into account, and the only burden considered should be the burden of treatment on the patient and not the burden on the family, clinical staff, or society. This reasoning avoids the danger of social Darwinism, of sacrificing the weaker members of the community to the interests of the more powerful ones. It is thus based on a position that acknowledges the basic rights of individuals, competent or incompetent, as a limit which cannot be overridden in favor of the presumed needs of a collectivity. It is articulated in the face of a perceived danger that the aggressive use of medical technology may fail to accept the limits of human finitude.

The care of patients with no detectable mental capacity is an extreme example of the ethical principles at stake in situations of asymmetric communication where the competence to decide on further treatment has to be *referred* to a proxy. Much more frequent in geriatric medical practice would be situations where the patient's autonomy is not totally lacking, but where its degree is in doubt. Then, the principle of autonomy can conflict with the principles of beneficence and nonmaleficence. Here, apart from the assessment of the patient's competence to make decisions, difficult judgments on the quality of life also come into consideration. It is in this latter situation that differences of perspective may play a critical role. For instance, the value placed on a patient's life by a professional staff member may differ quite considerably from that of family and life-long friends who will have empathy and insights from sharing life's experiences with the person.

ADVANCE DIRECTIVES

There has been a growing interest in many countries in the concept of advance directives. In the United States, the Patient Self Determination Act (1991) requires all health care institutions to advise patients of their rights to accept or refuse medical care and to execute an advance directive. Legal frameworks for advanced directives are also in existence in Belgium, Germany, Holland, and Switzerland. Directives can take the form of a written instruction or be expressed by the appointment of a proxy to make decisions on behalf of the patient under certain circumstances. Directives of this nature have been generally well received by physicians as they decrease the possibility of legal actions over decisions made in good faith, and they extend patient autonomy (Editorial, 1992). However, reservations have been

expressed about the meaning and durability of advance directives (Emanuel and Emanuel, 1990). Advance directives are based on the assumption that patients can anticipate their choice under future circumstances when death is imminent. Danis *et al.* in a prospective study found that some patients' wishes were unstable and suggested that the advance directive should be looked upon as an instruction for future care rather than a prediction of future wishes (Danis *et al.*, 1994). Preferences for life sustaining treatments appear only to be moderately stable, and the likelihood of choosing such treatments increases with worsening health (Emanuel *et al.*, 1994; Danis *et al.*, 1994). Under these circumstances it would be important to ask patients routinely how closely they wish their health care provider to adhere to their advance directives. There may also be problems both in providing and in eliciting the necessary information to make a properly informed advance directive. The patient will be required to make decisions about potential quality of life and a range of complex possible medical interventions. The listing of potential procedures may divert attention from the overall treatment goals and may give rise to inappropriate care (Brett, 1991).

Decisions about level of care are based on a complex interaction of the benefits and burdens of different therapies with individual patient goals. Fried and Gillick have shown that there are multiple points in the course of a community-dwelling patient's final illness at which choices about level of care can be made (Fried and Gillick, 1995). During this process, a significant number of elderly patients or their surrogates choose less intensive therapy. Many of these choices relate to diagnostic procedures and therapies whose relative benefits and burdens change depending upon the patient's condition, the aims of treatment, and the availability of different options. Decisions such as these, which are intimately dependent on specific circumstances, cannot easily be made by reference to advance directives. Moreover, Fried and Gillick point out that if alternatives are consistently explained during the course of an illness, the pattern of decisions made by a previously competent patient can provide guidance for both the physician and family when the patient can no longer take part in the discussions (Fried and Gillick, 1995). Dresser and Robertson have also pointed out that it is difficult, if not impossible, for competent individuals to predict their interests in future treatment situations when they are incompetent because their needs and interests will have changed radically (Dresser and Robertson, 1989). Research has shown that directives that are overly medicalized in format are largely ineffective in practice. In view of the complexity of advance decision making, a statutory basis for advance directives may, in fact, be contrary to the purpose of exercising autonomy.

BENEFICENCE AND PATERNALISM

Health care professionals need to be aware of the danger of regarding patients and family members who challenge their opinion as incompetent, and they must question the extent to which their own values may color their professional judgments (Finucane *et al.*, 1993). The frequency of end-of-life decisions that are most strongly determined by cultural factors, such as patients' autonomy, criteria for medical futility, or legal status (euthanasia, nontreatment decisions), varies much between countries (van der Heide *et al.*, 2003). The communication framework of Charles *et al.* which defines three distinct components of decision making – information exchange, deliberation about treatment options, and responsibility for the choice – may help model the physician–patient encounter (Charles *et al.*, 1999). There is also the danger that the principle of beneficence can lead to a paternalistic attitude. Data from the SUPPORT (Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatment) project canvassed about 1000 seriously ill elderly patients and found that only approximately one-quarter had ever discussed cardiopulmonary resuscitation (CPR) with a physician (Krumholz *et al.*, 1998). Beneficence must be balanced against a patient's right to take risks. There should always be respect for the personhood of others and patients must not be seen as problems but as persons with problems. The dignity of the individual is promoted through informed consent and opportunities for choice and risk taking (Everett, 1993). For instance, an elderly person considered to be at risk may wish to keep on living unsupervised and less protected in his or her own home instead of moving to a nursing home.

However, despite its potential abuse in situations of unequal power the principle of beneficence testifies to a society's concern for the elderly. Beneficence as an ethical principle is being eroded in a number of Western countries where doctors are being encouraged to regard their patients as customers (Randall, 1993). Under these circumstances it should not be surprising if the ethics of the market place begin to find a place at the patient's bedside.

MEDICAL FUTILITY

Most physicians accept that it is reasonable to withhold therapy when treatment offers potentially little benefit but might impose great burdens on a patient (Luchins and Hanrahan, 1993). This acceptance is borne out by the widespread introduction of "do not resuscitate" (DNR) policies in hospitals and nursing homes. However, it needs to be kept in mind that the presence of a DNR order may affect physicians' willingness to order a variety of treatments not related to CPR, and physicians should elicit additional information about patients' treatment goals to inform these decisions (Beach and Morrison, 2002; Zweig *et al.*, 2004). The preeminence given to autonomy in modern society as an ethical principle can sometimes lead physicians to disregard other moral considerations and common sense when making clinical decisions. The employment of futile treatments cannot be demanded in law or by ethics and it serves no purpose to discuss in detail with dying patients treatment propositions that

are unrealistic (Finucane and Harper, 1996). The discussion of medical futility has contributed an important dimension to the ethics of decision making near the end of life by focusing attention on the questions "what are we trying to achieve?" and "are we able to do it?" (Weber and Campbell, 1996) Doctors rarely receive training on how to deal with these complex ethical issues and there is a great need for educational programs which would foster the development of appropriate skills in this area (Husebo *et al.*, 2004; Hinka *et al.*, 2002).

Some physicians appear to believe that it is obligatory to use every available medical measure, no matter how futile, in order to prolong the life of a patient unless he or she is given or has been given directions to the contrary. Other physicians allow their own judgments to be overridden by acceding to the requests of patients (or their surrogates), who demand treatment which offers no benefit (Schneiderman *et al.*, 1990). Fried and Gillick have highlighted the conflicts which arise in long-term care when surrogates demand treatments which are viewed by the clinical staff as being excessively burdensome on the patients and technically futile (Kant, 1964a). They argue that the solution to the problem is to develop institutional policies within long-term care facilities that would restrict the scope of treatment facilities that could be made by surrogates. These policies would be derived from the experiences of the multidisciplinary team and would help construct a care plan for individual patients within which the proxy would be consulted on the implementation of specific therapies.

ETHICS AND GENETIC INFORMATION

The issue of freedom comes up again with regard to genetic information. The ethical problems of predictive genetic testing for incurable disease have become more of a concern for physicians in geriatric medicine in recent years. For instance, the relatives of patients suffering from Alzheimer's disease may be faced with the choice of discovering or ignoring their own genetic status (Post, 1994). The advantages of knowing lie in the possibility of relief from fear after a negative test result or in the ability to plan one's life and one's own reproductive choices after a positive test result. Yet, even here research on sufferers from Huntington's chorea and their families has shown that the relief of those family members who find out that they have been spared the defective gene is overshadowed by a sense of loss which has been compared to survivor's guilt (Burgess, 1994). The dangers of reducing persons to the sum of their genes or even further to their own one defective gene, of social discrimination, and of workplace and insurance disadvantages are equally present. The right to privacy opposes any obligation for genetic screening. The principle of equality is also endangered when data banks display genetic risk factors of affected citizens, thus enabling staff to predict the likely course of other people's lives. What is most at risk, however, when genetic screening is prescribed rather than being left to an individual's own initiative, is the realization of freedom as spontaneity. This means being able to embark on life's journey without knowing the outcome and being able to choose courses of action like everyone else without having to grieve in advance about future loss of self in a genetically predicted dementia.

KEY POINTS

- Integrating the unity of one's life is proposed as the genuine task of old age.
- Ageism should not be a factor in determining resource allocation, and when attempting to evaluate the quality of life of an older individual one must be aware of the limitations of purely professional assessments.
- Reports appear to substantiate the concerns of physicians and ethicists about the possibility of a 'slippery slope' phenomenon following legalization for physician-assisted death even under very restricted conditions. Research has shown that advanced directives, which are overtly medicalized, are usually ineffective in practice.
- The employment of futile treatments cannot be demanded in law or by ethics, and it serves no purpose to discuss in detail treatment possibilities with dying patients, which are unrealistic.
- Genetic testing may result in positive or negative consequences for an individual and these should be explained fully when counselling with regard to genetic testing.

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Restraints and Immobility

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INTRODUCTION

Immobility is strongly associated with functional decline among older adults. Restrictive devices such as physical restraints and siderails deter mobility. Despite a growing body of literature documenting the negative consequences associated with immobilizing older adults with restrictive devices, the practice persists in both acute and long-term health care settings, where most health care providers continue to believe that restraints are an effective strategy in keeping older adults safe. This chapter provides an overview of the effects of immobility, with an emphasis on the consequences of prolonged physical restraint and restrictive siderail usage. Finally, clinical strategies and organizational approaches to replace restraints and restrictive siderails, and the evidence to support their use are presented.

IMMOBILITY

Immobility is the restriction of time spent out of bed (or chair) by medical orders, restrictive devices, chemical restraints, lack of mobility aids, human assistance, or encouragement. Immobility has been correlated with muscle atrophy, loss of muscle strength and endurance, bone loss, joint contractures, and problems with balance and coordination that lead to increased incidence of falls (Bloomfield, 1997; Covertino *et al.*, 1997; Allen *et al.*, 1999). Moreover, reduced bone mass, which is a consequence of decreased weight-bearing and physical activity, can contribute to the increased likelihood that falls will result in serious injury (Grisso *et al.*, 1991). Other secondary effects of immobility include increased risk of infection, new pressure sores, contractures, and functional incontinence. Table 1 lists the effects of immobility (Lofgren *et al.*, 1989; Frengley and Mion, 1986; Robbins *et al.*, 1987).

It is well documented that functional decline, including new walking dependence occurs in one-third to one-half of older hospitalized patients (Fortinsky *et al.*, 1999; Hirsch *et al.*, 1990; Mahoney, 1998; Mahoney *et al.*, 1998; McCusker *et al.*, 2002). Functional decline or "deconditioning" refers to the loss of the ability to perform basic activities of daily living. Attributed primarily to the effects of immobilization by "forced bed rest, immobilizing devices (e.g. catheters), restraint use, and lack of encouragement of independence in self-care", (Inouye *et al.*, 1993; p., 1353) functional decline has been correlated with numerous negative consequences. A systematic review of thirty studies examining correlates of functional decline found that between 15 and 76% of hospitalized elders experience diminished performance in at least one activity of daily living at discharge. Of those with decline at discharge, only half will recover function at three months postdischarge, and, for many, this decline will result in permanent loss of independent living (McCusker *et al.*, 2002; Fortinsky *et al.*, 1999; Sager *et al.*, 1996; Covinsky *et al.*, 1997). Functional decline is considered a profound marker of morbidity and mortality (Thomas, 2002; Walter *et al.*, 2001) resulting in longer lengths of stay, greater costs, and increased rate of nursing home (NH) placement (Fortinsky *et al.*, 1999; Inouye *et al.*, 1993; Janelli, 1995; McCusker *et al.*, 2002).

There is strong support in the literature linking prolonged physical restraint use with the consequences of immobility (Inouye *et al.*, 2000; Inouye *et al.*, 1999; Selikson *et al.*, 1988; Mahoney, 1998). This process, labeled "spiraling immobility" by Tinetti and Ginter (1988), creates a "catch-22" situation in which an older person, perceived to be at risk of falling, is restrained to prevent falling and is then unable to ambulate again, independently or safely, due to the immobilizing consequences of physical restraint. Other restrictive devices (e.g. full enclosure siderails) or practices (e.g. lack of assistance out of bed) also contribute to immobilization. Table 2 summarizes the effects of physical restraints and siderails.

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Table 1 Effects of immobility

Musculoskeletal
Muscle atrophy
Loss of muscle strength and endurance
Osteoporosis
Joint contractures
Problems with balance and coordination
Gastrointestinal
Constipation
Impaction
Integumentary
Pressure Ulcers
Respiratory
Pneumonia
Atelectasis
Cardiovascular
Deep Vein Thrombosis
Pulmonary Embolism
Orthostasis

Table 2 Negative effects of physical restraints and siderails

Musculoskeletal
Immobility
Contractures
Falls
Decreased muscle mass, tone, strength
Osteoporosis
Fractures
Rhabdomyolysis
Neurological
Brachial plexus injury
Axillary vein thrombosis
Compressive neuropathy
Cardiovascular
Stress-induced cardiac arrhythmias
Orthostasis
Dependent edema
Psychological
Depression
Agitation
Increased Confusion
Integumentary
Pressure ulcers
Skin tears, bruises, abrasions
Cellulitis
Gastrointestinal/Genitourinary
Incontinence
Constipation
Infectious Disease
Nosocomial infections
Miscellaneous
Strangulation/Death
Entrapment
Asphyxiation
Hyperthermia

PHYSICAL RESTRAINTS

Physical restraints are defined as "any manual method or physical or mechanical device, material, or equipment attached or adjacent to the individual's body that the individual cannot remove easily which restricts freedom of movement or normal access to one's body" (Centers for Medicare and Medicaid Services, 1999). Examples of physical restraints include chest/vest, pelvic, combination of wrist, mitt or ankle, as well as geriatric chairs with fixed tray tables, and cushion tables in wheelchairs. These devices are generally not easily removed by the older adult (Braun and Capezuti, 2000).

Restraint use in NHs varies among countries and institutions as demonstrated in a study comparing restraint practices in NHs in Denmark, France, Ireland, Italy, Japan, Spain, Sweden, and the United States. A chair that prevents rising was the most common form of restraint while limb restraints were the least commonly used (CMS, 2004). Trunk restraints were more prevalent in Sweden and the United States than other restraint types (Ljunggren *et al.*, 1997). In general, the study found a very low prevalence of restraint use in Denmark, Iceland, and Japan with less than 9% of NH residents restrained at any time (Ljunggren *et al.*, 1997). Between 15 and 17% of the residents were restrained in France, Italy, Sweden, and the United States. Spain demonstrated the highest usage with almost 40% of residents restrained. Restraint practice patterns were attributed to cultural backgrounds and ethical views (Ljunggren *et al.*, 1997). Another study found that 24% of older adults are restrained in Sweden (Karlsson *et al.*, 1996), and at least 49% of residents in Dutch NHs are restrained (Hamers *et al.*, 2004).

In the United States, approximately 40% of NH residents were restrained in the 1980s (Evans and Strumpf, 1989). Combined with the research and heavy regulatory oversight in the United States, the prevalence of restraint use among NH residents dropped to 13% by 1998 and almost 9% in 2003 (Health Care Financing Administration, 1998; Zinn, 1994). In addition to diminished usage, restraints employed in NHs are "less restrictive" compared to the previous decade; wheelchair cushions and seat belts are more often used than the more restrictive vest restraints. Restraint use continues to vary widely throughout the United States (Phillips *et al.*, 1996), with some regions reporting almost 20% usage (Capezuti and Talerico, 1999) while others continue with even higher usage (Castle, 2002).

Spurred by the practice shift in the NH setting, reduction in hospital physical restraint use began in the early 1990s (Frengley and Mion, 1998; Sullivan-Marx and Strumpf, 1996). In the United States, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) developed standards to help reduce physical restraints (Capezuti *et al.*, 2000; Joint Commission on Accreditation of Healthcare Organizations, 1996; Bryant and Fernald, 1997). In American hospitals, the prevalence varies from 3.4 to 24.3% in nonintensive and intensive care settings, respectively (Minnick *et al.*, 1998). Restraint use is more often employed to prevent treatment interference than to avert falls, thus arm/limb restraints prevail over chest/vest restraints (Frengley and Mion, 1998; Mion, 1996; Mion *et al.*, 1996).

SIDERAILS

Siderails, also *referred* to as bed rails, cotsides, guardrails, safety rails, or sideboards, are adjustable metal or rigid plastic bars that attach to the bed and come in a variety of sizes (e.g. full-length, 1/2 length, split rails) (Braun and Capezuti, 2000). Many NH beds include bilateral, full-length siderails, while hospital beds generally have four "half" or "split" siderails, allowing diverse combinations of rails from one upper rail to both upper and lower rails (Levine *et al.*, 2000). Siderails are defined as restraints or "restrictive" devices when used to impede a patient's ability to voluntarily get out of bed (Capezuti, 2000). Since the use of restraints in bed have been drastically reduced in both NHs and hospitals, siderails have become the most frequently used restraint to prevent older adults from independent or accidental egress from bed (O'Keefe *et al.*, 1996; Capezuti *et al.*, 2002; van Leeuwen *et al.*, 2001).

In 1992, the United States Centers for Medicare and Medicaid Services (CMS; formerly the Health Care Financing Administration, 1992) issued guidelines to NHs that classified siderails as restraints when they prevent voluntary egress (Health Care Financing Administration, 1992). These guidelines were updated in both 1997 and 1999 to emphasize that restraints are defined according to their functional application as any device, material, or equipment that inhibits mobility or change in position, and are not easily removed by the person (Department of Health and Human Services, 1997; 1999). Similarly, the 1999 CMS Hospital Conditions of Participation and 2001 JCAHO standards redefined siderail use as restraints for hospitals using this functional definition (Capezuti and Braun, 2001).

Similar to physical restraints, siderail use varies among countries and institutions. Several surveys conducted in four areas of Australia described restraint prevalence among a sample of 36 000 NH residents as ranging from 15.3 to 26% (Retsas and Crabbe, 1997). Of those restrained, the most frequently used restraints were siderails. Australian nurses, like their American counterparts, frequently restrained residents due to fear of legal retribution. Interestingly, such fears are not raised in the British literature. A study conducted in a British hospital reported that 8.4% of patients had full-length siderails raised. Despite such low usage compared to American hospitals, the researchers questioned the appropriateness of bedrails (O'Keefe *et al.*, 1996). A British medical journal editorial described the "absurd" and "distasteful" use of siderails in the United States (Anonymous, 1984). The British aversion toward siderails is traced to a 1975 policy established by the Joint Working Party of the British Geriatrics Society and the Royal College of Nursing that clearly discourages routine bedrail use (Everitt and Bridel-Nixon, 1997). In 1999, the Royal College of Nursing issued guidelines aimed at further reduction of restraints; bedrails are listed as the most likely form of restraint.

There are no national statistics available for siderail prevalence in American NHs (Braun and Capezuti, 2000), however, several studies report rates of restrictive siderail use in NHs ranging from 18 to 64% (Tinetti *et al.*, 1991; Capezuti *et al.*, 2002; Wagner *et al.*, 2003). There are also no national figures or large multisite studies that quantify current siderail usage in American hospitals, though one study reports 20% usage following siderail reduction efforts (Si and Neufeld, 1999), and another reports a prevalence rate of 30% of nighttime use among patients in medical surgical units and 67% in the critical care setting (Capezuti *et al.*, 2000). The continued use of both restraint and siderail usage is based on embedded practices of health care providers who for decades have linked these devices to patient safety and protection (Brush and Capezuti, 2001; Strumpf and Tomes, 1993).

RISK FACTORS AND JUSTIFICATION

Use of restrictive devices depends on three factors: patient characteristics, organizational attributes, and health care providers' justification. Prevalence of restrictive devices varies with age, functional status, and cognition (Strumpf *et al.*, 1998). Greater age, worsened physical health, a previous fall, and the presence of depression or other psychiatric disorders have been associated with restraint use (Frengley and Mion, 1986; Tinetti *et al.*, 1991; Berland *et al.*, 1990).

Impaired cognition is the most significant patient factor associated with restraint and siderail use (Capezuti and Talerico, 1999; Strumpf and Tomes, 1993; Castle and Mor, 1998; O'Keefe *et al.*, 1996; Capezuti *et al.*, 1996). Among ambulatory NH residents, a restraint prevalence of 37% was reported in confused residents, while nonconfused residents were virtually never restrained (Capezuti *et al.*, 1996). In one study examining continued use of physical restraints following a restraint reduction intervention, patient factors such as physical dependency, lower cognitive status, behavior, presence of treatment devices, presence of psychiatric disorders, and perceived fall risk were all significantly associated with continued restraint use. Confused older adults and elders are also the most likely to be restrained in hospitals (Sullivan-Marx *et al.*, 1999; Bourbonniere *et al.*, 2003).

Castle and colleagues reported that organizational attributes, rather than patient factors, was more predictive of restraint use after the implementation of American federal regulations for NHs. These include high nursing aide–patient ratios, reduced occupancy rates, and prospective Medicaid reimbursement (Castle *et al.*, 1997). Similarly, in hospitals, high utilization of licensed practical nurses rather than registered nurses and nurse staffing patterns on weekend shifts are strongly associated with restraint use (Bourbonniere *et al.*, 2003).

Justification for restraints is also based on the health care providers' view that these devices prevent vulnerable older adults from injury secondary to falls, behavioral symptoms, or treatment interference. The most common reason cited for restraint and siderail use is prevention of falls (Braun and Capezuti, 2000). Among the cognitively impaired who demonstrate impaired gait and diminished safety awareness, restraints, and siderails are used to prevent independent

transfer from chairs or bed. There is no empirical evidence, however, to support the use of these devices to prevent falls.

Numerous studies demonstrate a significant incidence of falls and injury among restrained confused patients in both NH and hospital settings (Capezuti *et al.*, 1996; Neufeld *et al.*, 1999; Capezuti *et al.*, 1999a; Shorr *et al.*, 2002; Tinetti *et al.*, 1992). One study prospectively observed fall-related incidents and injuries after the initiation of physical restraints among previously unrestrained ambulatory NH residents. After adjusting for confounding factors such as disorientation, physical restraint was associated with continued fall-related incidents and, most importantly, serious injury. They also found that intermittent restraint use in ambulatory residents led to increased fall-related serious injuries. The researchers concluded that the immobilizing effect of intermittent restraint use on muscle and bone strength was responsible for these results. Another study examining the relationship between restraint use and falls among 332 NH residents found that restraints were not associated with a significantly lower risk of falls or fall-related injuries (Capezuti *et al.*, 1996).

There is also no evidence to support the use of restrictive siderails to prevent falls. One NH study examined resident outcomes associated with consistent restrictive siderail status when compared to residents with no or nonrestrictive siderail use for one year (Capezuti *et al.*, 2002). Controlling for cognition, functional and behavioral status, the study found no indication of a decreased risk of falls or recurrent falls with restrictive siderail use. Similarly, a retrospective hospital-based study found that the incidence of falls from bed with siderails elevated was equal to, or higher, compared to the outcome when siderails were not elevated. Those patients with impaired cognition status were found to be the most likely to fall from bed when the siderails were elevated (van Leeuwen *et al.*, 2001). The evidence to date demonstrates the ineffectiveness of restrictive devices in prevention of falls and fall-related injuries (American Geriatrics Society, The British Geriatrics Society and The American Academy of Orthopaedic Surgeons, 2001).

Another major reason that health care providers choose restrictive devices is to reduce or control behavioral symptoms. Interestingly, although restraints are employed to "treat" these symptoms, the use of these devices is strongly correlated with physical or verbal aggression, especially among those with dementia (Talerico and Evans, 2001; Talerico *et al.*, 2002; Kolanowski *et al.*, 1994; Cohen-Mansfield and Werner, 1995). Delirium has also been found to be highly correlated with restraint use in several large-scale studies (Inouye and Charpentier, 1996; McCusker *et al.*, 2001; Morrison and Sadler, 2001). Federal regulations and JCAHO standards in the United States prohibit usage of restrictive devices to manage behavioral symptoms in NHs or medical/surgical (nonpsychiatric) care settings.

Behavioral symptoms, such as anxiety, agitation, physical aggression, and delirium, may result in patient interference with medical treatments. Treatment interference refers to both removal and manipulation of a monitoring or treatment device (e.g. feeding tubes, urinary catheters, intravenous lines, oxygen therapy) (Bryant and Fernald, 1997; Werner and Mendelson, 2001; Matthiesen *et al.*, 1996; Sullivan-Marx and Strumpf, 1996). This can be especially dangerous when the treatment or device fulfills a life-saving or life-maintaining function such as mechanical ventilatory support. Hand restraints may not prevent unplanned extubations in agitated patients (Chevron *et al.*, 1998). Some suggest that since many of those with unplanned extubations do not require reintubation, the problem lies primarily with poor adjustment of sedation (Chevron *et al.*, 1998; Tung *et al.*, 2001). Thus, restraints may be a marker of insufficient sedation that requires more attention to implementation of evidence-based guidelines for sedation of intubated patients (Slomka *et al.*, 2000; Bair *et al.*, 2000). The lack of evidence to support routine restrictive device usage to prevent falls or reduce behavioral symptoms is thus compounded by the numerous complications associated with use of these devices.

COMPLICATIONS

Use of restrictive devices is not without risk. In the 1980s and 1990s, research describing the negative physical and psychological sequelae associated with restrictive devices was the major impetus for changing the practice in hospitals and NHs (Evans and Strumpf, 1989). Psychologically, restrained older adults experience anger, humiliation, depression, and low self-esteem (Strumpf and Evans, 1988; Mion *et al.*, 1989; Happ *et al.*, 2001).

As described earlier in this chapter, the most common physical consequence of prolonged restraint or siderail use is immobility (Selikson *et al.*, 1988; Capezuti and Talerico, 1999; Inouye *et al.*, 2000; Inouye *et al.*, 1999; Mahoney, 1998). Other harmful medical outcomes associated with restraint include hyperthermia (Greenland and Southwick, 1978), rhabdomyolysis (Lahmeyer and Stock, 1983), brachial plexus injury (Scott and Gross, 1989), axillary vein thrombosis (Skeen *et al.*, 1993), compressive neuropathy (Vogel and Bromberg, 1990), Hess' sign (O'Connor *et al.*, 2003) and stress-induced cardiac arrhythmias (Robinson *et al.*, 1993). Siderails have been identified as a vector for nosocomial infections. Microbes cultured from siderails have been associated with subsequent integumentary and respiratory ailments (Mayer *et al.*, 2003; Noskin *et al.*, 1995; Bonten *et al.*, 1996; Podnos *et al.*, 2001; Slaughter *et al.*, 1996; Catalano *et al.*, 1999).

Although less common, restrictive devices have also been associated with fatal outcomes such as strangulation and asphyxiation (Robinson *et al.*, 1993; Katz, 1987; Miles and Irvine, 1992). Strangulation can occur due to improper application of a vest restraint or when an older adult with a vest restraint slips between two half rails. Asphyxiation results from gravitational chest compression when an older adult is suspended by a vest or belt restraint in a bed or chair (Joint Commission on Accreditation of Healthcare Organizations, 1998; Miles and Irvine, 1991). Asphyxiation can also occur if a person is entrapped within siderails. Between 1995

and 2001, the United States Food and Drug Administration (FDA) received 381 reports of siderail entrapment cases. Of these, 237 were deaths, 73 were injuries, and 71 cases were of near misses (Joint Commission on Accreditation of Healthcare Organizations, 2002).

Entrapments occur through the siderail bars; through the space between split siderails; between the siderail and mattress; or between the head or footboard, siderail, and mattress (Parker and Miles, 1997; Miles, 2002). All deaths involved entrapment of the head, neck, or thorax, while most injuries involved fractures, cuts, and abrasions. Persons at high risk for entrapment include older adults with preexisting conditions such as altered mental status (dementia or delirium), restlessness, lack of muscle control, or a combination of these factors (Parker and Miles, 1997; Todd, 1997). More recently, cases of asphyxiation deaths due to patients becoming trapped between therapeutic overlay air mattresses and siderails have been reported (Miles, 2002). These negative consequences associated with restraint use have served as an impetus for research aimed at identifying alternative "best-practices" to restrictive devices.

OUTCOMES OF RESTRICTIVE DEVICE REDUCTION

In the last decade, several studies have described the relationship between restraint reduction and fall/ injury rates. In a longitudinal prospective study comparing NH residents in one facility before and after a restraint reduction intervention, physical restraint use was reduced from 31.2 to 1.6%; however, no major differences were found in the number of residents falling before and after the reduction of physical restraint use (Werner *et al.*, 1994). Evans *et al.* (1997) and reported the results of the first controlled clinical trial testing the effectiveness of two interventions designed to reduce restraint use (a six-month education program and the educational program combined with unit-based, individualized consultation by a gerontologic advanced practice nurse compared to a control NH). All three NHs reduced restraint use; however, only the education plus consultation NH significantly reduced their usage. Secondary analyses of this dataset demonstrated that there was no statistically significant correlation between restraint removal/reduction and increases in falls or fall-related minor injuries (Capezuti *et al.*, 1998a). Another secondary analysis of the Evans *et al.* data set also found no increase in falls following nighttime restraint removal among a subsample of confused NH residents (Capezuti *et al.*, 1999a).

Fall-related injuries are rarely examined statistically, since the number of subjects required is often cost-prohibitive for most research studies. Fall-related minor injury in older persons, however, has significant implications for morbidity and mortality (Grisso *et al.*, 1992). Capezuti and colleagues reported that continued restraint use (versus restraint removal) was the only characteristic to significantly increase risk of fall-related minor injury (bruises, abrasions, certain sprains, and other soft tissue injuries that do not result in hospitalization or bed rest) (Capezuti *et al.*, 1998a). A two-year prospective project of 2075 patients residing in sixteen diverse NHs in California, Michigan, New York, and North Carolina evaluated the effect of an educational intervention for physical restraint reduction. The 90% reduction in restraint use (from 41% to 4%) resulted in an increase in minor injuries and falls; however, there was significant decrease in the percentage of injuries of moderate to serious severity (Neufeld *et al.*, 1999).

The only published studies of fall outcomes following siderail reduction have been conducted in rehabilitation settings (Hanger *et al.*, 1999; Si and Neufeld, 1999). One study conducted in a 25-bed rehabilitation unit within a NH found that the reduction in restrictive siderails resulted in no significant increase in fall rates and there were fewer injuries in those without siderails (Hanger *et al.*, 1999). A second study was conducted in several rehabilitation units of a New Zealand hospital, where the researchers evaluated fall outcomes following a policy change and educational effort aimed at siderail reduction (Si and Neufeld, 1999). There was a significant decrease in siderail usage and yet the bed-related fall rate did not significantly change. In summary, results from studies of restrictive device reduction efforts have demonstrated that they can be removed without negative consequences.

Although none of the studies represent a randomized clinical trial, no significant differences were found in the number of patients falling prior to or following the reduction of physical restraint use. Further, the studies demonstrate no statistically significant difference in falls compared with historical controls when restrictive siderails are removed (Agostini *et al.*, 2001). The positive outcomes associated with restrictive device reduction may represent not only the safe removal of these devices, but also the effectiveness of interventions aimed at decreasing the likelihood of falling. Both individual alternatives and the most effective strategies used to implement these interventions have been evaluated in the NH and hospital settings.

APPROACHES TO REDUCE RESTRICTIVE DEVICE USAGE

Restrictive devices are used to reduce injury risk from falls or treatment interferences that are often due to multiple causative factors. Optimal resolution also requires multiple interventions that rely on coordination via interdisciplinary dialogue and action (Tinetti *et al.*, 1995). Comprehensive assessment, coordinated care management and individualized intervention plans targeting identified risk factors have been found to be the most successful strategies to reduce restrictive devices.

"Best practice" approaches to restrictive device reduction are described in the literature or by professional associations as clinical practice guidelines for use in the NH and acute-care hospital (Joint Commission on Accreditation of

Healthcare Organizations, 1998; van Leeuwen *et al.*, 2001; American Geriatrics Society, 1991; Happ, 2000b; Maccioli *et al.*, 2003; Hospital Bed Safety Workgroup, 2003). Professional standards as well as governmental and accreditation regulations emphasize that a decision to use physical restraints and/or siderails should only be made after clinical evaluation and interdisciplinary care planning determines the purpose for the intervention. Further, alternatives to restrictive devices should be implemented and evaluated prior to initiating restraints. Thus, a thorough assessment is necessary in the following situations: in patients who are at high risk for application of physical restraints or siderails, prior to and during restraint reduction efforts, or in situations where the provider is assessing the continued need for restrictive devices. In restrained NH residents, an assessment should be conducted at least quarterly by the primary care provider to determine necessity for continued use.

Multidisciplinary collaboration with physical and occupational therapists, nurses, dieticians, and social workers is an important part of any evaluation regarding the use of restraints and siderails. The following section describes clinical approaches that reduce the likelihood of restrictive device use.

Promote Mobility

Maintaining physical activity in hospitalized elders and NH residents is crucial to preventing the harmful effects of immobility. Careful consideration is warranted when ordering bed rest. The ability to move around in bed and to transfer and ambulate safely is also important to prevent falls and injuries (Capezuti *et al.*, 1999b). The assessment should include the patient's ability to perform the skills necessary for safe mobility and transfer, including the need for assistance and assistive devices (e.g. walkers, canes). If there are problems, then a physical or occupational therapist should be consulted. Rehabilitation therapists may suggest transfer devices to enable or assist in safe transfer and promote stability when standing, which may include a trapeze, transfer pole or bar, or raised 1/4 or 1/2 length siderail directly attached to or adjacent to the top of the bed. These may also serve as assistive bed mobility devices.

Certain activities by nursing staff promote mobility, such as encouraging or assisting patients with changing position in bed, transferring out of bed to chair, and ambulating. Organized group walks around the nursing unit at specific times during the day promote mobility, provide diversion, and involve the patient in his/her recovery. Bed and toilet seat height should be adjusted to the patient's lower leg height in order to promote safe transfers.

Facilitate Observation

Patients at risk for falls or treatment interference should be located in rooms closer to the nurses' station to facilitate observation. Increased time spent out of rooms in hallways, at the nurses' station or in "day" rooms with other patients facilitates surveillance. Encourage family and friends to visit, especially during mealtimes and treatments, and at night to provide both meaningful distraction and assistance to staff. Providing communal dining when possible serves both this purpose and an opportunity for socialization.

Volunteers or paid "companions" can be an alternative when families are unable to stay with the patient (Jenson *et al.*, 1998). This, however, can incur significant cost and must be evaluated in relationship to the potential harm of leaving a patient alone. Patients at high risk for restraint, (i.e. confused persons unable to safely transfer/ambulate unassisted, who are agitated and have removed treatment devices, restraints, or have gotten out of bed with raised siderails) are also those most likely to suffer a restraint/siderail-related injury. When these patients are restrained, they require frequent observation, especially in a new environment. Thus, these patients may need to be targeted for "one-on-one" companions if other means of increased staff surveillance are not available.

An open intercom, "nursery", or "baby" monitor will promote audio contact between staff and patients. Video monitoring may be an option in some hospitals as well as motion-sensor lights or alarms in rooms that alert staff that the resident is ambulating in their room unassisted. Elopement control devices are used for "wanderers" who may walk into unsafe areas. They work similarly to department store tag devices. An identification tag placed on the resident's wrist or ankle will signal the detection monitoring device when the resident walks by it, thus, setting off the alarm (Connell, 1996).

Devices such as alarms are useful; however, staff must be available to respond quickly. There are various types of alarms: pressure-sensor activated, cord activated, and patient worn (Health Devices, 2004). Pressure-sensor activated alarms sound as shifts in weight occur on a pad placed over the mattress or chair cushion. Alarms worn by patients (usually on the thigh) are sensitive to resident position changes (e.g. from lying to standing). A call bell or similar device attached to clothing will sound when the resident rises and disconnects the cord from the socket. Alarms require individualization of delay time to minimize number of "false" alarms. Also, the occurrence of "nuisance" sounds may increase agitation in confused patients. Models that sound at the nurses' station, light a hallway call system, or activate a staff pager, reduce nuisance alarms (Health Devices, 2004). Some alarms include a voice "alarm", that is, a tape recorder that can play an individualized message addressing the resident by name and calmly instructing the resident to remain in his/her chair until the nurse arrives to provide assistance.

Offer Activities

It is not surprising that patients will attempt to ambulate without assistance or remove tubes when isolated in a

room without meaningful activities. Television is not the solution; it may actually incite agitation. Recreation or activities therapists, if available, should be consulted. Family members can be encouraged to bring in favorite music or videotapes, hobby materials (e.g. knitting), or other items that the patient may enjoy. Staff or volunteers can also provide activities based on the patient's interest and cognitive level, for example, towels to fold, magazines to read, and stuffed animals to hold. Activities also serve to distract patients from "investigating" or disturbing tubes, monitor, leads, and dressings (Happ, 2000a). A well-tested hospital model employing volunteers focuses on reduction of delirium risk factors by, among others, promoting mobility and providing meaningful activities. The Hospital Elder Life Program has demonstrated significantly reduced cognitive and functional decline in at-risk older hospitalized patients (Inouye *et al.*, 1999; Inouye *et al.*, 2000; Rizzo *et al.*, 2001).

Maintain Continence

Often patients attempt to ambulate unassisted because of an urgent need to void. Assess the patient's ability to safely use a bedside commode or urinal, which may reduce the distance traveled to the bathroom and thus reduce falls. Query the patient or nursing staff regarding a change in toileting patterns including nocturia, bowel and bladder incontinence, which may require further evaluation by a continence specialist.

Promote Comfort

Comfort needs include equipment individualized to a patient's medical/functional condition and appropriate pain management. Providing comfortable and individualized seating is a major challenge, especially in the NH setting. In the NH, most patients spend the majority of their day in a wheelchair (Capezuti and Lawson, 1999). The prevalence of wheelchairs in NHs exceeds 50% and many patients spend their time in chairs that do not fit, and are uncomfortable (Brechtelsbauer and Louie, 1999). Wheelchairs were originally designed for transport only, not for long periods of sitting. Their sling-back seats do not provide the appropriate support. Seating problems such as poor back support; wheelchair being too tall, heavy, or wide; foot rests too high; and the hammock effect of the sling, are all associated with pain and agitation (Rader *et al.*, 2000). All these effects increase the risk for falling and use of physical restraints, since the patient may be uncomfortable and attempt to transfer unsafely.

Many products are available to adapt the chair to the individual resident's seating needs. Other adaptations for the wheelchair include a wedge cushion inserted under the resident's buttocks and thighs, which tilt the resident backward. A wedge seat prevents the resident from sliding forward. Similarly, leaning to the side is corrected with lateral supports or cushions. Stroke victims with hemiplegia (one-sided weakness) are at risk for shoulder subluxation if the weakened arm slips off the side of the chair. This can be prevented with devices attached to a wheelchair: an arm trough, elevated armrest, lateral arm support, or half tray. Patients who spend considerable time in a wheelchair are to be referred to a physical or occupational therapist for a seating evaluation (Rader *et al.*, 2000; Rader *et al.*, 1999).

The patient's comfort in bed can be improved with an overlay mattress cushion, air mattress, or sheepskin mattress pads (Capezuti *et al.*, 1999b). Pillows and leg separator cushions can be used to facilitate positioning. Heel pads and/or bed cradles are good choices for those with significant peripheral vascular disease or pressure ulcers. Refer to a Wound, Ostomy, and Continence (WOC) Nurse or physical therapist for device recommendations.

Chronic and acute pain is common in older adults; however, many are inadequately treated. Pain management includes both administration of analgesics and other treatments (e.g. physical rehabilitation exercise, relaxation training, biofeedback, hot packs). Older adults with dementia have the same types of medical conditions as nondemented elders; however, evidence suggests that they are unlikely to receive pain treatment (Scherder *et al.*, 1999). Thus, routinely scheduled (not "PRN," whenever necessary) analgesia is strongly recommended (American Geriatrics Society, 1998). Since they may not be able to report or describe pain, observation of nonverbal signs of pain is necessary. These indicators of pain include facial grimacing, physical aggression, pacing, uncooperativeness, or restless behavior (Decker and Perry, 2003).

Investigate Mental Status Changes

A change in mental status is important to assess since impaired cognitive status is highly associated with increased risk of falling and use of restrictive devices (van Doorn *et al.*, 2003). New behavioral symptoms (e.g. physical aggression) should first trigger a comprehensive evaluation of potential physical and/or environmental causes prior to initiating any physical or chemical restraint. Behavior can be used to communicate a need, threat to self-esteem, a state of arousal, or anxiety (Strumpf *et al.*, 1998). Confused older adults may not be able to express verbally that they are experiencing pain or have the need to use, for example, the toilet, and will often act out with some form of behavior (e.g. anxiety, wandering) (Talerico *et al.*, 1995; Miller and Talerico, 2002). Complicated cases will require a geriatric psychiatry consultation.

Address Fall Risk

If a patient has been deemed at risk of falls or has fallen, then a thorough evaluation of amenable risk factors contributing to future risk should be conducted. Falls, especially sudden

onset of repeated falls, may indicate underlying acute pathology, such as infection, hypoglycemia, or dehydration (Gray-Miceli *et al.*, 1994). Evaluation of fall risk is addressed by several professional associations and academic institutions: the American Geriatrics Society, The British Geriatrics Society and The American Academy of Orthopaedic Surgeons (2001), American Medical Directors Association and The American Health Care Association (1998) and the University of Iowa (Ledford, 1996) and Assessing Care of Vulnerable Elders (ACOVE) Project on Falls Prevention (Rubenstein *et al.*, 2001).

Medications are associated with an increased risk for falling. All types of psychoactive medications (hypnotics, antidepressants, anxiolytics, benzodiazepines, and antipsychotics) have consistently been linked to an increased risk for falling (Yip and Cumming, 1994) due to the risk for adverse side effects such as syncope and orthostasis (Thapa *et al.*, 1995; Beers, 1997; Leipzig *et al.*, 1999). Ray *et al.* (2000) identified benzodiazepine users in NH residents having a rate of falls 44% greater than those not taking benzodiazepines. Additionally, fall risk increased with a higher dose of benzodiazepine use. Those on antidepressants, both tricyclic antidepressants and selective serotonin-reuptake inhibitors have a higher risk for falls when compared to nonusers (Thapa *et al.*, 1998; Thapa *et al.*, 1995). Thus, prescription of these medications must be carefully balanced against the risk of falls and related injuries. A general rule of geriatric pharmacology is to minimize the number of medications, assess the risk and benefit of each medication, and use those medications with the shortest half-life, least centrally acting or least associated with hypotension, and at the lowest effective dose. A pharmacist may be consulted to uncover potential drug–drug interactions and to make suggestions regarding inappropriate drug usage.

Environmental modifications may reduce falls. For example, a nonskid mat placed at the side of the bed and/or toilet and raised-tread socks can reduce the likelihood of slipping (Capezuti *et al.*, 1998b). For those patients unable to stand safely but who may accidentally roll out of or unsafely exit from bed, bed bumpers on mattress edges, concave mattresses, pillows, "swimming pool noodles" or rolled blankets under the mattress edge demarcate bed perimeters (Capezuti and Lawson, 1999).

Reduce Injury Risk

Since falling onto hard surfaces may increase the likelihood of fractures, a bedside cushion such as an exercise mat or an egg crate foam mattress may be used to reduce impact (Capezuti *et al.*, 1999b). Hip protector pads are the best studied single intervention strategy for fall-related injury prevention among high-risk older adults. Hip protectors are pads held in place next to the greater trochanter that reduce the force transmitted in a fall (Cameron, 2002). There exists several, large-scale, randomized, and controlled clinical trials that demonstrate a strong association between reduced hip fracture rates and hip pad usage (Cameron *et al.*, 2001; Kannus *et al.*, 2000). Compliance with wearing the hip protectors, however, is a significant problem due to discomfort and poor fit (Parker *et al.*, 2002). Incontinent NH residents experience discomfort when wearing the garment (Wallace *et al.*, 1993; Ross *et al.*, 1993).

For residents with a history of climbing around or over siderails, reducing the risk of an entrapment injury is paramount. Since restraint-related deaths can occur in less than a few minutes, these devices necessitate increased, not decreased staff observation. Inspect bed frames, siderails, and mattresses to identify possible entrapment areas (Parker and Miles, 1997; Hospital Bed Safety Workgroup, 2003).

Address Treatment Interference

Discomfort caused by unstable tube placement can increase the chances of self-removal or disruption of tube performance. Commercial tube holders to stabilize Foley catheters, intravenous lines, and feeding, drainage, and endotracheal tubes should be used (Capezuti and Wexler, 2003). Waterproof tape can decrease accidental extubations (Tominaga *et al.*, 1995). Devices can be camouflaged by hiding them under cloth (e.g. abdominal binder), undergarments or clothing, sheets, or blankets, to divert the patient's attention from a treatment. Infusion sites can be covered with commercial holders, bandages, or stockinettes (Capezuti and Wexler, 2003). For confused patients who "pick" or who are seeking tactile stimulation, provide fabric, stuffed animals, or an activity apron. Finally, periodically assess the need for any treatment like bladder catheterization or intravenous fluids; determine if it can be discontinued or if a less invasive treatment can replace it (Strumpf *et al.*, 1998).

CONCLUSION

In summary, physical restraints and restrictive siderails play a limited role in providing medical care to frail older patients. Rather, use of restraints and siderails leads to the harmful effects of immobility. Several studies have demonstrated that restraints and siderails can be removed without negative consequences.

Primary care providers can reduce the use of physical restraints and restrictive siderails by conducting a careful assessment and implementing appropriate individualized interventions. The use of nonrestrictive measures has been correlated with positive patient outcomes and helps to promote mobility and functional recovery. Most of these products, however, have not been prospectively evaluated in large randomized clinical trials for their individual contribution to reduction of falls or treatment interference (Agostini *et al.*, 2001; American Geriatrics Society, The British Geriatrics Society and The American Academy of Orthopaedic Surgeons, 2001). Further research on the efficacy of individual interventions that replace restrictive devices and improve mobility is still needed (Capezuti, 2004).

KEY POINTS

- Immobility is correlated with functional decline, which is considered a profound marker of morbidity and mortality.
- There is strong support in the literature linking physical restraint and restrictive siderail use with the consequences of immobility.
- The continued use of both restraint and siderail usage is based on embedded practices of health care providers who for decades have linked these devices to patient safety and protection.
- Restrictive devices are associated with numerous negative outcomes, including strangulation and asphyxiation.
- Research demonstrates that restrictive devices can be safely eliminated.

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Centenarians

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AN OPTIMISTIC VIEW

The prevalent notion that "the older you get, the sicker you get" often leads the lay public to assume that those who achieve exceptional longevity must have numerous age-related illnesses that translate into a very poor quality of life. Among researchers and clinicians, the observation that the prevalence and incidence of dementia increases with age, leads many to assume that dementia is inevitable for those who survive to age 100 and older (Ebly *et al.*, 1994; Thomassen *et al.*, 1998). For example, the East Boston Study indicated that almost 50% of people over the age of 85 have Alzheimer's disease (Evans *et al.*, 1989; Hebert *et al.*, 1995). Over the past decade or so, however, significant light has been shed on this assumption with a number of nonagenarian and centenarian studies addressing the prevalence and incidence of dementia amongst the oldest old; these are summarized in Table 1.

As most of the studies noted in Table 1 indicate, dementia is not inevitable with very old age. Conservatively, approximately 20% of centenarians are cognitively intact. Among centenarians who have some form of cognitive impairment, in one study, over 90% of these individuals compressed the time that they experienced functional impairment well into their 90s (Hitt *et al.*, 1999). The Heidelberg Centenarian Study recently proposed that those who develop dementia at extreme age have a shorter period of functional decline prior to the end of their lives (Kliegel *et al.*, 2004). Thus, centenarians are of interest in the study of dementia not only for the fact that some of them escape dementia, but also because most of them markedly delay in clinically expressing the disease until very late in their exceptionally long lives.

COMPRESSION OF MORBIDITY VERSUS DISABILITY

The compression of functional impairment toward the end of life that is observed among centenarians would at first glance appear to be consistent with James Fries's compression-of-morbidity hypothesis (Vita *et al.*, 1998). Fries proposes that as the limit of human lifespan is approached, the onset and duration of lethal diseases associated with aging must be compressed toward the end of life (Fries, 1980). While we found that functional impairment was compressed toward the end of life among centenarians, we noted, however, that some centenarians had long histories of an age-related disease. Perhaps an unusual adaptive capacity or functional reserve allowed some of these persons to live a long time with what normally would be considered a debilitating, if not fatal, disease while delaying its attendant morbidity and death by as much as decades (Lee, 2003; Richards and Sacker, 2003; Scarmeas and Stern, 2003; Stern, 2003; Wilson *et al.*, 2003).

To explore this hypothesis in our centenarian sample, we conducted a retrospective cohort study exploring the timing of age-related diseases amongst individuals achieving exceptional old age (Evert *et al.*, 2003). Three profiles emerged from the analysis of health history data. Forty-two percent of the participants were "survivors," in whom at least one of the 12 most common age-associated diseases was diagnosed before the age of 80. Forty-five percent were "delayers," in whom one of these age-associated diseases was diagnosed at or after the age of 80, which was beyond the average life expectancy for their birth cohort. Thirteen percent were "escapers," who attained their 100th birthdays without diagnosis of any of the 10 age-associated diseases studied. That most centenarians appear to be functionally independent through their early 90s suggests the possibility that "survivors" and "delayers" are better able to cope with illnesses and remain functionally independent compared to the average aging population. Thus, in the case of centenarians, it may be more accurate to note a compression of disability rather than a compression of morbidity. As would be expected, this is not generally the case with illnesses associated with high mortality risks. When examining only the most lethal diseases of the elderly such as heart disease, non-skin cancer, and stroke, 87% of males and 83% of females delayed or escaped these

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Table 1 Studies addressing the prevalence or incidence of dementia amongst the oldest old

Study	Comments
Dutch population–based centenarian study	10 centenarians in a population of 100 000 people were all noted to have clinically evident dementia (Thomassen *et al.*, 1999). Expansion of the study to a population of 250 000 led to finding 15 of 17 centenarians as having dementia (Blansjaar *et al.*, 2000).
Swedish population–based study of people age ≥77	The prevalence of dementia amongst the 94 subjects age ≥95 was 48% (30% for men and 50% for women) (von Strauss *et al.*, 1999).
Canadian Study of Health and Aging	Dementia prevalence of subjects age ≥95 ($n = 104$) was 58%. The rate of increase in prevalence slowed at very advanced ages (Ebly *et al.*, 1994).
Study of Japanese Americans in King County, Washington	Dementia prevalence for subjects age ≥95 was 74% (Graves *et al.*, 1996).
MRC-ALPHA Study, of older people in Liverpool	Dementia prevalence amongst centenarians was 47% (Copeland *et al.*, 1999).
Northern Italian Centenarian Study	Dementia was diagnosed in 62% of 92 centenarians (Ravaglia *et al.*, 1999).
Finnish population-based centenarian study	56% of 179 centenarians had cognitive impairment (Sobel *et al.*, 1995).
Meta-analysis of nine epidemiologic studies of dementia among people age ≥80	Prevalence of dementia leveled off at around age 95 at a rate of 40% (Ritchie and Kildea, 1995).
New England Centenarian (population-based) Study	Cognitive impairment prevalence was 79% (Silver *et al.*, 2001).
Danish Centenarian Study	Dementia prevalence was 67% (Andersen-Ranberg *et al.*, 2001).
Coordinated study of dementia prevalence among centenarians in Sweden, Georgia (US), and Japan	Dementia prevalences ranged from 40% to 63% (Hagberg *et al.*, 2001).
Heidelberg Centenarian Study	Cognitive impairment prevalence was 75% (Kliegel *et al.*, 2004).
French Centenarian Study	Dementia prevalence was 65% among female and 42% among male centenarians (Robine *et al.*, 2003).

diseases (relatively few centenarians were "survivors" with such diseases). These results suggest there may be multiple routes to achieving exceptional longevity. The survivor, delayer, and escaper profiles represent different centenarian phenotypes, and probably different genotypes as well. The categorization of centenarians into these and other groupings (for example, cognitively intact persons or smokers without smoking-related illnesses) should prove useful in the study of factors that determine exceptional longevity.

NATURE VERSUS NURTURE

The relative contribution of environmental and genetic influences to life expectancy has been a source of debate. Assessing heritability in 10 505 Swedish twin pairs reared together and apart, Ljungquist *et al.* (1998) attributed 35% of the variance in longevity to genetic influences and 65% of the variance to nonshared environmental effects. Other twin studies indicate heritability estimates of life expectancy between 25% and 30% (Herskind *et al.*, 1996; McGue *et al.*, 1993). A study of 1655 old order Amish subjects born between 1749 and 1890 and surviving beyond age 30 resulted in a heritability calculation for life span of 0.25 (Mitchell *et al.*, 2001). These studies support the contention that the life spans of average humans with their average set of genetic polymorphisms are differentiated primarily by their habits and environments. Supporting this idea is a study of Seventh Day Adventists. In contrast to the American average life expectancy of 78 years, the average life expectancy of Seventh Day Adventists is 88 years. Because of their religious beliefs, members of this religious faith maintain optimal health habits such as not smoking, a vegetarian diet, regular exercise, and maintenance of a lean body mass that translate into the addition of 10 years to their average life expectancy as compared to other Americans (Fraser and Shavlik, 2001). Given that in the United States, 75% of persons are overweight and one-third are obese (Fontaine *et al.*, 2003), far too many persons still use tobacco (Wechsler *et al.*, 1998) and far too few persons regularly exercise (Wei *et al.*, 1999), it is no wonder that our average life expectancy is about 10 years less than what our average set of genes should be able to achieve for us.

Of course, there are exceptions to the rule. There are individuals who have genetic profiles with or without prerequisite environmental exposures that predispose them to diseases at younger ages. There is also a component of luck, which good or bad, plays a role in life expectancy. And finally, there is the possibility that there exist genetic and environmental factors that facilitate the ability to live to ages significantly older than what the average set of genetic and environmental exposures normally allow. Because the oldest individuals in the twin studies were in their early to mid-80s, those studies provide information about heritability of average life expectancy, but not of substantially older ages, for example, age 100 and older. As discussed below, to survive the 15 or more years beyond what our average set of genetic variations is capable of achieving for us, it appears that people need to have benefited from a relatively rare combination of what might be not-so-rare environmental, behavioral, and genetic characteristics, which are often shared within families.

Studying Mormon pedigrees from the Utah Population Database, Kerber *et al.* (2001) investigated the impact of family history upon the longevity of 78 994 individuals who achieved at least the age of 65. The relative risk of survival (λ_s) calculated for siblings of probands achieving the 97th percentile of "excess longevity" (for males this corresponded with an age of 95, and for women with an age of 97) was 2.30. Recurrence risks among more distant relatives in the Mormon pedigrees remained significantly greater than 1.0 for numerous classes of relatives, leading

to the conclusion that single-gene effects were at play in this survival advantage. The Mormon study findings closely agree with a study of the Icelandic population in which first-degree relatives of those living to the 95th percentile of surviving age were almost twice as likely to also live to the 95th percentile of survival compared with controls (Gudmundsson *et al.*, 2000). Both research groups asserted that the range of recurrent relative risks that they observed indicated a substantial genetic component to exceptional longevity.

To further explore the genetic aspects of exceptional old age, Perls *et al.* analyzed the pedigrees of 444 centenarian families in the United States that included 2092 siblings of centenarians (Perls *et al.*, 2002a). Survival was compared to 1900 birth cohort survival data from the US Social Security Administration. As shown in Figure 1, female siblings had death rates at all ages that were about one-half the national level; male siblings had a similar advantage at most ages, though diminished somewhat during adolescence and young adulthood. The siblings had an average age of death of 76.7 for females and 70.4 for males compared to 58.3 and 51.5 for the general population. Even after accounting for race and education, the net survival advantage of siblings of centenarians was found to be 16 years greater than the general population.

Siblings might share environmental and behavioral factors early in life that have strong effects throughout life. It would make sense that some of these effects are primarily responsible for the shared survival advantage up to middle age. Recent evidence of effects of early life conditions on adult morbidity and mortality points to the importance of adopting a life course perspective in studies of chronic morbidity and mortality in later life as well as in investigations of exceptional longevity (Barker, 1998; Blackwell *et al.*, 2001; Costa, 2000; Elford *et al.*, 1991; Elo, 1998; Hall and Peekham, 1997; Kuh and Ben-Shlomo, 1997; Mosley and Gray, 1993). Characteristics of childhood environment are not only associated with morbidity and mortality at middle age, but they have also been found to predict survival to extreme old age (Preston *et al.*, 2003, 1998). Stone (2002) analyzed effects of childhood conditions on survival to extreme old age among cohorts born during the late nineteenth century. Key factors predicting survival from childhood to age 110 plus for these individuals, most of whom were born between 1870 and 1889, were farm residence, presence of both parents in the household, American-born parents, family ownership of its dwelling, residence in a rural area and residence in the non-South; characteristics similar to those that had been previously shown to predict survival to age 85 (Preston *et al.*, 2003, 1998).

In general, however, environmental characteristics such as socioeconomic status, lifestyle, and region of residence, are likely to diverge as siblings grow older. Thus, if the survival advantage of the siblings of centenarians is primarily due to environmental factors, that advantage should decline with age. In contrast, the stability of relative risk for death across a wide age range suggests that the advantage is due more to genetic than to environmental factors.

Whereas death rates reflect the current death rate at a moment in time, survival probability reflects the cumulative experience of death up to that moment in a cohort's life history. Thus, a relatively constant advantage from moment to moment (as seen in the relative death rates) translates into an increasing survival advantage over a lifetime (as seen in the relative survival probabilities (RSP)). This increase is seen in Table 2, which shows the RSP of the male and female siblings of centenarians at various ages.

By the age of 100, the relative survival probability for siblings of centenarians is 8.2 for women and 17 for men. From the analysis of death rates, we know that the siblings' survival advantage does not increase as the siblings age. Rather, the siblings' relative probability of survival is a cumulative measure and reflects their life-long survival advantage over the general population born around the same time. The marked increase in relative survival probability and sustained

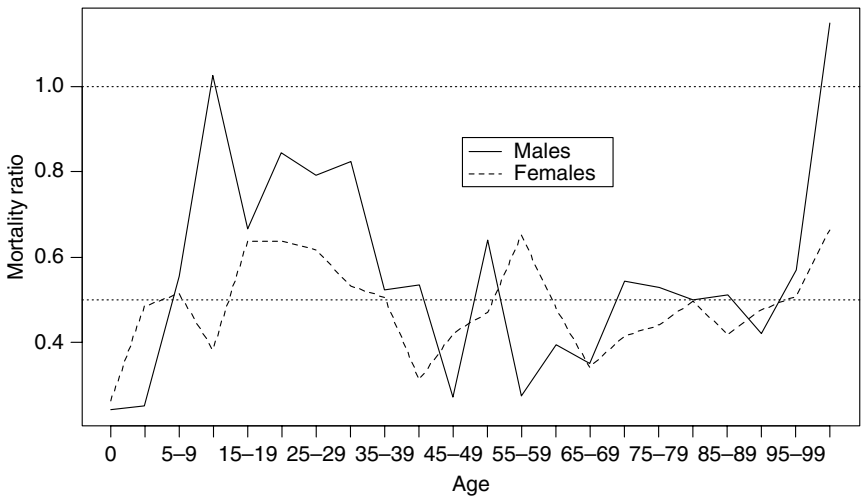

Figure 1 Relative mortality of male and female siblings of centenarians compared with birth cohort matched individuals (controls) from the general American population (survival experience of the controls comes from the Social Security Administration's 1900 birth cohort life table)

Table 2 Relative survival probabilities (RSP) with 95% confidence intervals (CI) of siblings of centenarians versus the US 1900 birth cohort

	Males			Females		
Age	RSP	Lower 95% CI	Upper 95% CI	RSP	Lower 95% CI	Upper 95% CI
20	1.00	1.00	1.00	1.00	1.00	1.00
25	1.00	0.99	1.01	1.01	1.00	1.02
60	1.18	1.15	1.21	1.12	1.09	1.14
65	1.29	1.25	1.33	1.16	1.13	1.19
70	1.48	1.42	1.53	1.24	1.21	1.28
75	1.68	1.60	1.77	1.36	1.31	1.41
80	2.03	1.90	2.16	1.54	1.47	1.60
85	2.69	2.47	2.91	1.83	1.73	1.93
90	4.08	3.62	4.54	2.56	2.39	2.74
95	8.35	6.98	9.71	4.15	3.73	4.57
100	17.0	10.8	23.1	8.22	6.55	9.90

survival advantage in extreme old age could be consistent with the forces of demographic selection, in which genes or environmental factors (or both) that predispose to longevity win out over those that are associated with premature or average mortality. The substantially higher relative survival probability values for men at older ages might reflect the fact that male mortality rates are substantially higher than female mortality rates at these ages and, thus, that men gain a greater advantage from beneficial genotypes than women do. Another possibility is that men require an even more rare combination of genetic and environmental factors to achieve extreme age than women do (Perls and Fretts, 1998). Either possibility could explain why men make up only 15% of centenarians.

CENTENARIAN OFFSPRING: FOLLOWING IN THE FOOTSTEPS OF THEIR PARENTS

The familiality of exceptional longevity demonstrated amongst centenarians and their siblings appears to extend to the offspring of centenarians as well. Centenarian offspring currently in their 70s and 80s have approximately half the relative prevalence of hypertension, diabetes, and cardiovascular disease (including coronary artery disease, myocardial infarction, congestive heart failure and/or arrhythmia) and cardiovascular risk factors compared to controls whose parents died at or before the average life expectancy of their birth cohort or to spousal controls (Atzmon *et al.*, 2004; Terry *et al.*, 2003). Among the centenarian offspring who did develop these conditions, the age of onset was significantly delayed when compared to the age at onset for controls (Terry *et al.*, 2004a). Examining the causes of death for deceased centenarian offspring and controls, centenarian offspring had a 62% risk reduction in all-cause mortality, an 85% risk reduction in coronary heart disease-specific mortality and a 71% risk reduction in cancer-specific mortality (Terry *et al.*, 2004b). Barzilai *et al.* (2001) have demonstrated that centenarian offspring, when compared to spousal controls, have favorable lipid profiles. These individuals have significantly larger HDL (high-density lipoprotein) and LDL (low-density lipoprotein) particle sizes compared to controls (Barzilai *et al.*, 2003). The larger particle sizes are associated with lower prevalences of cardiovascular disease, hypertension, and metabolic syndrome and are hypothesized to be predictive for longevity.

In addition to lipid profiles, another biomarker, heat shock protein 70 (HSP70), has been examined in the offspring of centenarians compared to spousal controls. Heat shock proteins, which help to chaperone, transport, and fold proteins when cells are exposed to a variety of stresses, may protect against or modify the progression of atherosclerosis. In a pilot study of 20 centenarian offspring and 9 spousal controls, Terry *et al.* (2004c) demonstrated a nearly 10-fold difference in levels of circulating HSP70.

GENETIC FINDINGS

Centenarians may be rare because a complex set of environmental and genetic variables must coexist for such survival to occur. The first genetic association with exceptional longevity, that has also withstood the test of time and numerous studies, has been the observation that the apolipoprotein E epsilon-4 (apo ε-4) allotype is rare amongst centenarians. Individuals who are homozygous for apo ε-4 have a 2.3–8 times greater risk of developing AD compared with the general Caucasian population (Corder *et al.*, 1993; Evans *et al.*, 1997). The allelic frequency of apo ε-4 drops off dramatically in the oldest age groups, presumably because of its association with Alzheimer's disease and vascular disease (Schachter *et al.*, 1994). Interestingly, the effect of apolipoprotein E allotype upon Alzheimer's disease incidence appears to decrease with age at these very old ages (Sobel *et al.*, 1995).

Richard Cutler, in what is now a classic paper in gerontology, proposed that persons who achieve extreme old age do so in great part because they have genetic variations that affect the basic mechanisms of aging and result in a uniform decreased susceptibility to age-associated diseases (Cutler, 1975). Our studies and those of others researching the oldest old have noted that persons who achieve extreme old age probably lack many of the variations (the "disease genes") that substantially increase risk for premature death by predisposing persons to various fatal diseases, both age-associated and non-age-associated (Schachter, 1998). More controversial is the idea that genetic variations might confer protection against the basic mechanisms of aging or age-related illnesses (the "longevity-enabling genes") (Perls *et al.*, 2002b).

The elevated relative survival probability values found among the siblings of centenarians support the utility of performing genetic studies to determine what genetic region or regions, and ultimately what genetic variations, centenarians and their siblings have in common that confer their survival advantage (McCarthy *et al.*, 1998). Centenarian sibships from the New England Centenarian Study were included in

a genome-wide sibling-pair study of 308 persons belonging to 137 families with exceptional longevity. According to nonparametric analysis, significant evidence for linkage was noted for a locus on chromosome 4 at D4S1564 with an Maximum Lod Score (MLS) of 3.65 ($p = 0.044$) (Puca *et al.*, 2001). A detailed haplotype map was created of the chromosome 4 locus that extended over 12 million base pairs and involved the genotyping of over 2000 single-nucleotide polymorphism (SNP) markers in 700 centenarians and 700 controls. The study identified a haplotype, approximating the gene microsomal transfer protein (MTP) (Geesaman *et al.*, 2003). All known SNPs for MTP and its promoter were genotyped in 200 centenarians and 200 controls (young individuals). After haplotype reconstruction of the area was completed, a single haplotype, which was underrepresented in the long-lived individuals, accounted for the majority of the statistical distortion at the locus (~15% among the subjects versus 23% in the controls). MTP is a rate-limiting step in lipoprotein synthesis and may affect longevity by subtly modulating this pathway. Given that cardiovascular disease is significantly delayed among the offspring of centenarians and that 88% of centenarians either delay or escape cardiovascular disease and stroke beyond the age of 80, it makes sense that the frequency of genetic polymorphisms that play a role in the risk for such diseases would be differentiated between centenarians and the general population (Evert *et al.*, 2003; Terry *et al.*, 2003).

Dr. Nir Barzilai and his colleagues studying Ashkenazi Jewish centenarians and their families recently found another cardiovascular pathway and gene that is differentiated between centenarians and controls (Barzilai *et al.*, 2003). In Dr. Barzilai's study, controls are the spouses of the centenarians' children. They noted that HDL and LDL particle sizes were significantly larger among the centenarians and their offspring and the particle size also differentiated between subjects with and without cardiovascular disease, hypertension, and metabolic syndrome. In a candidate gene approach, the researchers then searched the literature for genes that impact upon HDL and LDL particle size and hepatic lipase and cholesteryl ester transfer protein (CETP) emerged as candidates. Comparing centenarians and their offspring against controls, one variation of CETP was noted to be significantly increased among those with or predisposed for exceptional longevity.

A PROPOSED MULTIFACTORIAL MODEL FOR EXCEPTIONAL LONGEVITY AND EXCEPTIONAL SURVIVAL PHENOTYPES

The fact that siblings of centenarians maintain half the mortality risk of their birth cohort from age 20 to extreme age suggests that multiple factors contribute to achieving exceptional longevity. For example, socio-demographic advantages may play key roles at younger ages, while genetic advantages may distinguish the ability to go from old age to extreme old age. Undoubtedly, exceptional longevity is much more complicated, with temporally overlapping roles for major genes, polygenic, environmental, and stochastic components. Such a scenario would be consistent with a threshold model, where predisposition for the exceptional longevity trait can be measured on a quantitative scale. Figure 2 illustrates the standard threshold model proposed by Falconer (1965) where it is predicted that the proportion of affected relatives will be highest among the most severely affected individuals. In the case of exceptional longevity, perhaps severity can be measured by additional years beyond a certain age (threshold) or by additional years of delay in age at onset for disease.

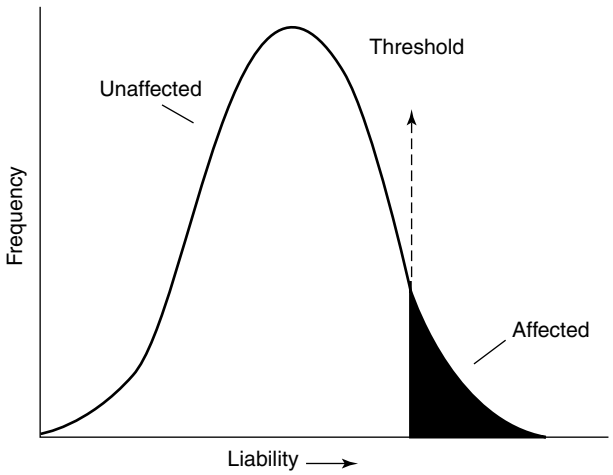

Figure 2 Threshold model of a multifactorial trait

Examples of phenotypes fitting the threshold model are early onset breast cancer or Alzheimer's disease, where relatives of patients who develop these diseases at unusually young ages, are themselves at increased risk or liability. Thus, a 108-year-old's "liability" or predisposition for exceptional longevity is further beyond the threshold than someone more mildly affected, as for example, a person who died at age 99. One interpretation of data indicating the higher relative survival probability of male siblings of centenarians compared to female siblings is that the males carry a higher liability for the trait, given the presence of the requisite traits. The model predicts that if a multifactorial trait is more frequent in one sex (as is the case with exceptional longevity which is predominantly represented by females), the liability will be higher for relatives of the less "susceptible" sex (males, in the case of exceptional longevity) (Farrer and Cupples, 1998). While we have not yet looked at relative survival probability of siblings of male versus female probands (something that certainly needs to be done), these elevated risks for male versus female siblings are interesting in this context. The model also predicts that the risk for exceptional longevity will be sharply lower for second-degree relatives compared to first-degree relatives, another observation we hope to test by having access to many expanded pedigrees. The ramifications of this model holding true for exceptional longevity (and/or exceptional survival phenotypes) include:

(1) the older the subject, the better the chances of discovering traits predisposing for exceptional longevity and (2) there are gender-related differences in both relatives and probands in "liability" for exceptional longevity, given the presence of specific traits conducive to exceptional longevity.

CONCLUSION

While centenarians are rare, one per 10 000 people in industrialized societies, they are also the fastest growing age category of our population. It is unlikely that they are rare because of any one rare factor. Rather, becoming a centenarian might entail achieving the right combination of genetic and environmental factors, much like winning the lottery requires the right combination of numbers. Each number by itself is not rare, but the right combination of five or six numbers certainly is. Complicating matters, the right combination of factors also likely varies from one person to the next, although there are similarities within families. One reason why the incidence of centenarians is growing may be understood by comparing with the analogy that the selection of lottery numbers is left less and less to chance. Better health-related behaviors and more effective public health and medical interventions make it significantly more likely for people to reach older age and for some to achieve extreme old age.

With the power of demographic selection, centenarians have already proven helpful in deciphering some polymorphisms and genetic loci associated, positively or negatively, with exceptional old age. The offspring of centenarians, who seem to be following closely in their parents' footsteps, might yield additional discoveries about phenotypic and genetic correlates of successful aging. Discovering genes that could impart the ability to live to old age while compressing the period of disability toward the end of life should yield important insight into how the aging process increases susceptibility to diseases associated with aging and how this susceptibility might be modulated (Hitt *et al.*, 1999; Perls *et al.*, 2002a). We anticipate that human longevity-enabling genes will be found to influence aging at its most basic levels, thus affecting a broad spectrum of genetic and cellular pathways in a synchronous manner. Another approach that researchers are in the early stages of understanding is differential gene expression in models known to slow the aging process, such as caloric restriction (Lee *et al.*, 1999). This may be another tool for discovering longevity-enabling genes. The centenarian genome should also be an efficient tool for ferreting out disease genes. Comparison of SNP frequencies implicated in diseases in centenarians and in persons with the diseases should show clinically relevant polymorphisms. The hope, of course, is that these approaches to gene discoveries will help identify drug targets and create drugs that would allow persons to become more "centenarian-like" by maximizing the period of their lives spent in good health.

KEY POINTS

- An optimistic view. Centenarians support the observation "the older you get, the healthier you've been".
- Compression of morbidity versus disability. Achieving exceptional old age likely requires a compression of disability, not necessarily morbidity, toward the relative end of life.
- Nature versus nurture. The majority of variation in average life expectancy is likely related to health-related behaviors. However, there appears to be a strong familial component to exceptional longevity and for truly extreme old ages, such as >103 years, specific genetic variations may play a prominent role.
- Centenarian offspring. Following in the footsteps of their parents. The offspring of centenarians are a valuable model for the study of environmental and genetic factors related to successful aging.
- Genetic findings. Reproducible genetic associations with exceptional longevity are still rare, reflecting the likely complex nature of gene–gene and gene–environment interactions that dictate the ability to survive to extreme old age.

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PART III

Medicine in Old Age

Section 15

Diagnostic Interventions

Diagnostic Imaging and Interventional Radiology

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INTRODUCTION

Diagnostic imaging and interventional radiology in the elderly is little different from that of the adult population in general, but there are certain specific considerations. The problems and difficulties which can arise in diagnostic imaging and interventional radiology are not unique to the elderly; they are, however, more common in old age than in younger or middle-aged adults. Nevertheless, it is not unusual to occasionally encounter 80 or even 90 year olds who are fitter and more cooperative than some 50-year-old patients. Coupled with the increasing numbers of older people in the population at large plus the higher incidence and prevalence of many pathological conditions requiring investigation and treatment in this age-group, those difficulties which can arise assume an increasing importance; this justifies particular attention and care needed, in order to achieve a satisfactory investigation/intervention and to avoid undue distress or discomfort to the elderly patient. In particular, neoplastic disease and vascular disorders (cardiovascular, cerebrovascular, and peripheral vascular diseases) are more common in elderly patients than in younger or middle-aged patients.

Requests for radiological investigation of older patients, both for in- and outpatients, are received from many sources in addition to those from departments of geriatric medicine, but the potential problems are the same. Some nongeriatric clinical specialties have a high proportion of elderly patients (e.g. urology, gynecology, and general medicine), although referral of such patients can be from almost any clinical speciality (with the notable exceptions of obstetrics and pediatrics!). A large number of elderly referrals also emanate from general practice.

Appropriate choice of relevant investigation, with clear information/explanation to the patient and/or his/her relatives or carers can have a significant effect in alleviating or reducing unnecessary anguish in these patients, who are frequently already anxious, distressed, or in pain or discomfort as a result of their condition and age. Kindness and patience can pay dividends.

GUIDELINES TO GOOD PRACTICE IN RADIOLOGICAL IMAGING

The use of radiological investigations is an accepted part of medical practice, but there is no known safe radiation dose. In requesting any radiological investigation, it should be remembered that all X-rays are potentially carcinogenic and tetragenic. The patient's interest will be best served only if the likely disadvantages of the examination (inconvenience, discomfort, the risk of radiation to those X-rayed, and the benefits which might have to be foregone when resources are committed to the X-ray examination) are less than the anticipated benefits. Man-made radiation now accounts for 15% of the total radiation burden to the population, of which 97% is due to diagnostic medical exposures. No investigation should be requested unless it can be clinically justified and its result is likely to influence patient management. Many measures, including technical features of X-ray equipment design and radiographic technique, are utilized to reduce the radiation dosage to patients from necessary radiological examinations.

Some of the reasons for avoiding or reducing exposure to ionizing radiation from radiological examinations are not relevant in the elderly (e.g. avoiding radiation to the developing embryo or fetus in pregnant patients) or are of lesser significance than in younger patients (e.g. risks of mutation in germ cells), but it is, nevertheless, a sound and recommended practice to avoid unnecessary irradiation of patients and to keep that which is necessary to a minimum for the sake of the patient and the operator(s). Many elderly patients will still have a fairly long life expectancy,

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so radiation-induced cancer cannot be dismissed. There is no threshold for the induction of such effects, any ionizing radiation is theoretically dangerous and its use must be justified, that is, the potential benefit must outweigh the small risks. Requests for radiological investigation should follow the guidelines published by the Royal College of Radiologists (RCR) in the booklet *Making the Best Use of a Department of Clinical Radiology: Guidelines for Doctors* (3rd edn) (RCR Working Party, 2003). These guidelines are not intended to replace clinical judgement but to support it in times of doubt or difficulty. The guidelines state that a useful investigation is one in which the result – positive or negative – will alter management or add confidence to the clinician's diagnosis. A significant number of radiological investigations do not fulfil these aims. Unnecessary investigations increase waiting time, waste limited resources (Audit Commission, 1995), lower standards, and may add unnecessarily to patient irradiation (The Ionising Radiation (Protection of Persons Undergoing Medical Evaluation or Treatment) Regulations 1988, (POPUMET); The Ionising Radiation (Medical Exposure) Regulations 2000, (IR(ME)R 2000); European Directive 97/43/Euratom (The Medical Exposures Directive). Such is the perceived risk of medical litigation that X rays are sometimes requested even when they are not considered clinically necessary by the referring doctor. If, as a result of careful clinical examination, it is decided that an X ray is not necessary for the future management of the patient and this is recorded in the patient's notes, it is unlikely that the decision will be challenged on medicolegal grounds. The position of clinicians following the guidelines will be further strengthened because it will have the support of the RCR. Apart from the medicolegal issue, the chief causes of the wasteful use of radiology are:

1. *Investigation when results are unlikely to affect patient management*: because the anticipated "positive" finding is usually irrelevant, for example, degenerative spinal disease (as " normal" as gray hairs from early middle age) or because a positive finding is so unlikely.

DO I NEED IT?

2. *Investigating too often*: that is, before the disease could have progressed or resolved, or before the results influence treatment.

DO I NEED IT NOW?

3. *Repeating investigations which have already been done*: for example, at another hospital, in an outpatient department, or in the accident and emergency department, or already requested by another member of the clinical team caring for the patient.

HAS IT BEEN DONE ALREADY?

4. *Failing to provide appropriate clinical information and questions that the radiological investigation should answer*: Deficiencies may lead to the wrong radiographs being obtained (e.g. the omission of an essential view).

HAVE I EXPLAINED THE PROBLEM?

5. *Performing the wrong investigation*: Imaging techniques are developing rapidly. It is often helpful to discuss the investigation with a radiologist before it is requested.

IS THIS THE BEST INVESTIGATION?

Continued use of the RCR *Guidelines* leads to a reduction in the number of referrals for investigations and also to a reduction in medical radiation exposure (Roberts, 1988; National Radiological Protection Board and The Royal College of Radiologists, 1990; RCR Working Party, 1991; RCR Working Party, 1992; Roberts, 1992). Nevertheless, the primary objective of the RCR *Guidelines* is to improve clinical practice. Such guidelines work best if they are used in conjunction with clinicoradiological dialogue and as part of the audit process.

The *Ionizing Radiation* (POPUMET) *Regulations* (1988) require all concerned to reduce unnecessary exposure of patients to radiation. Health authorities, NHS trusts, and individuals using ionizing radiation must, by law, comply with these regulations. One important way of reducing radiation dose is to avoid repeating investigations unless there is a sound clinical reason to do so.

Table 1 shows the effective doses delivered by different examinations, the approximate equivalent number of chest

Table 1 Relative radiation doses and their equivalent natural radiation period

Examination	Effective dose (mSv)	Equivalent number of chest X rays (approx.)	Equivalent period of natural background radiation
Extremities[a] (e.g. knee)	0.01	0.5	1.5 days
Chest (single PA film)	0.02	1	3 days
Skull	0.1	5	2 weeks
Cervical spine	0.1	5	2 weeks
Dorsal spine	1.0	50	6 months
Lumbar spine	2.4	120	14 months
Hip	0.3	15	2 months
Pelvis	1.0	50	6 months
Abdomen	1.5	75	9 months
Biliary tract	1.3	65	7 months
Barium studies			
Esophagus	2.0	100	1 year
Stomach & duodenum	5.0	250	2.5 years
Small bowel	6.0	300	3 years
Large bowel	9.0	450	4.5 years
IVU	4.6	230	2.5 years
CT head[b]	2.0	100	1 year
CT chest or abdomen	8.0	400	4 years
Radionuclide studies[c]			
Lung ventilation (^{81m}Krypton)	0.1	5	2 weeks
Lung perfusion	1.0	50	6 months
Kidney	1.0	50	6 months
Thyroid	1.0	50	6 months
Bone	5.0	250	2.5 years
Myocardium (^{201}Thallium)	18.0	900	9 years

Source: Reprinted from *Clinical Radiology*, V39, Roberts CJ, Towards the more effective use of diagnostic radiology, pp 3–6, Copyright 1988, with permission from The Royal College of Radiologists.

[a]On the basis of a survey carried out in the mid-1980s. [b]On the basis of studies carried out in 1989. [c]Courtesy of Dr RA Shields, Manchester.

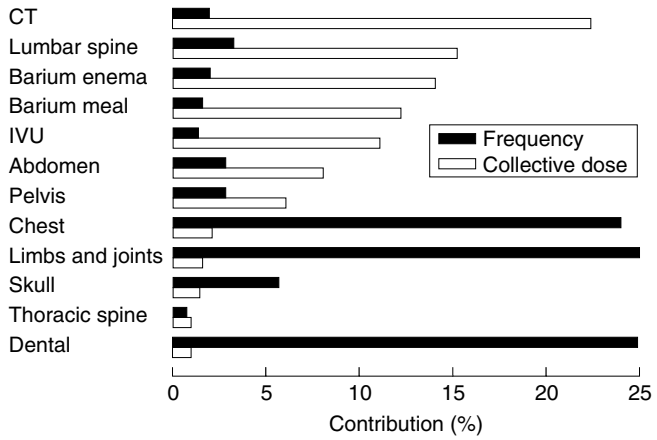

Figure 1 Frequency of, and collective dose from, different radiological investigations in the United Kingdom (Reprinted from *Clinical Radiology*, V39, Roberts CJ, Towards the more effective use of diagnostic radiology, pp 3–6, Copyright 1988, with permission from The Royal College of Radiologists)

radiographs, and the equivalent period of natural background radiation. The *effective dose* is a weighted sum of equivalent doses (in millisieverts, mSv) to a number of body tissues, where the weighting used for the different tissues depends upon the relative risks of fatal malignancy or severe hereditary defect for low radiation doses. The effective dose is the dose of uniform whole-body irradiation which would carry the same risk of malignant disorders as the examples listed, all of which involve nonuniform irradiation. Figure 1 shows the relative frequency of X-ray examinations and their contributions to the collective population dose. The dose imparted by computed tomography (CT) is high and should be minimized. In recent studies, the contribution of CT to the collective dose from all X-ray examinations has increased to one-third and is probably still rising (National Radiological Protection Board, 1992). In many situations, potentially less harmful imaging modalities such as ultrasound or magnetic resonance imaging (MRI) can be substituted for CT.

PROBLEMS IN RADIOLOGY – GENERAL CONSIDERATIONS

The problems which can arise in radiological examination of the elderly are mainly related to locomotor and communication difficulties resulting from the aging process and diseases occurring more commonly in old age. Complications which can occur in diagnostic imaging and interventional radiology relate not only to radiation but also to drugs used and procedures performed in the clinical radiology department (Ansell *et al.*, 1996).

For elderly outpatients, actually getting to the X-ray department can be difficult; such patients may be unable to use a car or public transport, or afford a taxi fare. Elderly patients may never have driven or have owned a car, or may have had to give up driving because of failing eyesight or musculoskeletal disabilities preventing driving or getting into or out of a car, or walking to it. Where car transport cannot be provided by a friend, relative or carer, or a taxi is unaffordable or inappropriate, the patient will be dependent upon a hospital car or the ambulance service. In cases of severe disability, ambulance transport is the only possibility. The patient may be unable to walk far and may require transfer into and out of the ambulance by wheelchair.

Suitable facilities at the hospital allow wheelchair access to departments, for example, wheelchair ramps alongside small flights of steps and adequate and appropriately sited provision of passenger lifts. This is easier to achieve in modern purpose-built hospitals and radiology departments than in those housed in older (e.g. Victorian) buildings, where such access was not originally planned.

Within the radiology department, the reception and waiting areas, changing cubicles, examination rooms, and toilets need adequate provision for wheelchair access. Modified changing cubicles are required, larger than normal, with extra-wide or double doors to accommodate not only the patient and wheelchair, but also a friend, relative, carer, nurse, or radiography helper for those patients who need assistance in dressing and undressing to change into an examination gown for radiographic procedures.

Problems can be encountered within the X-ray examination room in moving patients on and off the examination table. Most conventional radiographic imaging tables are quite high off the ground, the tabletop being anything between 24 and 28 inches above floor level; physically getting the less mobile patient on and off such tables, whether from a standing position or from a wheelchair, can present difficulties. This can be overcome by using specially designed elevating examination tables, which rise and lower hydraulically from a minimum height of 20 inches up to a maximum of 36 inches. Transfer of a patient to and from such variable-height tables is thus considerably easier than with conventional tables, and involves a minimum of lifting of the patient; some wheelchair patients are able to move themselves on and off such tables with only a little assistance (Figure 2). An additional advantage of this type of examination table is that it has a "floating" tabletop. Once the patient is lying on the table, it is not necessary to physically move him/her for radiographic positioning, as the entire tabletop is readily mobile longitudinally and laterally on release of electronic locks operated by foot switches. Thus, the patient and the part of the body to be radiographed can be easily positioned relative to the overhead X-ray tube without moving the patient relative to the tabletop, avoiding any potential discomfort. The precise position is delineated in the usual way for radiographic exposures by means of a light-beam collimator, which illuminates with visible light the shape, size, and position of the area on the patient to be radiographed. Some types of X-ray equipment (e.g. CT scanners) use low-power laser light beams for precise patient positioning.

For transferring patients on to examination tables, assistance from staff (radiographers, nurses, radiography helpers) is often required. Proper training of staff in patient-lifting techniques is essential to avoid injury to patients and staff.

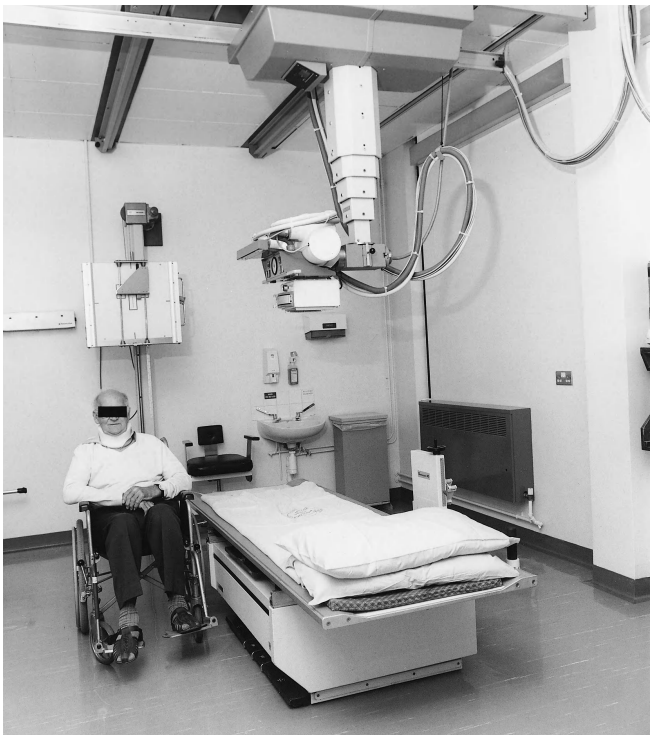

Figure 2 Elevating adjustable height, floating table top X-ray examination table

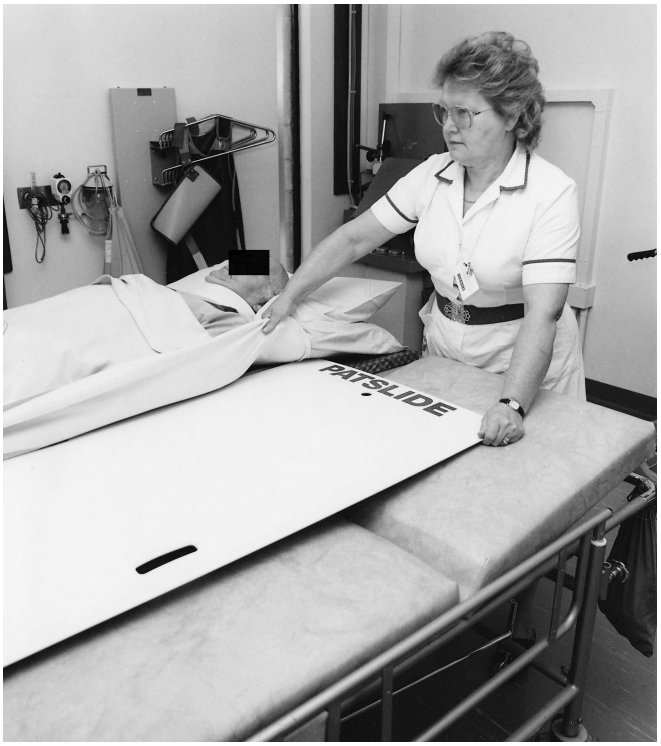

Figure 3 Placement of the Patslide® to transfer a patient from an X-ray examination table onto a hospital trolley

Lifting of patients without such training has the potential of back injury to the lifter and risks of the patients being dropped. Large numbers of back injuries currently occur to NHS staff as a result of lifting (Health and Safety Executive, 1992). Some hospitals and trusts have adopted "no-lifting" policies; all patient transfers and lifting being by mechanical aids – this has led to a significant reduction in the incidence of back injuries in staff (Royal College of Nursing, 1996). Mechanical lifting hoists are available for handling immobile patients. There are a variety of hoists available depending on patient's needs, but these hoists have tended to be used only in extreme cases as they have been felt to be cumbersome and time consuming to use. Newer battery-powered lifting hoists such as the Arjo Maxilift™ are much more versatile and user friendly, and are helpful for transfer of wheelchair patients onto examination tables.

Facilitation of transfer of patients from stretchers/trollies or inpatient beds on to examination tables can be helped using the Patslide®, a large, low-friction, semiflexible plastic sheet measuring about 5-feet long by 2-feet wide, that can be used to bridge the narrow gap between stretcher and examination table. The patient is rolled partly onto his/her side, the Patslide® positioned beneath the patient and a slide sheet, and the patient then rolled onto his/her back again and easily slid across it onto the examination table, because of the low coefficient of friction of the Patslide® surface plus the ease of maneuver of the slide sheet (Figure 3). Many hospital beds and stretcher trollies can be adjusted in height to ease such transfers, allowing a slight downhill slope for easier movement of patients both on and off. Slide sheets which aid the user to turn patients and to move them up and down the bed into a sitting position easily without causing discomfort to the immobile patient and without causing undue stress to either the patient or the carer can also help in the transfer of patients from hospital bed to trolley and then onto the X-ray table.

Some elderly patients are unable to stand without assistance, or to stand still enough or for long enough for erect radiographs to be obtained, for example, PA (posteroanterior) or lateral chest radiographs. These can be performed with the patient seated, using a special hydraulic examination chair with removable back and arm rests which can be left *in situ* except during the actual radiographic exposure (Figure 4). The seat can be raised, lowered, rotated, and locked in position with ease.

There are a variety of reasons why patients may need assistance getting on and off radiographic examination tables, including:

Immobility

- Joint stiffness and/or pain – arthritis, including osteoarthritis, rheumatoid arthritis, gout, ankylosing spondylitis, and other erosive arthropathies
- Muscle stiffness and pain – rheumatism, lumbago, and so on
- Neuralgia – sciatica, and so on
- Paralysis – stroke
- General weakness/debility
- Obesity

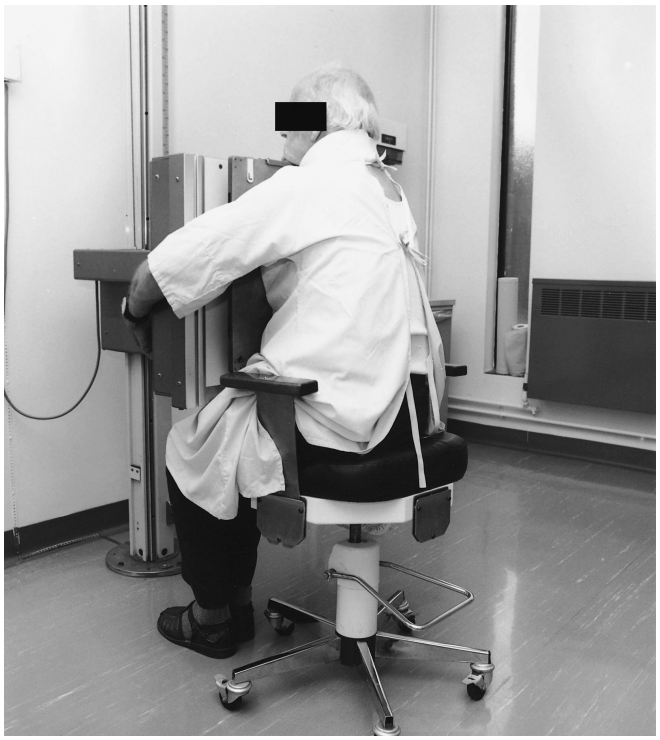

Figure 4 Use of hydraulic chair for erect chest radiographs for patients unable to stand

- Amputation
- Neurological disorders – Parkinson's disease, ataxias, multiple sclerosis
- Tendency to fall – vertigo, faintness

Inability to cooperate

- Deafness
- Blindness
- Failure to comprehend or remember instructions – dementia, lack of understanding of the language of communication

Unwillingness to cooperate

- Dementia – Alzheimer's disease, multi-infarct, and so on
- Psychological – depression, psychiatric illness, stubbornness, pride, dignity, shame, apprehension, claustrophobia.

Physiological handling of intravascular contrast media and of drugs used in radiology may be impaired in the elderly due to diminished renal and hepatic function; this must be allowed for in the choice and dosage of these agents.

IMAGING TECHNIQUES AND INTERVENTIONAL PROCEDURES – SPECIFIC PROBLEMS

Various problems can arise related to specific imaging investigations or interventional procedures. The following list is not intended to be exhaustive; it covers those examinations most frequently performed in elderly patients plus less common procedures where there are special considerations.

Plain Film Radiography

The general problems previously discussed, which can make getting on and off X-ray examination tables difficult, can also cause difficulties in patient positioning and radiographic exposure. Problems can be encountered in keeping patients still for sufficient time for the radiographic exposure; in these circumstances it is helpful to keep the exposure time as short as possible to minimize movement effects. This can be achieved by use of higher kilovoltage (kV) techniques when soft tissue contrast is not critical. Since radiographic exposure depends on the mAs (milliamp.seconds) setting, the use of as high a tube current as possible within the limits of the X-ray tube capacity and the generator output will shorten the time. For most X-ray sets, however, the mAs setting is combined in one control, so exposure time cannot be separately selected.

For abdominal exposures of the renal tract, kidney, ureter and bladder (KUB), the use of compression reduces the exposure, and hence the exposure time, by moving soft tissues not of interest out of the field of view. Bowel preparation can reduce the X-ray exposure for KUB radiographs by emptying the colon of feces (Hasan *et al.*, 1996). Immobilization devices such as sandbags, retaining straps and supports, and compression bands can be helpful in preventing involuntary movements.

The chest radiograph is useful in assessing heart size – clinical assessment can be misleading in the elderly patient (Mulkerrin *et al.*, 1991). Breath holding is important to avoid movement blur in radiographic examination of the chest or abdomen; achieving this can be difficult if the patient is unable to hear or understand instructions, has a very poor memory, or is unwilling or unable to cooperate for the reasons previously discussed. Shortage of breath may present similar problems in breath holding, even in cooperative patients. Breathlessness due to cardiac failure, airways obstruction (chronic obstructive airways disease – COAD – or asthma) can present problems, but fortunately the exposure for chest radiographs is short, typically 0.01 seconds. Anxious or agitated patients may have difficulty in keeping still; careful explanation and reassurance by the radiographer are essential.

Extremes of weight (i.e. gross obesity or emaciation) in some elderly patients can make correct radiographic exposure difficult. Emphysema necessitates relative underexposure of chest radiographs to avoid an overexposed "black" film. An abdomen distended by ascites or by a fecally overloaded colon from severe constipation, or the abdomen of a grossly obese patient requires relative overexposure. Exposure factors in plain film radiography are largely controlled automatically by means of automatic exposure control (AEC) ionization chambers, which are sensors that react to the amount of radiation passing through them *en route* to the film, terminating the exposure when sufficient; the skill of

the radiographer is nonetheless paramount in obtaining good radiographic exposure as well as positioning.

For patients who are too unwell to be moved from the ward to the department of clinical radiology, portable radiographic examinations can be performed. These will seldom be of as good quality as departmental radiographs, owing to the limited power output of the portable X-ray machine, and particular difficulties arise in positioning the patient, achieving adequate film-focus distance, and controlling exposure. Portable exposures are best confined to chest radiographs, although a reasonable quality abdominal radiograph is possible, except in obese patients. Transfer of the patient to the radiology department in his/her hospital bed is a better alternative to portable radiography; even if the patient is still radiographed in bed, as higher-quality radiographs can be obtained.

Digital Radiography

In digital or "filmless" radiography, an X-ray image produced by an image intensifier is recorded digitally and stored in a computer memory, replacing the conventional X-ray film. (An image intensifier is a device for greatly enhancing the faint fluorescence of an input phosphor screen in response to radiation, by electron release and capture, causing much brighter fluorescence of an output phosphor screen viewed by a TV camera). The resulting image is viewed on a TV monitor. Hard copy can be made using a laser imager or other imaging devices (Harding and Roberts, 1996). The exposure time is usually shorter in digital radiography than in conventional radiography – this can be advantageous in patients who have difficulty in keeping still or in breath holding. Clinical Radiology Departments and hospitals generally are moving more and more towards computerised digital systems with paperless electronic requesting and reporting, and filmless PACS (picture archiving communication systems) without hard copy, and allowing simultaneous multi-site access to images by radiologists and clinicians.

Barium Studies of the Gastrointestinal Tract

Barium Swallow

The cooperation of the patient in drinking adequate volumes of barium quickly enough, and at the right time, is essential for diagnostic studies of the esophagus, and particularly for rapid sequence radiography (at 2, 3, or 4 frames per second) or videoradiography of the oropharynx and upper esophagus. Elderly patients are more likely to aspirate barium into the larynx, trachea, and bronchial tree during barium swallows and meals. This can lead to aspiration pneumonia requiring physiotherapy and can be fatal (Ansell, 1987).

Patients who are unable to stand can still have an erect barium swallow on an overcouch X-ray table by raising the footstep and sitting the patient on it. If there is difficulty in drinking from an ordinary cup, a feeding cup with a spout can be substituted, or the patient can drink through a large-bore flexible straw. In extreme cases, the barium can be spooned into the patient's mouth.

Barium Meal and Barium Follow-through

An empty stomach is mandatory for barium meal and barium follow-through (upper gastrointestinal) studies. Compliance of the patient with fasting instructions is essential. Diabetic patients are best scheduled first or second in early-morning barium lists to lessen risks of hypo- or hyperglycemia. Diabetics on insulin or oral hypoglycemic therapy should withhold these agents until after eating breakfast immediately following the barium meal. Patients taking other oral medication need to withhold this because of fasting for a barium meal or follow-through; pills and capsules should be taken with a small glass of water before the barium study, notwithstanding the requirements of fasting, and this must be made clear in the patient information/instruction sheet. It is necessary to emphasize the importance of taking a small cupful of water with tablets or capsules, as these can otherwise remain in the esophagus for long periods of time without being absorbed (Evans and Roberts, 1976). In addition to being therapeutically ineffective in this situation, some medications will cause esophagitis.

Orally ingested barium can subsequently cause severe constipation in susceptible elderly subjects (Ansell, 1987). This should be explained to the patient, relative, or carer, and the patient advised to eat plenty of high-fiber food, fruits, and so on after the barium meal, or to take a mild laxative.

Smooth-muscle relaxants are frequently administered to patients undergoing barium meals (and barium enemas) to allow adequate gaseous distension of the stomach (or colon) in double-contrast examinations, where fine mucosal detail can be evaluated. Buscopan (hyoscine *N*-butyl bromide, 20 mg intravenously) is often used, but should not be given to patients suffering from cardiac arrhythmias, coronary artery disease, or closed-angle glaucoma (Fink and Aylward, 1995), all of which are more common in the elderly. Glucagon 0.5 mg i.v. may be substituted in these patients (Goei *et al.*, 1995). An effervescent agent – sodium bicarbonate granules, powder, or tablets, sometimes with citric acid as an adjuvant – is swallowed before the barium to produce carbon dioxide gas for the double-contrast technique. The patient must refrain from burping or belching, or a double-contrast barium meal will not be possible.

A normally conducted barium meal means changing patient position from erect to prone and supine, and quite a lot of turning between prone and supine positions – patients have to be fit to undergo a barium meal! The examination can, however, be tailored with limited views and fewer changes of position in very ill patients.

Barium Enema

Bowel preparation for barium enema requires several days of dietary modification/restriction and strong oral laxatives on

the day before the examination. This can make some patients unwell to the extent that outpatients will contact the radiology department requesting that the examination be cancelled or postponed; it is advisable to try to persuade these patients to attend regardless, as it is a pity to have undergone the fairly arduous preparation and then not to have the enema and, even worse, to have to undergo bowel preparation a second time. In particular, patients can feel unwell because of the bowel preparation during hot summer weather. Dehydration can occur; adequate fluid intake must be maintained. Migraine attacks may be precipitated in susceptible patients.

If a large or even moderate amount of fecal residue is present in the colon, a double-contrast examination is unlikely to be diagnostic; filling defects such as polyps or tumors can be missed, and ulceration can be difficult to evaluate. It is said that the radiologist who attempts a double-contrast barium enema on the inadequately prepared patient requires (and acquires) only a knowledge of feces! Such patients are better examined by a single-contrast technique using barium followed by water – this is far more likely to achieve a diagnostic result even without the superior mucosal detail afforded by double-contrast studies. A single-contrast examination is also more suitable for patients who have difficulty in retaining barium – it is quicker, less uncomfortable, and patients who cannot retain air insufflated for double-contrast examinations can often retain fluid in a barium/water examination. Multiple "spot" radiographs can be obtained on 100-mm cut film (as commonly used for barium meals) taken from the output phosphor screen of an image intensifier by a camera using a similar mirror arrangement to that in single-lens reflex cameras. This allows rapid alternation between a TV camera (during fluoroscopic screening) and a spot film camera (to record hard copy). There is the advantage of a shorter exposure time than with conventional radiographic film exposure, avoiding movement blur in restless or breathless patients, plus the added advantages of shortening the examination time, as 100 mm film changing is automatic and quick, and reducing radiation exposure compared with conventional film. In patients likely to have difficulty retaining barium, the use of a balloon retention barium enema catheter can help, but patient cooperation is still required – the inflated balloon catheter can be expelled rectally by uncooperative patients. The use of smooth-muscle relaxants makes the barium enema examination less uncomfortable for the patient, in addition to improving diagnostic quality. For patients with anal strictures or fistulae, in whom a normal-sized catheter cannot be inserted, a smaller Foley bladder catheter can be substituted.

Intravenous Urography (IVU)

Renal function declines in the elderly (Cox *et al.*, 1991). Higher doses of contrast medium may be required for opacification of the renal tract. Modern low-osmolality nonionic contrast media are much more patient-friendly than the older ionic contrast media, but there are still risks of allergy and precipitation of cardiac failure (Holtas and Tornquist, 1987; Harding, 1996a). Renal function of patients undergoing contrast examinations may become impaired, particularly if there is pre-existing renal disease (Trewhella and Dawson, 1990). Patients with diabetes are more likely to have some degree of impairment of renal function than the normal population and are said to be at greater risk of contrast nephropathy. Metformin (glucophage) therapy for non-insulin-dependent diabetes mellitus may occasionally cause severe life-threatening lactic acidosis in patients with impaired renal function, with mortality greater than 50% (Monson, 1993; Sirtori and Pasik, 1994). The combination of metformin and X-ray contrast media may have adverse affects because contrast media impair or further impair renal function and hence metformin excretion. Significant numbers of patients attending for diagnostic and interventional radiological procedures involving contrast medium administration, such as during IVU, will be taking metformin. All patients who are to receive intravascular X-ray contrast media (whether for IVU, vascular studies, or enhancement of CT scans) should be asked if they are diabetic and, if so, whether they are receiving metformin (glucophage) therapy. The advice of The Royal College of Radiologists is that if a patient is receiving metformin therapy, the drug should be stopped for 48 hours before and 48 hours after any X-ray contrast medium examination. This should be discussed fully with the patient's referring clinician or general practitioner (GP) – adjustment of the control of the patient's diabetes may be needed. Renal function should be checked 48 hours after the injection of X-ray contrast medium and prior to the resumption of metformin therapy. X-ray contrast medium–enhanced procedures in emergencies should continue to be carried out without delay. However, the patient's referring clinician or GP and the local renal physicians should be consulted. Obesity and constipation can obscure renal detail, although this can be overcome by tomography in patients able to cooperate with adequate breath-holding (tomography requires a longer exposure time than plain radiographs).

Vascular Radiology

Patient cooperation in keeping very still is essential for arteriography and venography, especially when digital subtraction is utilized. Digital subtraction angiography (DSA), previously known as *digital vascular imaging* (DVI), is similar to digital radiography, but may be included as an "add-on" to older fluoroscopic imaging equipment, as well as being built into digital radiographic equipment.

In DSA, summated TV frames early in a sequence of images during a dynamic vascular examination are subtracted pixel by pixel from later-summated TV frames, following intravascular injection of a radiographic contrast medium. This results in imaging only those structures in the field of view opacified by the contrast medium, with subtraction of overlying bony or gas-filled structures. This is analogous to

a similar technique applied in the past using photographic subtraction of a plain radiograph taken before contrast medium injection from a later one in which the blood vessels were opacified by contrast medium. DSA is very sensitive and can satisfactorily image considerably diluted contrast medium. For example, faintly opacified arteries can be imaged following intravenous injection of contrast medium, which becomes diluted by mixing with blood during its passage through the right heart chambers, the pulmonary vascular system, and the left side of the heart before entering the systemic arterial circulation. This is a less invasive procedure than conventional arteriography and can be performed on an outpatient basis (Harding and Lenaghan, 1985). The image data may be recorded digitally, as in digital radiography, or on older systems may be recorded on magnetic recording tape in analog form. The subtraction images can be viewed dynamically on a TV monitor either as a continuous real-time image showing gradual appearance and disappearance of contrast medium in the blood vessels being studied, or as regularly upgraded static images at short time intervals. The optimal images can then be frozen for production of hard copy.

Very small amounts of patient movement during DSA can be compensated for on postexamination analysis by registering the position of the early mask relative to the contrast-filled images, or even utilizing a post-opacification mask, but larger amounts of movement make the technology unusable. For abdominal angiography breath holding is essential.

Vascular access for angiography by the Seldinger technique (Seldinger, 1953) requires local anesthesia to avoid excessive pain. Systemic intravenous sedation and analgesia may be needed in addition for apprehensive patients, but it must be remembered that older patients are frequently more sensitive to such agents because of diminished metabolic clearance, and a slowly administered, titrated lower dose is usually necessary, along with careful monitoring of pulse, respiration, blood pressure, and arterial oxygen saturation by pulse oximetry. If a patient is sedated to a semiconscious level, anesthetic assistance is the ideal; at the least, a trained and experienced nurse should be dedicated to the task of monitoring and caring for the patient (Skelly, 1996).

For some vascular procedures, and particularly for more difficult superselective arteriography and interventional vascular procedures, such as angioplasty, stenting, or embolization, a patient may be lying on the X-ray fluoroscopy table for several hours.

Many invasive vascular investigations are now being replaced by other noninvasive imaging modalities, for example, ultrasound, including Doppler and power Doppler, CT angiography, and MRI angiography.

ULTRASOUND

Ultrasound scanning uses a probe operated by the piezoelectric effect to emit ultrasound of frequency 3.5–10 MHz into the patient and receive returning echoes from internal structures, producing a real-time, gray-scale image displaying the echo intensity as a 2D image on a TV monitor. Doppler ultrasound allows flow within blood vessels to be displayed. In duplex Doppler, the 2D image and Doppler waveform are displayed simultaneously, allowing accurate placement of the sampling gate over the region of interest. Color flow Doppler assigns different colors (usually red and blue) to flow in different directions, so that adjacent arteries and veins are displayed in different colors superimposed on the monochrome ultrasound image.

Abdominal and pelvic ultrasound scanning needs the patient's cooperation in keeping still, turning into position, and breath holding including deep inspiration for examination of the liver, gallbladder, spleen, and kidneys. Adequate ultrasound examinations are more difficult to perform and interpret in obese patients, and also in very thin patients. Pelvic ultrasound for examination of the uterus, ovaries, and adnexa needs a full urinary bladder. Other ultrasound scans, for example, of the thyroid gland, breast, and testes, and arterial and venous Doppler ultrasound, do not usually present any special problems in the elderly.

NUCLEAR MEDICINE

Nuclear medicine imaging or gamma camera scanning produces images from γ-rays emitted by a radionuclide injected in to the patient. The most common radionuclide used is technetium (^{99m}Tc), which is tailored to image different structures or physiology by chelating it with compounds to target specific organs and/or physiological functions. The emitted γ-rays are detected by a gamma camera, which consists of a large lead-shielded crystal that scintillates when a γ-ray enters it. Groups of photomultiplier tubes behind the crystal detect and localize the scintillations and a computer analyzes the resulting electrical signals and reconstructs an image.

Nuclear medicine demonstrates physiology rather than anatomy. Because of the requirement to keep the radiation dose to the patient as low as possible, gamma camera scans typically need long imaging periods ranging from 5 to 30 minutes, during which the patient must remain absolutely still – this can be difficult for elderly patients. Patients with orthopnea due to cardiac failure can have difficulty lying flat for nuclear medicine examinations.

COMPUTED TOMOGRAPHY

Computed tomography (CT; computer-assisted tomography – CAT scanning) uses measurements of X-ray attenuation recorded by an array of detectors from a thin fan-beam of X rays. The X-ray source and detector array rotate circumferentially around the patient. This results in millions of measurements of X-ray attenuation, which can be used to

reconstruct an image of an axial slice through the patient by computer analysis using a back-projection method. Images can be reformatted in other planes, for example, coronal and sagittal, by summating information from adjacent axial slices, and 3D reconstructions are possible. The latest generation of CT scanners use helical or spiral scanning instead of planar scanning of individual axial slices, resulting in decreased scanning time and allowing better dynamic imaging of blood vessels following contrast medium injection.

Patients must keep absolutely still during CT scans or image artefacts will occur. For examination of the thorax or abdomen, breath holding is necessary. It is possible to scan the entire thorax or abdomen during a single breath-hold in cooperative patients using helical scanning. CT angiography following intravenous contrast medium injection can produce diagnostic images, including 3D reconstructions, avoiding the need for conventional invasive arteriography.

MAGNETIC RESONANCE IMAGING

MRI uses the principles of nuclear magnetic resonance (NMR) to produce cross-sectional images without the use of ionizing radiation. The patient is placed in a very strong magnetic field, typically 0.5–1.5 tesla (5000–15 000 gauss; cf. the earth's magnetic field is 0.7 gauss). Radio frequency pulses are applied at the same frequency as the precession frequency of the protons (hydrogen atoms) present in the body, causing them to resonate, like tuning forks of the same frequency. Some of the protons which are aligned with the applied magnetic field will invert or "flip" as a result, and if the radio frequency pulse is long enough, the protons will all precess in phase rather than randomly. When the radio frequency pulse is removed the protons will revert to their former state; those which have inverted will return to their earlier alignment, and they will again precess randomly. This results in very small magnetic field changes which can be detected by receiving coils, amplified, and reconstructed into cross-sectional images in any plane (Harding, 1996b).

Examination sequences range from less than 1 minute to more typical times of 4 to 5 minutes, depending on the pulse sequence employed. During each examination sequence, complete freedom from movement is essential to avoid artefacts. Various immobilization devices and supports can aid this, often incorporated into surface coils, which give better visualization of localized body areas such as the head, neck, or knees.

MRI scanning can be a daunting experience for elderly patients, due to the confined space within the scanner and the noise generated during scanning when the magnetic field gradients are changing rapidly. For the patient, entering the aperture of the MRI scanner can be reminiscent of a coffin entering a crematorium – this certainly frightens some patients and about 5% of all patients refuse MRI scanning because of claustrophobia or fear. The noise during scanning with knocking and hammering sounds which can be similar to a pneumatic drill in operation, although not quite as loud, can be upsetting; ear plugs can minimize the problem, though this makes patient communication a little more difficult. Conventional headphones cannot be incorporated into ear muffs as they would be nonoperative in the high magnetic field within the scanner, tens of thousand times the strength of the earth's magnetic field.

There are various contraindications to MRI, most of which are more common than the average in elderly patients, for example, cardiac pacemakers, ferromagnetic implants such as some surgical clips, some prosthetic cardiac valve replacements, and cochlear implants.

THERMAL IMAGING

Thermography is not widely utilized in the United Kingdom, but is undertaken in some centers. It has the advantages of being noninvasive and free of risks. It can be performed by a contact technique using liquid crystal detectors or with a thermal imaging camera which detects infrared (IR) radiation emitted by the patient, displayed as an image on a TV monitor. Thermal imaging is mainly used in the investigation of back pain syndromes and vascular disorders. In the author's experience it has proved a very useful examination tool in the initial investigation of deep venous thrombosis (DVT) (Harding, 1995, and in the investigation of osteomyelitis complicating diabetic foot ulceration, where diagnostic thermographic changes occur before radiological abnomalities, enabling earlier aggressive therapy, with significant reduction in morbidity (Harding *et al.*, 1998, 1999)).

INTERVENTIONAL RADIOLOGY

Interventional procedures may be undertaken under X-ray fluoroscopic control, ultrasound, CT, or MRI guidance. The range of interventional radiological procedures is constantly increasing in scope and complexity (Watkinson and Adam, 1996; Wilkins *et al.*, 1989; Rickards and Jones, 1989; Harding, 1993). Careful selection of patients for interventional radiological procedures is essential, jointly decided between the radiologist and referring clinician.

Informed consent is essential before performing interventional radiological procedures, and is best obtained by the radiologist personally rather than by junior clinical medical staff who may not be familiar with the details of the procedure to be performed. Consent should be obtained before the patient comes to the radiology department. This gives the radiologist the opportunity to build a relationship with the patient and, although time-consuming, this is time well spent. The importance of good communication between the radiologist and the patient cannot be overstated. The radiologist can assess the apprehensions and likely reactions of the patient away from the pressures of the radiology department. The benefits and potential risks of the procedure can be

explained under circumstances in which the patient is better able to concentrate and more likely to remember the points that have been made. It also gives the patient time to gain confidence in the radiologist, to ask questions, and to have a chance to reflect on what has been said before the procedure is performed. "Good communication is the greatest antagonist to litigation" (Oscar Craig, past President of the Royal College of Radiologists) (Allison and Allison, 1996).

Deep sedation and analgesia will be required for interventional radiological procedures, and for certain patients or procedures general anesthesia will be necessary. The patient sedated for interventional radiology will require careful clinical and electromechanical monitoring.

Clinical monitoring includes assessment of the level of consciousness, anxiety and/or pain, respiratory rate, depth and regularity, skin color, temperature and pulse rate, character, and regularity. Electromechanical monitoring includes pulse oximetry and blood pressure. ECG monitoring is a useful adjunct to pulse oximetry for patients at increased cardiovascular risk where myocardial ischemia and/or arrhythmia is present or may be precipitated. The elderly are particularly susceptible to both the wanted and unwanted effects of all benzodiazepine sedatives (Skelly, 1996).

- *Biopsy, and so on* – guided biopsy, aspiration cytology, and preoperative tumor localization.
- *Drainage* – percutaneous drainage of obstructed systems, collections, or abscesses.
- *Fistula creation, and so on* – deliberate creation of fistulae, ostomies, or shunts.
- *Stricture dilatation, and so on* – dilatation, stenting, or bypassing of strictures or recanalization of occlusions.
- *Embolization* – deliberate obliteration of occlusion of vessels or aneurysms.

Needle biopsy or aspiration cytology of masses under imaging guidance is used for diagnosis and staging in many parts of the body, for example, liver, pancreas, abdominal and pelvic lymph nodes, kidney, adrenal glands, spleen, retroperitoneum, lung, pleura, mediastinum, and musculoskeletal system. Preoperative breast tumor localization with a wire marker makes the surgical approach easier and more accurate.

Percutaneous drainage of abscesses or collections is frequently performed, including subphrenic and other intra-abdominal abscesses, intrahepatic abscesses, pyonephrosis, perinephric abscess, pelvic collections, and pancreatic cysts or pseudocysts. In the thorax, pleural, intrapulmonary, and mediastinal collections can be accurately drained under CT or ultrasound control.

Vascular procedures include percutaneous transluminal angioplasty and vascular stenting for arterial stenosis or occlusion, arterial thrombolysis for acute obstruction in peripheral limb arteries and coronary arteries, aspiration thromboembolectomy, and mechanical thrombectomy and venous thrombolysis. Percutaneous transcatheter embolization is used for deliberate occlusion of aneurysms or selective occlusion of blood vessels supplying arteriovenous malformations (AVMs) and fistulae, or varices. Emergency embolization for hemorrhage is most commonly required for gastrointestinal hemorrhage, massive hemoptysis usually from bronchial arteries, and trauma to kidney, liver, or pelvis. Pulmonary artery embolization is also occasionally performed, for hemoptysis is not responsive to bronchial (and nonbronchial systemic) embolization.

Dilatation and stenting can be undertaken in superior vena cava (SVC) obstruction. Complications relating to intravascular lines and, in particular, venous catheters are not uncommon, and can usually be easily remedied in the radiology department. Foreign bodies can be retrieved from the vascular system by percutaneous catheter techniques, for example, fragments of central venous catheters, inferior vena caval filters, metallic stents, and misplaced embolization coils.

Bronchial stenting for palliation of malignant tracheobronchial stenosis can be placed under a combination of direct (endoscopic) vision and radiological fluoroscopic screening.

The TIPS (transjugular intrahepatic portosystemic shunt) procedure is used to create a fistula between the portal and hepatic venous systems for the relief of portal hypertension with recurring variceal bleeding.

DVT can be prevented from causing pulmonary emboli by percutaneous insertion of devices into the inferior vena cava (IVC) under fluoroscopic control. IVC filters are not used in first-line prophylaxis against pulmonary embolic disease, but have a small but increasingly well-defined role in those patients who are unsuitable for conventional prophylaxis with anticoagulant therapy or who need temporary protection.

In the urinary tract, interventional procedures include percutaneous nephrostomy drainage and ureteric stenting for ureteric obstruction, percutaneous dilatation of ureteral strictures, percutaneous occlusion of ureteral fistulae, and percutaneous suprapubic cystostomy and urethral stenting for bladder outlet obstruction. Percutaneous nepholithotomy for renal calculi is used occasionally in selected cases, but has been largely superseded by extracorporeal shock wave lithotripsy (ESWL).

Biliary obstruction can be treated by percutaneous transhepatic biliary drainage or percutaneous cholecystostomy, which is also used for drainage of acute empyema of the gallbladder or for access for gallstone removal. Benign and malignant biliary structures can be dilated and stented percutaneously and calculi in the intrahepatic and extrahepatic tree removed. Interventional radiology may be combined with endoscopic procedures in the biliary tract.

In the gastrointestinal tract, interventional radiological procedures are performed in the treatment of esophageal structure by balloon dilatation and stenting. Percutaneous gastrostomy, transgastric jejunostomy, and percutaneous jejunostomy are used for enteral nutrition therapy or gastrointestinal decompression. Radiologically guided cacostomy can be used in colonic obstruction as a temporizing measure in high-risk surgical patients. Colonic strictures following surgical anstomosis can be dilated by balloon catheter techniques.

KEY POINTS

- An aging population is generally associated with multiple comorbid conditions.
- Good communication and an understanding approach is essential for successful investigation and intervention.
- Assessment of risk/benefit outcome is critical for successful resource utilization and clinical benefit for patients.
- Specific adaptations of radiology unit and equipment to facilitate management of older disabled patients are of cardinal importance.
- CT, MRI, Ultrasound, and barium studies are often essential investigations for older people, but require their cooperation.

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PART III

Medicine in Old Age

Section 16

Infectious Disorders

Infectious Diseases

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INTRODUCTION

It is at the extremes of age when susceptibility to infection and the complications thereafter are the greatest. With the rapid growth of the number of elderly persons in most developed countries, an understanding of the unique features of infectious diseases in the aged is essential. The many causes of increased morbidity and mortality from infections in the elderly are outlined in Table 1. Aging is associated with the presence of chronic diseases as well as declines in cellular and humoral immune function. In addition to the physiologic changes of aging, a segment of the older population lives in congregate settings such as group homes and long-term care facilities (LTCF), which present special issues related to the spread of infectious diseases.

The incidence of some infections, such as influenza, decreases with advancing age, yet the morbidity is substantially higher. However, many infections increase in both frequency and severity in older age-groups (Tables 2 and 3). It is also important to recognize that the specific types of organisms affecting older persons differ from those affecting younger age-groups and that older persons may not exhibit the typical clinical manifestations of infection that are observed in healthy young adults. Infections of specific organ systems will be discussed separately in their respective articles. This article will review the epidemiology, clinical manifestations, and general approach to infections in older persons. In addition, sexually transmitted diseases (STDs), severe acute respiratory syndrome (SARS), specific problems unique to LTCF, and current recommendations for vaccination in the elderly will be discussed.

EPIDEMIOLOGY OF INFECTIONS

Infections are among the most common causes of hospitalization and death in both community-dwelling and institutionalized older persons. The incidence of infection depends on the place of residence and functional status of the groups studied. Although 95% of older adults do not live in LTCFs, specific data on infection rates in community-dwelling elderly are limited. In a 2 year prospective study of 417 independent older persons, investigators found that 224 (54%) experienced a total of 494 infections (Ruben *et al.*, 1995). Respiratory tract, genitourinary and skin infections accounted for 53, 24, and 18% of the infections, respectively. Of note, 144 (35%) of these 417 persons were hospitalized 260 times. One hundred of the 260 admissions (38%) involved infection and, in half, infection was the primary diagnosis. In addition, hospitalized older persons have been shown to experience higher rates of nosocomial infections which are associated with a higher mortality rate (Emori *et al.*, 1991). The number of infections occurring in nursing homes approaches that of acute-care hospitals. The demographics of nursing-home populations are very different compared to those of community-dwelling older persons. Nursing-home residents are generally 85 years or older (40%), female (71%), and white (92%) (Verghese and Berk, 1990). Single day prevalence studies yield highly variable infection rates with upper limits of 32.7% and incidence rates up to 20 infections per 100 resident-months, resulting in approximately 1.5 million nosocomial infections per year in LTCF in the United States (Smith *et al.*, 1991). In addition to the chronic problems of respiratory, urinary tract, and skin infections, nursing homes are prone to epidemics of certain diseases, such as tuberculosis (TB), conjunctivitis, scabies, gastroenteritis, and influenza. Infection is the most common problem, necessitating transfer from nursing homes to acute-care hospitals, accounting for between 10 and 49% of all transfers.

Specific Infections

Bacterial Respiratory Infections

Pneumonia is one of the most important infectious causes of morbidity and mortality in persons of any age, but it is

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Table 1 Causes of increased morbidity and mortality of infections in older persons

Immunosenescence
Diminished mobility
Physiologic change in organ systems
Poor circulation
Edema of soft tissues
Weakening of respiratory muscles
Depressed gag reflex
Obstructive uropathy
Changes in vaginal flora associated with diminished estrogen levels
Comorbid diseases
Cardiac
Pulmonary
Diabetes
Malignancies
Dementia
Peripheral vascular disease
Iatrogenic
Intravenous lines
Implantable cardiac devices: valves, pacemakers, defibrillators
Feeding tubes
Bladder catheters
Congregate living

Table 2 Infections that increase in frequency with age

Pneumonia
Tuberculosis
Urinary tract
Chronic bacterial prostatitis
Herpes zoster
Skin/soft tissue
Contiguous focus osteomielitis
Endocarditis
Bacteremia
Diverticulitis
Cholecystitis
Intrabdominal abscess
Clostridium difficile diarrhea

Adapted from Yoshikawa (1994).

Table 3 Increased mortality associated with infections in older persons

Infection	Relative risk of mortality of elderly compared to young adults
Pneumonia	3
Influenza	6–16
SARS	3–9
Pyelonephritis	5–10
Bacteremia	3
Appendicitis	15–20
Cholecystitis	2–8
Tuberculosis	10
Infective endocarditis	2–3
Bacterial meningitis	3
Herpes zoster	7
HIV	5

Adapted from Yoshikawa (1994).

in the young children and the elderly where its impact is greatest felt (*see* **Chapter 61, Respiratory Disease in the Elderly**). The incidence of pneumonia is 10 times greater in adults over 70 years compared to persons between 20 and 29 years old (Woodhead, 1994). In addition, the likelihood of requiring hospitalization for pneumonia rises dramatically with age; from 0.54 cases per 1000 among persons aged 35 to 44, to 11.6 cases per 1000 persons over age 75 (Marrie, 1994). The incidence of community-acquired pneumonia in all adult age-groups is highest during the winter months, and is likely due to winter respiratory viruses.

Pneumonia is the leading cause of nosocomial infection related deaths. In the National Nosocomial Infection Surveillance (NNIS) System study in the United States, pneumonia accounted for 18% of the infections and 48% of the deaths between 1986 and 1990 (Emori *et al.*, 1991). The risk of nosocomial infections increases from a relatively constant rate of 10/1000 discharges for persons under age 50 to 100/1000 over age 70 (Gross *et al.*, 1983). Other risk factors associated with nosocomial pneumonia in the elderly include neurologic disease, renal disease, dependency in activities of daily living, difficulty with oropharyngeal secretions, presence of nasogastric tubes, poor nutrition, intubation, and intensive care admission (Hanson *et al.*, 1992; Harkness *et al.*, 1990). Similar to the acute-care hospital, pneumonia is the second most common infection in chronic care facilities, but remains the most common cause of death (Niederman, 1993). The susceptibility to infection correlates strongly with the degree of functional impairment (Alvarez, 1990). Underdiagnosis of pneumonia is common because of nonspecific symptoms, the infrequent use of chest radiographs, and difficulty in obtaining sputum. Prevalence rates of lower respiratory tract infection in nursing homes range from 1.9 to 2.5% with incidence rates of approximately 47 per 100 resident-months (Garibaldi *et al.*, 1981).

The spectrum of pathogens that cause pneumonia in the elderly is broader than in young adults and includes nontypable *Hemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* and gram-negative bacilli. Nevertheless, *S. pneumoniae* remains the most common bacterial pathogen causing up to 60% of community-acquired pneumonias in the elderly (Woodhead, 1994). Lastly, the "atypical" pathogens *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are relatively uncommon in persons over age 65. Hospital-acquired pneumonia in the elderly is frequently caused by enteric gram-negative rods and accounts for as many as 60 to 80% of all cases (Niederman, 1993). The NNIS study showed that nosocomial pneumonia was due to Pseudomonas in 18%, Enterobacter sp. in 11%, *Klebsiella pneumoniae* in 8%, *E. coli* in 6%, and *S. aureus* in 15% of cases.

Viral Respiratory Tract Infections

Rates of upper respiratory tract infections, the majority of which are caused by viruses, decline with advancing age and average one infection per year. However, the rates of infection depend in large part on the place of residence with increased rates of infection observed in seniors living in congregate settings (*see* **Chapter 58, Epidemiology of Respiratory Infection**). A recent study by Hodder *et al.* (1995) showed that the overall rate of respiratory infections

was 2.5/100 person-months in community-dwelling elderly in contrast to 10.8/100 person-months in an adult daycare setting. Rates of infection in nursing homes are highly variable due to the epidemic nature of most respiratory viruses.

Influenza virus is the most well recognized viral cause of serious illness in elderly persons. Although nonpandemic influenza attack rates are 20 to 30% in preschool and school-age children and drop to 10% for older adults, complications rates are highest in the elderly (Glezen and Couch, 1978). During epidemics of influenza H3N2, hospitalization rates are approximately 6 to 15/1000 for persons over age 65 (Glezen, 1982). Lower respiratory tract involvement with influenza also increases with age, rising from 4 to 8% in under age 50 up to 73% in persons over age 70 (Betts, 2000). The risk of death from influenza increases 39-fold by the presence of chronic medical conditions such as cardiovascular disease, diabetes, renal disease, anemia or immunosuppression, and the presence of both pulmonary and cardiovascular disease raises the mortality 870-fold.

Respiratory syncytial virus (RSV) is now recognized as the second most important respiratory viral pathogen in older persons with a disease burden similar to nonpandemic influenza (Thompson *et al.*, 2003). Outbreaks of RSV in nursing homes have been described with average attack rates of 20% and rates of pneumonia ranging from 5 to 67% and death ranging from 0 to 53% (Falsey and Walsh, 2000). Although the precise incidence is unknown, recent studies indicate that RSV is a cause of excess morbidity and mortality in community-dwelling elderly as well (Zambon *et al.*, 2001). In addition to influenza and RSV, a number of other viral pathogens such as coronaviruses, rhinoviruses, parainfluenza, and the newly described human metapneumovirus can also cause significant illness in older persons.

Urinary Tract Infection

Bacteriuria is the most common bacterial infection affecting older persons (Nicolle, 1997). The prevalence of bacteriuria in community-dwelling women under age 60 is <5%, which rises to 5 to 10% in women aged 60 to 70 years and 20 to 30% in those 80 years or above (Boscia *et al.*, 1986). For men, bacteriuria is rare before age 60 (<1%) but also becomes more common with increasing age. Bacteriuria is even more common in institutionalized older persons with prevalence rates of 30 to 50% in women and 20 to 30% in men, and correlates with functional disability, and is virtually 100% after 30 days with an indwelling urethral catheter (Warren *et al.*, 1982). Antimicrobial treatment of asymptomatic bacteriuria does not affect mortality and morbidity and is associated with adverse side effects, emergence of resistant flora and high relapse rates (*see* **Chapter 126, Urinary Incontinence** and **Chapter 127, Renal Diseases**).

Compared to the high incidence of asymptomatic bacteriuria, symptomatic urinary tract infection rates are relatively low. Despite this, they account for approximately 24% of all infections diagnosed in healthy older persons and are also the most common cause of bacteremia in both institutionalized and ambulatory elderly populations (Setia *et al.*, 1984). *Escherichia coli* is the most common pathogen in geriatric patients; however, the proportion of infections due to other gram-negative pathogens, such as Proteus, Klebsiella, Serratia, Enterobacter, and Pseudomonas, is higher than in younger groups (Baldassarre and Kaye, 1991). *Staphylococcus saprophyticus*, a common pathogen in young women, is unusual in older women. Of note, isolates from elderly men are frequently gram-positive organisms, such as Group B Streptococcus and *Enterococcus* sp (Boscia *et al.*, 1986).

Skin and Soft Tissue Infections

After the urinary and respiratory tract, the skin is the third most common site of infection in the elderly and the incidence of cellulitis, diabetic foot ulcers and other cutaneous infections all increase with age (Alvarez, 1990; Ruben *et al.*, 1995). In community-dwelling older persons, the incidence for all types of skin infections is 12.7/100 person years and the incidence of cellulitis is 3.2/100 person years (Ruben *et al.*, 1995). New skin infections occur at a rate of approximately 1.6 per 100 resident-months in nursing homes (Scheckler and Peterson, 1986).

Herpes Zoster

Varicella zoster virus remains latent in the dorsal root ganglion after primary infection and may reactivate at any time throughout life. The lifetime risk of zoster is approximately 10 to 20%; however, risk increases dramatically with advanced age (Straus *et al.*, 1988). The incidence of zoster in the general population is 215/100 000 but increases to 1424/100 000 in persons over age 75 (Donahue *et al.*, 1995). Approximately, 1% of persons over age 80 will develop herpes zoster each year with a significant risk of post herpetic neuralgia (Kost and Straus, 1996). Pain lasting over 1 year has been reported in 4, 22, and 48% of patients under age 20, over 55 and over 70 years, respectively (*see* **Chapter 148, Infections of the Central Nervous System**).

Infectious Diarrhea

Although the overall incidence of diarrhea in older persons in the general population is not increased, the impact of these illnesses is significant. A study of approximately 87 000 hospitalizations for gastroenteritis found that 85% of the 514 deaths were adults over the age of 60 with a case fatality of 3% in persons older than age 80 (Slotwiner-Nie and Brandt, 2001). Nursing-home residents are at highest risk for developing diarrheal illness because of outbreaks that tend to occur in closed populations. Outbreaks of Salmonella, *Escherichia coli* 0157:H7, rotavirus, Norwalk-like viruses, giardia, and cryptosporidiosis have all been reported in chronic care facilities. Lastly, age is associated with an increased risk of developing *C. difficile* colitis. Clusters of *C. difficile* have been reported from a number of nursing homes and control of outbreaks is very difficult because of the prolonged carrier state, hardy spores, and fecal

oral contamination in demented and incontinent patients. Although more common, *C. difficile* colitis does not appear to have a worse clinical outcome with older age. Despite delayed diagnosis and higher white blood cell counts than younger persons, mortality was not significantly higher in older patients in several recent studies.

Meningitis

The incidence of meningitis in persons aged 60 or older is approximately 2 to 9/100 000 per year with a case-fatality rate of 35 to 81% (Miller and Choi, 1997). The spectrum of pathogens that cause meningitis in older persons is different from the ones that cause meningitis in healthy young adults (Schuchat *et al.*, 1997). Although *Streptococcus pneumoniae* is the most frequently isolated organism in all adult age-groups (32–68%), *Listeria monocytogenes* which is uncommon in young adults accounts for 10 to 25% of case of meningitis in the elderly. Viruses and *Neisseria meningitidis* that are common in children and young adults are uncommon in the elderly, whereas gram-negative bacillary meningitis occurs more frequently in older adults (Durand *et al.*, 1993). Although TB meningitis is not common at any age, the incidence of active TB rises with advancing age and therefore the diagnosis should be considered in any older person with "aseptic" meningitis (*see* **Chapter 148, Infections of the Central Nervous System**).

Bacteremia

Bacteremic illnesses increase in both frequency as well as mortality with advancing age (Richardson, 1993). The genitourinary tract accounts for 24 to 56% of cases of bacteremia with other sources including the abdomen, skin, and respiratory tract. The most commonly isolated species from community-dwelling elderly are *E. coli*. and *Klebsiella* sp., whereas other gram-negatives such as *Providencia stuartii, Proteus* sp., and *Pseudomonas* sp. are more frequently found in residents of long-term care. *S. aureus, Enterococcus* sp., and *S. pneumoniae* are the most common gram-positive bloodstream isolates. In LTCF, methicillin-resistant *S. aureus* can be a significant problem (Mylotte *et al.*, 2002). Mortality in bacteremic elderly patients varies from 9.1% in the community-dwelling elderly with gram-negative infections to 47.2% in elderly persons with nosocomial bacteremia (Richardson, 1993). Risk of death is increased in patients with nosocomial bacteremia, a nonurinary source, respiratory infection, *S. aureus* or inappropriate antibiotic treatment.

Infective Endocarditis

In the preantibiotic era, the most common endocarditis patient was a young person with rheumatic heart disease, whereas recent reviews show that the incidence of endocarditis now is substantially higher in patients over the age of 50 reaching a peak at 70 to 74 years (Selton-Suty *et al.*, 1997; Terpenning *et al.*, 1987; Wells *et al.*, 1990). With the decline of rheumatic heart disease, degenerative valvular lesions, such as calcified aortic valves and mitral annulus calcification, as well as mitral valve prolapse with redundancy are common predisposing conditions in the elderly persons (McKinsey *et al.*, 1987). In addition, nosocomial endocarditis due to invasive medical procedures is more common in older adults and accounts for 23% of cases (Terpenning *et al.*, 1987). α-Hemolytic streptococci and *S. aureus* remain the most frequently isolated pathogens; however, *Enterococcus* sp., *Streptococcus bovis,* and coagulase negative staphylococci are more common in elderly persons than in younger age-groups. As with almost all infectious diseases, mortality with endocarditis at older age is associated with increased mortality. Elderly patients with endocarditis have an approximately twofold higher risk of death compared to younger persons (Wells *et al.*, 1990). In addition, neurologic complications and permanent disability requiring subsequent long-term care are more common in older patients who survive an acute episode of endocarditis (*see* **Chapter 147, Infective Endocarditis in the Elderly**).

CLINICAL PRESENTATION

Most elderly patients exhibit typical clinical features of infectious processes. However, a significant proportion of older persons with serious infections may present with atypical or nonspecific signs and symptoms due to the effects of aging, dementia, and comorbid diseases (Table 4). This is particularly true for frail institutionalized persons whose cognitive impairment may prevent them from communicating specific focal symptoms. For instance, a number of studies have shown that elderly persons with pneumonia are less likely to complain of cough and pleuritic chest pain. Symptoms of dysuria, urgency, and frequency are often absent in elderly patients with cystitis, particularly in those who have indwelling catheters (Baldassarre and Kaye, 1991). In addition, flank pain and fever, which suggest pyelonephritis in young, healthy adults, are commonly absent in older patients. Underlying diseases, such as osteoarthritis, may mask the symptoms of a joint infection in the elderly adult. Similarly, meningismus may be difficult to detect in persons with cervical arthritis or parkinsonism, making it an unreliable diagnostic sign of meningitis in the elderly. Lastly, intra-abdominal processes are more likely to be overlooked in the

Table 4 Atypical symptoms of infection in older persons

Acute confusion
Change in functional status
Anorexia, weight loss
Weakness
Urinary incontinence
Falls
Tachypnea
Tachycardia
Hypotension
Hypothermia

Table 5 Causes of diminished febrile response in older persons

Artifact
Oral temperature
Inability to cooperate
Mouth breathing
Biologic
Drugs – aspirin, nonsteroidal anti-inflammatory drugs, acetaminophen, phenothiazines
CNS – diminished temperature perception, decreased thermal circadian rhythm
Metabolic – decreased basal metabolic rate
Vasomotor – diminished vasoconstriction, decreased efficiency or shivering
Decreased response to endogenous pyrogens (IL-1, IL-6, TNF)

CNS, central nervous system; IL, interleukin; TNF, tumor necrosis factor.

older person because of atypical presentations, and thus result in delays in definitive surgery.

Fever is a cardinal symptom of infection; however, 20 to 30% of elderly persons have a diminished febrile response (Norman, 2000). Reasons for this are complex and are listed in Table 5. The traditional definition of fever as an oral temperature of $>101\,^{\circ}F$ or $38.3\,^{\circ}C$ may be inappropriate in aged persons. Aside from technical difficulties in the measurement, febrile responses may be blunted because of lower baseline temperatures in older persons. Although baseline temperatures are lower, most elderly individuals who were afebrile using standard criteria did demonstrate a change in temperature from baseline of $>1.3\,^{\circ}C$ during infectious episodes. If fever is defined as a rectal temperature of $>37.5\,^{\circ}C$, most infected nursing-home patients will have fever; therefore, authorities recommend the following guidelines for defining fever in older persons.

1. Persistent elevation of body temperature at least $>1.3\,^{\circ}C$ above baseline values.
2. Oral temperature of $37.2\,^{\circ}C$ or greater on repeated measurement.
3. Rectal temperatures of $37.5\,^{\circ}C$ or greater.

FEVER OF UNKNOWN ORIGIN

Persistent fever without a known cause is a diagnostic challenge in any age-group, but it is particularly problematic in the elderly person who may not tolerate a prolonged and invasive workup. Fever of unknown origin (FUO) was originally defined by Petersdorf and Beeson as fever $>38.3\,^{\circ}C$ for at least 3 weeks, which remains undiagnosed after 1 week of in-hospital evaluation. The causes of FUO in the older patient differ somewhat from those in younger age-groups (Norman, 2000). Of infectious causes, intra-abdominal abscess are most common followed by TB and endocarditis. Unlike younger age-groups, viral infections are relatively infrequent causes of FUO. Collagen vascular disorders, particularly temporal arteritis and polymyalgia rheumatica, are important causes of FUO in the elderly accounting for 31% of cases in one study (Knockaert *et al.*, 1993). The most common malignancies causing fever in the elderly are non-Hodgkin's lymphoma or Hodgkin's disease. In addition, recurrent pulmonary emboli and drug fever should be considered as possible causes of FUO in this population. The etiology of FUO can be established in approximately 90% of elderly persons and many of these conditions are potentially treatable. After a thorough routine evaluation, a CT scan of the abdomen is the highest yield procedure for infectious processes and lymphomas. If diagnosis remains elusive, temporal artery biopsy should be considered in elderly patients with FUO, particularly if erythrocyte sedimentation rate is elevated.

INFECTION CONTROL IN LONG-TERM CARE FACILITIES

Infection prevalence rates in LTCFs range from 1.6 to 32.7 and incidence rates range from 2.7 to 9.5 infections per 1000 resident-months (Nicolle, 2000). Elderly residents of institutions are particularly vulnerable to infection because of their debilitated state, impaired mental status, and the frequent use of urinary catheters. Studies have shown that at any point in time, 8% of nursing-home patients are receiving systemic antibiotics (Nicolle *et al.*, 2000). Frequently, workup has been inadequate, and in 25 to 75% of cases antibiotic choices are inappropriate, leading to the development of resistant organisms. The necessity of hands-on contact between residents and staff may facilitate transmission of pathogens. A unique problem in the LTCF is the wandering resident who may be incontinent or coughing and be a vector for the spread of infectious agents. Additionally, limited access to laboratory tests and X ray facilities make the diagnosis of infection more difficult. Lastly, problems with infection control may be exacerbated by the lack of accessible hand-washing facilities and private rooms, as well as communal dining and bathroom facilities. Unlike hospitals, the LTCF is a home for its residents, and infection control practices must be balanced with resident needs and comforts. Guidelines for infection control practitioners in LTCFs have been developed to assist with surveillance, diagnosis, treatment, and containment of infectious diseases in various types of facilities (Bentley *et al.*, 2001). Hand washing is the cornerstone of any infection control program in long-term care. Unfortunately, while this is simple and effective, compliance is often poor. New alcohol gel hand sanitizers offer high antimicrobial activity and ease of use and may improve compliance. One recent study showed a 30% decrease in infections in LTCF units with gel sanitizers compared to those without them (Fendler *et al.*, 2002).

Influenza

Outbreaks of influenza virus in LTCFs are characterized by high attack rates with significant morbidity and mortality (Centers for Disease Control, 2004). Influenza virus is spread

Table 6 Influenza chemoprophylaxis: recommended dosage for persons over age 65

Drug	Activity	Route of administration	Dosage
Amantadine	Influenza A	Oral	$\leq 100\,mg\,day^{-1}$ [a]
Rimantadine	Influenza A	Oral	$\leq 100\,mg\,day^{-1}$ [b]
Zanamivir	Influenza A and B	Inhaled	Not approved
Oseltamivir	Influenza A and B	Oral	$75\,mg\,day^{-1}$ [c]

[a]Further dose adjustment required for creatinine clearance less than 50 ml/minute. Dosing interval should be increased to every 48 to 72 hours.
[b]Dose should be decreased with severe hepatic or renal disease (creatinine clearance less than 10 to 20 ml/minute).
[c]Dose should be adjusted with severe real disease (creatinine clearence <20 ml/minute).

via small particle aerosols and patients may be infectious for up to 2 hours prior to becoming symptomatic. Thus, institutional outbreaks may be explosive and difficult to control. Critical to the control of influenza is an effective yearly vaccination program for all residents and staff. When influenza activity is prevalent in the community, resident furloughs should be restricted to those medically necessary and visitors with respiratory illnesses limited. Once influenza has been identified within the institution, ill patients should be restricted to their rooms with their doors closed, and employees should wear masks and gloves upon entering. Residents and staff should be cohorted if possible and affected wards closed to new admissions. Vaccination should be offered again to all unvaccinated staff and residents, and the use of prophylactic antiviral drugs considered. In the United States, institution-wide chemoprophylaxis is recommended for all residents (regardless of vaccination status) once influenza virus has been identified in an LTCF (Table 6) (Arden, 2000). Because of side effects, cost, and the issue of resistance, some authorities prefer a more conservative approach of administering amantadine only to individuals who are ill less than 48 hours, and to roommates of ill residents. Institution-wide prophylaxis should be considered if over 10% of residents are ill or if there has been a major antigenic change in the influenza virus. In the past, only two antivirals were available, amantadine and rimantadine, which are effective only for the treatment of influenza A, and their use was limited by the emergence of resistant viruses on therapy. In addition, amantadine is associated with significant central nervous system (CNS) toxicity in the elderly. More recently, two additional agents, zanamivir and oseltamivir, which are neuraminidase inhibitors, have been developed. All four drugs are equally efficacious for the treatment and prophylaxis of influenza. There are several advantages to the new agents in that they are active against both influenza A and B viruses, resistance is uncommon, and side effect profiles are considerably better. However, cost is the primary limitation and many LTCFs continue to rely on the older drugs for influenza A outbreaks.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections emerged as a problem in acute-care hospitals in the 1970s and, as is true with most nosocomial infections, became endemic in many LTCFs shortly thereafter. In the 1980s, many LTCFs denied admission to MRSA patients with the hope of excluding MRSA from their institution. Despite these policies, MRSA colonization rates in LTCFs range from 8 to 46% (Bradley, 2002). Since rates of MRSA colonization in LTCFs may be as high as in acute-care hospitals, exclusion of the MRSA patient is not warranted. It is appropriate to identify MRSA infected patients prior to transfer because patients with draining wounds or copious sputum are more likely to spread MRSA. Since it has not been established that nasal carriers are at high risk of spreading MRSA, it is not necessary to screen all transfers. During nonoutbreak situations, isolation of the MRSA resident depends on the individual (Bradley, 1999). Functionally dependent persons should be placed on contact isolation. Functionally independent nasal carriers should be allowed to participate in group activities. Patients with infected wounds should also be allowed to participate as long as wounds are properly covered. A person who cannot handle secretions and who has MRSA in the sputum, or a tracheostomy, should be placed in isolation until MRSA clears. Elimination of the MRSA carrier state by treatment with local or systemic antibiotics is frequently unsuccessful and can be associated with the development of further resistance. Therefore, routine use of antibiotics to eradicate MRSA carriage in the LTCF should be discouraged.

Clostridium Difficile

Clostridium difficile is a spore-forming, toxin-producing, gram-positive rod that may reside in the large intestine. Pseudomembranous colitis (PMC) results from overgrowth of this organism under antibiotic pressure, with subsequent toxin production. Transmission occurs via hand carriage from person to person, and environmental contamination. Spores may survive in the environment for up to 3 months and are resistant to routine soaps. Glutaraldehyde or chlorinated compounds are required for eradication. Asymptomatic carriage of *C. difficile* is found in 2% of healthy adults, 7% of healthy elderly, 9% of LTCF residents (not on antibiotics), and 16 to 56% of hospitalized elderly (Bentley, 1992). Continuous outbreaks lasting 6 weeks to 11 months have been reported, and during outbreaks, asymptomatic carriage rates have been found to be very high (27–73%). Symptoms of PMC in LTCF residents tend to be milder and more nonspecific compared with those in other groups. Symptomatic patients should be treated with oral metronidazole or vancomycin and systemic antibiotics limited if possible. Since the environment may be contaminated, infected persons should be placed in isolation. Staff and visitors should wear gloves upon entering the resident's room. Body secretion spills should be cleaned with a 20 to 25% sodium hypochlorite solution.

Tuberculosis

In developed countries, LTCFs are a repository for TB. Today's octogenarians were infected 50 to 70 years ago when 90% of the adult population was exposed to TB. Endogenous reactivation of TB remains the leading cause of TB in older persons. However, exogenous reinfection or primary infection from a fellow resident with unsuspected TB within nursing homes has been well documented. A full discussion of TB in the elderly is beyond the scope of this article, but several general points regarding infection control in the LTCF should be made. First, all new admissions to an LTCF should have a two-step purified protein derivative (PPD) skin test and reactions should be documented in the chart (Zevallos and Justman, 2003). A positive PPD is classified as >10 mm of induration; however, >5 mm of induration is also considered positive in those who are in close contact with persons with infectious TB or who have chest radiographs suggestive of previous TB. Some authorities recommend PPD retesting annually or every 2 years for all residents with a negative PPD. At a minimum, nonreactors should be retested whenever a new active case of TB is diagnosed or suspected. Individuals with a positive PPD who were negative during the preceding 2 years and who have normal chest radiographs should receive isoniazid prophylaxis for 9 months under close supervision. Even for patients at advanced ages the benefits of such practice outweigh the risks. Previous recommendations included chemoprophylaxis for individuals with a positive PPD of unknown duration with certain high-risk conditions such as diabetes, renal failure, immunosuppression, chronic steroid use, and silicosis as well as those with abnormal chest radiographs. In 2000, the US Center for Disease Control and Prevention (CDC) with the American Thoracic Society revised the recommendations, such that any high-risk individual with a positive PPD should receive chemoprophylaxis regardless of age or duration of positive PPD. Residents of nursing homes are considered high risk. The decision to treat such individuals remains somewhat controversial. A high index of suspicion for active TB should be maintained by clinicians, because signs and symptoms may be atypical and the PPD negative in older persons. Employees of LTCFs are also at increased risk of infection with TB. They should have a PPD placed at the time of employment and also annually (Zevallos and Justman, 2003).

SPECIFIC INFECTIONS

Sexually Transmitted Diseases

Despite the perception among health-care providers that elderly adults are not at risk for STDs, many older adults remain sexually active and are at risk for STDs (Calvert, 2001). The Janus report on sexual behavior found that 69% of American men over the age of 65 and 74% of woman report some form of sexual activity at least weekly. Additionally, in a survey of persons between the ages of 80 to 100, 62% of men and 30% of women engaged in sexual intercourse. Because of cultural, social, and religious practices of older adults, they may be less likely to speak freely of STDs and thus, it is important for providers to be mindful of such issues. The finding of an STD in a nursing-home resident should always prompt an investigation because of concerns for elder abuse.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is a cause of enormous morbidity and mortality worldwide. While it is predominantly a disease of younger persons, data reported to the CDC in the United States indicates that approximately 10% of Acquired Immune Deficiency syndrome (AIDS) cases are in persons >50 years (Chiao *et al.*, 1999). Before 1989, 15% of AIDS cases in older persons were transfusion related. However, since 1996, the epidemiology of HIV in older adults has changed. Transfusion now only accounts for 2.4% of cases, whereas men who have sex with men accounts for the largest percentage at 36% and intravenous drug use (IVDU) accounts for 19%. Although IVDU is the second most common risk factor, it is significantly less than in individuals of ages between 13 and 49. Both heterosexual contact (14%) and unknown risk (26%) are significantly greater in adults over 50 years of age compared to younger age-groups.

Numerous studies indicate that older age is associated with a shortened interval between time of HIV diagnosis and the development of AIDS as well as time from onset of AIDS to death (Adler *et al.*, 1997). Hemophiliacs >55 years have a relative mortality of 4.7 after developing AIDS compared to younger counterparts. The reason for decreased survival in older AIDS patients is likely multifactorial and includes comorbidities, delay in diagnosis, and age-related immune dysfunction (Calvet, 2003). Studies by Adler *et al.* (1997) have demonstrated that destruction of T-cells of young and old patients progress at the same rate but older persons have an impaired ability to replace functional T-cells.

Clinical presentation of AIDS in older persons is similar to that in younger adults, but diagnosis remains challenging because common medical problems associated with aging may confuse or delay workup. Thus, patients may undergo extensive workups for cerebrovascular disease, Alzheimer's disease, malnutrition, cancer or depression before the diagnosis of HIV is even entertained. Although several studies have shown that the clinical presentation of AIDS in older patients is similar to the young and that pneumocystitis pneumonia (PCP) is the most common opportunistic infection in both groups, some differences are worth mentioning. 1996 CDC data indicates that older individuals are significantly more likely to develop wasting syndrome and HIV encephalopathy than are patients aged 13 to 49 years (Calvet, 2003). In addition, 14% of older adults develop malignancies; most commonly Kaposi's sarcoma or non-Hodgkin's lymphoma. HIV encephalopathy in older persons deserves special mention, given the prevalence of Alzheimer's and

cerebrovascular disease in this population. HIV is associated with subacute encephalitis, which leads to a subcortical dementia in contrast to Alzheimer's disease which is a cortical disease often leading to aphasia and other manifestations of cortical dysfunction. The progression of HIV encephalopathy is expected to be relatively rapid with decline over months compared to the more slowly evolving Alzheimer's. In addition, HIV dementia is associated with pleocytosis in the cerebrospinal fluid (CSF) in 25% of cases, whereas CSF is normal in Alzheimer's disease. It is important to consider HIV in the workup of dementia since antiretrovirals may slow progression or improve symptoms.

The treatment of HIV infection in older age has not been well studied. Most trials of antiretroviral medications have excluded persons over age 60. A recent cross-sectional survey of HIV infected individuals taking highly active antiretroviral therapy (HAART) found that persons over age 55 tolerated therapy as well as younger subjects with no significant differences in adherence rates or the need for modification of treatment because of side effects (Manfredi *et al.*, 2003). However, older patients had lower mean drop in viremia (0.5 $\log_{10}$ vs 1.0 $\log_{10}$) and immune recovery was significantly slower and more blunted. Interestingly, other investigators found that compliance with HAART was better in persons >50 years compared to younger age-groups. At present, more studies of HAART in older age-groups are needed to evaluate efficacy; but age alone is not a sufficient reason to deny treatment.

Prevention of HIV is critical in all age-groups. A problem unique to older age-groups is that both health-care professionals as well as patients themselves do not perceive the risk appropriately. In AIDS behavioral studies in the United States, less than 7% of subjects who were sexually active, >50 years, and who resided in cities with a high prevalence of HIV had ever had HIV testing done (Calvet, 2003). Additionally, less than 11% of older people had ever discussed HIV testing with their doctor. As a result of decreased concerns about pregnancy, older adults are also much less likely to use condoms than younger people. Clearly, STD testing and safe sex practices need to be addressed in older age-groups.

Syphilis

Primary and secondary syphilis are not common in persons over age 55 accounting for only 4% of cases reported in the United States in 1997 (Calvert, 2001). Although uncommon, syphilis should be considered in any sexually active patient with an unexplained rash or a new genital ulceration. While early syphilis is not frequent, latent syphilis is primarily a problem of older age. A serum rapid plasma reagin (RPR) is typically included in a routine dementia workup. If the confirmatory specific *Treponema pallidum* antibody is positive, then all patients with infection for greater than 1-year duration should have a lumbar puncture performed. This includes most elderly adults with a positive RPR. It is particularly important to evaluate the CSF if any neurologic signs or symptoms are present (including deafness), the patient has co-infection with HIV or other signs of tertiary syphilis such as aortitis or gummas. Unfortunately, there is no gold standard for the diagnosis of neurosyphilis and CSF – venereal disease research laboratories (VDRL) are positive in only 50% of cases of neurosyphilis. Thus, even mild pleocytosis or elevation of protein may indicate CNS involvement and are indications for treatment. The optimal treatment of neurosyphilis is 18 to 24 million units of intravenous penicillin for 10 to 14 days. Follow-up is required to insure a response to therapy.

Herpes Simplex

Herpes Simplex virus type 2 (HSV-2) or genital herpes simplex is extremely common, affecting 22% of the adult population in the United States (Calvet, 2003). Seroprevalence for HSV-2 rises with increasing age, the highest prevalence being in previously married, black women aged 60 to 74 years. Approximately 70 to 80% of individuals with HSV-2 antibodies are not aware of their infection. Thus, HSV-2 should be kept in mind when evaluating perineal ulcers or rash even if the patient does not have a known history of genital herpes. The best method of diagnosis remains to be viral culture of early lesions. The virus is relatively hardy and grows rapidly; usually within 48 hours. However, a negative culture does not rule out the infection. Treatment includes acyclovir and the new formulations, famciclovir and valacyclovir, which offer improved oral absorption. Treatment may be initiated for primary infection to decrease symptoms or with recurrent disease to suppress outbreaks. Patients should be counseled that transmission can occur even if the patient has no symptoms, and therefore the use of condoms at all times is encouraged.

Gonorrhea

Infection with *Neisseria gonorrhea* is uncommon in the elderly and occurs at a rate of 4/100 000 in persons 65 years and older. There is no clear evidence that gonorrhea (GC) is more severe in elderly persons compared to the young although cases of disseminated GC in the elderly have been reported (Calvet, 2003). Diagnosis is usually made by urethral or cervical culture but can also be accomplished by polymerase chain reaction (PCR). Treatment of uncomplicated GC: a single dose of Ceftriaxone 125 mg IM, Cefixime 400 mg PO or an oral quinolone. Local resistance patterns and travel should be kept in mind when selecting therapy.

Severe Acute Respiratory Syndrome (SARS)

In March of 2003, the World Health Organization issued a global alert regarding a severe atypical pneumonia in China, Hong Kong, and Vietnam referred to as *Severe Acute Respiratory Syndrome* (SARS). A newly discovered coronavirus

(SARS-Cov) was subsequently identified as the cause of SARS (Peiris *et al.*, 2003). It is hypothesized that SARS-Cov is an animal virus, which crossed the species barrier into humans possibly from "game food" in southern China. Infected persons initially present with fever, myalgias, and rigors. Cough is common, but dyspnea and chest tightening may only present later in the illness. Unlike other common respiratory viruses, rhinorrhea and sore throat are uncommon. Diarrhea may occur in approximately 20% of cases. Laboratory findings include ground glass opacifications on chest radiographs, lymphopenia, and elevations of liver function tests. Although fever is present in over 90% of patients with SARS, afebrile cases of SARS can occur in the elderly. In one such case, an elderly adult presented with malaise and poor appetite with a hip fracture secondary to a fall but no fever.

The case-fatality rate during recent outbreaks was 9.6% (range 0–40%). Advanced age is the single most important risk factor for death; patients >60 years have a case-fatality rate of 45% and the relative risk of death is 1.5 to 1.8 per each decade of life increased (Christian *et al.*, 2004). Patients are most infectious later in the illness when symptoms progress, requiring hospitalization. Transmission is believed to be through direct or indirect contact of mucous membranes (eyes, nose, mouth) with infected secretions but spread via small particle aerosols has not been completely ruled out. Diagnosis can be made by viral culture, reverse transcriptase-polymerase chain reaction (RT-PCR) or serology; however, no test is very sensitive early in illness. Despite initial enthusiasm for high dose steroids and ribavirin, at present there is no specific therapy for SARS. Intensive work on antivirals and vaccines is ongoing.

VACCINATION

Vaccination is one of the most cost-effective strategies available to reduce the morbidity and mortality associated with a number of infectious diseases. Although vaccine response rates are diminished in older persons and cost effectiveness has been debated, three vaccines are recommended for all older persons: tetanus toxoid, pneumococcal vaccine, and influenza virus vaccine.

Tetanus–diphtheria Toxoid

The annual incidence of tetanus cases in developed countries is very low (Bentley, 1992). However, over 50% of the tetanus cases occur in persons over the age of 50, with 60% mortality. More than 90% of the deaths from tetanus are in persons over age 50 (Richardson and Knight, 1991). Because there is no natural immunity to tetanus, disease occurs almost exclusively in those who are inadequately or unimmunized. Since routine vaccination of school children and armed forces personnel did not begin until the 1940s, many elderly persons never received a primary series of tetanus toxoid immunization. In addition, the recommended booster doses every 10 years are frequently neglected in older persons. Studies from the United States, Britain, Germany, Denmark, and Sweden have shown that 45 to 80% of community-residing elderly and 30 to 50% of nursing-home residents lack immunity (Gergen *et al.*, 1995). Although commonly associated with accidental trauma, a significant number of tetanus cases occur in the setting of chronic skin ulcers, gangrenous extremities or recent surgery (Bentley, 1992). The current vaccine contains formaldehyde-denatured tetanus toxoid and diphtheria toxin (Td), and will provide protection to diphtheria as well as tetanus. Although studies have shown that the antibody levels achieved by older adults are lower than those of young adults, protective antibody titers are present in 100% of older persons after the third dose of primary immunization. Duration of antibody may also be somewhat diminished but booster doses are highly effective at raising antibody to protective levels. Vaccination is well tolerated by older persons and the only contraindication is a history of neurological or severe hypersensitivity reactions to previous Td. The current recommendations are that all older persons who are inadequately immunized or whose history of immunization is unknown receive primary immunization with Td. Although standard recommendations are for a single Td booster every 10 years after primary immunization, some authorities feel that a single booster given at age 65 is the most cost-effective practice (Balestra and Littenberg, 1993). All older patients evaluated for wounds should be questioned regarding immunization status, and Td immunization given as appropriate. In addition, immunity status should be determined prior to elective bowel surgery and for nursing-home patients with decubitus ulcers or vascular complications.

Pneumococcal Vaccine

Pneumococcal infections are an important cause of illness and death in older persons, thus making prevention of these infections by vaccination highly desirable. Approximately 30 to 50% of community-acquired pneumonias are due to *Streptococcus pneumoniae* (Fedson *et al.*, 1994). At least 16 000 cases of invasive pneumococcal disease occur yearly in the United States among people over age 65. Case-fatality rates are as high as 40% for bacteremia and 55% for meningitis, despite prompt diagnosis and treatment with appropriate antibiotics (Bentley, 1992). Vaccination has become even more important with the rapid increase and global spread of antibiotic-resistant pneumococci.

Pneumococcal vaccine contains purified capsular polysaccharide antigens from different serotypes of *S. pneumoniae*. The first vaccine, licensed in 1977, contained 14 of the 83 different serotypes. In 1983, an expanded 23-valent vaccine became available. Vaccine-associated reactions occur within 24 hours in 10 to 15% of elderly vaccinees and consist primarily of local discomfort. Fever of >100 °F occurs in approximately 2% of vaccinees and usually lasts less than 24 hours. Severe local and systemic reactions have been reported more often in younger persons and

revaccinated individuals (Bentley, 1992). Pneumococcal vaccine and influenza vaccine may be administered simultaneously at different sites without affecting immunogenicity or side effects. Most healthy young adults maintain adequate antibody levels for 5 to 6 years. Several studies suggest that, while older persons respond to pneumococcal vaccine, they may have lower peak titers and antibody levels may diminish at a more rapid rate. Early studies involving small numbers of young individuals showed high rates of local Arthus-type reactions when subjects were revaccinated. More recent data indicate that older persons who received the 14-valent vaccine may be revaccinated with the 23-valent vaccine 6 years after primary vaccination with no significant side effects and a boost of antibody levels.

Much debate has been generated concerning the efficacy of pneumococcal vaccine in high-risk populations, particularly older persons. Pneumococcal vaccine was shown to be highly effective when tested in young healthy South African gold miners, a group in whom the incidence of disease is very high. However, the results of controlled trials in older persons in the United States have been inconclusive because of the small sample sizes used. Retrospective case-control studies have shown pneumococcal vaccine to be between 50 and 80% effective for the prevention of invasive pneumococcal disease in older persons (Fedson *et al.*, 1994). Vaccine efficacy has been shown to decrease progressively over time and is least efficacious in very elderly persons (>85 years). Yet, in the largest case-control study published, the 5-year efficacy in immunocompetent patients aged 65 to 74 was 71%, and in those 75 to 84 years of age the 3-year efficacy was 67% (Shapiro *et al.*, 1991). Analyses of the cost effectiveness of pneumococcal vaccine have estimated that routine vaccination of all persons over age 65 is a cost-saving procedure (Fedson *et al.*, 1994). The most recent analysis of the effectiveness of pneumococcal vaccine involved 47 000 adults over age 65 and confirmed a significant reduction in the risk of bacteremia associated with vaccination but did not show a beneficial effect for nonbacteremic pneumonia (Jackson *et al.*, 2004).

Pneumococcal vaccine is recommended for immunocompetent persons at increased risk of pneumococcal disease for a variety of chronic illnesses such as cardiovascular disease, pulmonary disease, diabetes mellitus, cirrhosis and, alcoholism (Table 7) (Center for Disease Control and Prevention, 1997). It is also recommended for patients with CFS leaks, and for persons aged 65 or older. Revaccination should be considered for those individuals at highest risk of fatal pneumococcal disease and who received the 23-valent vaccine over 6 years ago. It should also be considered for patients who have a rapid decline in antibody titers,for example, patients with nephrotic syndrome. Revaccination is also recommended for healthy elderly persons who received vaccine before age 65 and more than 10 years has passed. Routine revaccination of elderly persons is not currently recommended (Bentley, 1992). This is because of concerns about reduced immunogenicity of repeat vaccinations with polysaccharide vaccines. A recent study from Sweden examined the effect of revaccinating elderly adults after 5 years with pneumococcal vaccine (Torling *et al.*, 2004). Although there was a significant increase in the mean geometric antibody concentration, levels were lower than after primary vaccination. These issues have stimulated interest in the pneumococcal conjugate vaccines in adults (Abraham-Van Parijs, 2004). While these vaccines offer the advantage of stimulating T lymphocytes and memory, they include only seven antigenic types compared to 23 in the polysaccharide vaccines.

Table 7 Indications for pneumococcal vaccine

Primary vaccination
Over age 65 years
Ages 2–64 years
Chronic illnesses including CHF, COPD, diabetes, alcoholism, liver disease
Nephrotic syndrome, CSF leaks
Asplenia
Immunocompromised
Special ethnic groups including Native Americans and other groups with high rates of invasive pneumococcal disease
Revaccination (greater than 5 years since primary vaccination)
Patients with rapid decline in antibody levels
Asplenia
Nephrotic syndrome
Renal failure or transplantation
HIV
Other forms of immunosuppression
Over age 65
If primary vaccination took place under age 65
Vaccine status is unknown

Adapted from Center for Disease Control and Prevention (1997)

Influenza Vaccine

Influenza continues to be an important cause of excess morbidity and mortality throughout the world, especially in the elderly (Centers for Disease Control, 2004). The current vaccine contains two type A and one type B influenza virus strains representing the viruses predicted to circulate during the upcoming year. The vaccine is made from highly purified, egg-grown inactivated viruses in a trivalent preparation. Whole virus, subunits, and purified surface antigen preparations are available. Acute local reactions such as mild soreness at the vaccination site occur in approximately one-third of vaccinees. Systemic reactions, including fever, occur in less than 1% of vaccinees, and appear to be less severe in older persons. Influenza vaccine is contraindicated in persons with an anaphylactic or immediate hypersensitivity reaction to eggs.

The efficacy of influenza vaccine depends on the age and immunocompetence of the subjects as well as the match of the vaccine to the epidemic strain. In placebo-controlled trials of young healthy persons, efficacy rates for reducing influenza infection ranged from 67 to 92% (Bentley, 1992). Effectiveness in other populations, especially the elderly, has been more variable with occasional reports of vaccine failure. One of the few prospective, randomized, placebo-controlled trials of influenza vaccine efficacy, from the Netherlands, demonstrated that vaccination resulted in a

Table 8 Groups in which yearly influenza vaccination is recommended

Groups who are at increased risk for influenza-related complications
Persons > age 65
Residents of nursing homes and chronic care facilities
Persons with chronic cardiac or pulmonary disorders
Persons who have required regular medical follow-up during the preceding year because of chronic metabolic diseases (including diabetes), renal dysfunction, hemoglobinopathies or immunosuppression
Persons who can transmit influenza to high-risk groups
Physicians, nurses, and other health-care personnel
Employees of nursing homes with patient contact
Providers of home care
Household members of persons in high-risk groups

Adapted from Centers for Disease Control (2004).

58% reduction of influenza infection in vaccines (Govaert *et al.*, 1994). A recent three-year case-control study from the United States found influenza vaccine to be both efficacious and cost effective (Nichol *et al.*, 1994). Although vaccine recipients had more coexisting illnesses at baseline than those who did not receive the vaccine, vaccination was associated with a reduction in yearly hospitalization rates during the 3-year period for pneumonia and influenza by 48 to 57% and for all chronic respiratory conditions by 27 to 39%. Vaccination was also associated with a 37% reduction in the rate of hospitalization for congestive heart failure (CHF) when influenza A was epidemic. In the three influenza seasons studied, vaccination was associated with decreases of 39 to 54% in mortality from all causes. While effective in all older adults, benefit from influenza vaccine is greatest in those with high-risk conditions (Hak *et al.*, 2002). In addition, influenza vaccine is associated with a reduction in hospitalizations for cardiac disease and strokes in the elderly (Nichol *et al.*, 2003). In LTCFs, the efficacy of influenza vaccine in preventing uncomplicated influenza infection is low (28–37%) (Centers for Disease Control, 2004). However, the efficacy in reducing complications, including hospitalization (47%), pneumonia (58%), and death (76%), is substantial. Achieving a high rate of vaccination among nursing-home residents has been shown to reduce the spread of infection in such a facility, thus preventing disease through herd immunity.

A number of well-designed studies have shown influenza vaccine to be a highly cost-effective intervention and provide compelling evidence for increasing programs aimed at improving compliance with recommendations for annual influenza vaccination. Groups in whom vaccination is recommended are listed in Table 8.

KEY POINTS

- Infections are a leading cause of hospitalization and death in older persons.
- Susceptibility to infection in the elderly is multifactorial and includes diminished immune function, comorbid diseases, and congregate living residences.
- Signs and symptoms of infection in the elderly may be more subtle or atypical compared to young adults.
- LTCF have high prevalence rates of infection. Hand washing and antibiotic control are important measures for limiting the spread of resistant organisms in these facilities.
- Influenza and pneumococcal vaccine are beneficial and cost-effective methods to reduce morbidity and mortality associated with these infections in all groups of older adults.

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Tuberculosis

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INTRODUCTION

In the year 2004, tuberculosis (TB) remained one of the leading infectious causes of illness and death worldwide. Estimates of morbidity and mortality from TB vary widely, but reliable sources report approximately two billion people currently infected with quiescent but viable tubercle bacilli, with two to three million deaths occurring from TB each year.

In the United States, during the past two decades, the excess in morbidity reflected a changing epidemiologic pattern. Human immune deficiency virus (HIV) infection, poverty, homelessness, substance abuse, and immigration from countries with a high prevalence of TB all contributed to TB morbidity. Overburdened public health TB services were not only unable to manage the resurgence in the 1980s but were also unprepared to cope with emerging multidrug resistance. Since the mid-1990s to the present, aggressive TB control, implementation, and enhanced resources have resulted in a substantial decline in the overall incidence of TB.

The geriatric population across all racial and ethnic groups and both genders are at substantial risk for *Mycobacterium tuberculosis* (*Mtb*) infection, perhaps because of both biological (compromised nutrition and immune status, underlying disease, medications, and possible racial predisposition) and socioeconomic factors (poverty, living conditions, and access to health-care). Most vulnerable are frail elderly residents of nursing homes and other long-term care facilities. Because of the highly communicable potential of *Mtb*, the inevitable endemic transmission between residents and from resident to staff has been demonstrated in such facilities. (For the purpose of clarity, TB infection, or latent TB, refers to contained and asymptomatic primary infection with a positive tuberculin skin test reaction, whereas TB disease indicates overt clinical manifestations of TB).

The Institute of Medicine report, *Ending Neglect: The Elimination of TB in the US,* which was undertaken through sponsorship from the Centers for Disease Control and Prevention (CDC), reviews the lessons learned from the neglect of TB between the late 1960s and the early 1990s and reaffirms commitment to a more realistic goal of elimination of TB in the United States (Institute of Medicine, 2000).

This chapter will review the epidemiology, pathogenesis and immunologic aspects, subtle clinical characteristics, diagnosis, management and prevention of *Mtb* infection in community-dwelling and institutionalized aging adults, as well as highlight the updated revised guidelines for targeted tuberculin skin testing and treatment of latent TB infection (LTBI).

EPIDEMIOLOGY

Developed nations including the United States and parts of Southeast Asia report an estimated 380 million persons infected with *Mtb*; about 80% of infected persons in Europe are 50 years of age or older (Rajagopalan, 2001). Population-based surveys of both TB infection and TB disease reveal that the overwhelming burden of disease and the highest annual risk for infection are borne by those living in developing countries.

In the United States, TB prevails among the foreign-born and minorities. From 1985 to 1992, TB incidence increased among all ethnic groups except non-Hispanic whites and Native Americans/Alaskan Natives. Among the different ethnic groups, Hispanics experienced the greatest increase in reported cases (74%) (Centers for Disease Control and Prevention, 1993). From 1992 to 2000, the overall incidence of TB in the United States declined by 45%, largely because of improved funding resources channeled into TB control programs, which allowed for the implementation of directly observed therapy (DOT). In 2000, the TB incidence ratio was 5.8 cases/100 000 population, the lowest ever recorded in this country (Centers for Disease Control and Prevention, 2002a). However, the percentage of cases among foreign-born persons increased from 27% in 1992 to 46% in 2000 (Centers for Disease Control and Prevention, 2002b).

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TB also occurs with disproportionate frequency among the elderly (Reichman and O'Day, 1978; Narain *et al.*, 1985). Elders living in communal settings such as nursing homes or other long-term care facilities have a TB incidence rate approximately four times greater than the general population (Schultz *et al.*, 2001). The aggregate TB incidence rate for nursing home residents is 1.8 times higher than the rate seen in community-dwelling elderly (Hutton *et al.*, 1993). The enhanced efficiency of TB transmissibility within congregate settings such as prisons, nursing facilities (nursing homes), chronic disease facilities, and homeless shelters has raised concerns about TB infection and disease in the institutionalized elderly (Ijaz *et al.*, 2002; Rajagopalan and Yoshikawa, 2000). Positive tuberculin reactivity associated with prolonged stay among residents of long-term care facilities for the elderly has been demonstrated, implying an increasing risk of TB infection.

PATHOGENESIS AND IMMUNOLOGIC ASPECTS

The pathogenesis of TB infection and disease begins in most cases with the inhalation of the tubercle bacilli (Adler and Rose, 1996). The usual inoculum is no more than one to three organisms, which are taken up by alveolar macrophages and carried to regional lymph nodes. Spread may occur via the lymphohematogenous route with dissemination to multiple organs. From two to eight weeks after infection, cell-mediated immunity (CMI) and delayed-type hypersensitivity (DTH) responses develop, leading to the characteristic reactive tuberculin test and to the containment of infection. Chemoattractants cause monocytes to enter the area and become transformed into histiocytes forming granulomas. Although the bacilli may persist within macrophages, additional multiplication and spread is curtailed. Healing usually follows with calcification of the infected focus. Caseous necrosis may result secondary to the immune response. Erosion into a bronchiole causes cavity formation where bacilli can multiply and spread. Solid necrosis can result from production of hydrolases from inflammatory cells causing tissue liquefaction and creating a prime medium for microbial replication, generating up to 10 billion bacilli/ml.

Individuals who develop active disease either fail to contain the primary infection or develop reactivation as a result of relative or absolute immune suppression at a point remote from primary infection. This is most likely to occur in immunocompetent adults within the first 3 years after exposure. Factors related to progression of disease reflect a weakened immune status and include physiological states, for example, normal aging; associated intercurrent disease – particularly diabetes mellitus, malignancies causing primary immunosuppression or requiring toxic chemotherapy, or corticosteroid-dependant diseases such as asthma or collagen vascular disease; poor nutritional status particularly related to alcohol and drug abuse; smoking and HIV infection.

Although, it is likely that the increased frequency of TB in the elderly could partly be due to CMI that is impaired by senescence (shown in murine models), other concomitant age-related diseases (diabetes mellitus, malignancy), chronic kidney disease and renal insufficiency, poor nutrition, and immunosuppressive drugs may also contribute to this increase (Yoshikawa, 1992). In the elderly, approximately 90% of TB disease cases are due to reactivation of primary infection. Persistent infection without disease may occur in 30 to 50% of individuals. Some elderly persons previously infected with *Mtb* may eventually eliminate the viable tubercle bacilli and revert to a negative tuberculin reactor state. These individuals are thus at risk of new infection (reinfection) with *Mtb*. There are therefore three subgroups of older persons potentially at risk for TB: One subgroup never exposed to TB that may develop primary TB disease, a second subgroup with persistent and latent primary infection that may reactivate, and a third subgroup that is no longer infected and consequently at risk for reinfection.

SUBTLE CLINICAL CHARACTERISTICS

Clinicians must be aware that frail older persons with TB disease may not demonstrate the overt and characteristic clinical features of TB such as fever, night sweats, or hemoptysis. They may exhibit more subtle clinical manifestations of "failure to thrive" with anorexia, functional decline and low-grade fever, or weight loss (Perez-Guzman *et al.*, 1999). Although, several published works have attempted to delineate clear-cut differences between younger and older TB patients, such studies have provided quite variable findings. In a meta-analysis of published studies, comparing pulmonary TB in older and younger patients, evaluating the differences in the clinical, radiologic, and laboratory features of pulmonary TB, no differences were found in the prevalence of cough, sputum production, weight loss, fatigue/malaise, radiographic upper lobes lesions, positive acid-fast bacilli (AFB) in sputum, anemia or hemoglobin level, and serum aminotransferases (Perez-Guzman *et al.*, 1999). A lower prevalence of fever, sweating, hemoptysis, cavitary disease, and positive purified protein derivative (PPD), as well as lower levels of serum albumin and blood leukocytes were noticed among older patients. In addition, the older population had a greater prevalence of dyspnea and some underlying comorbid conditions, such as cardiovascular disorders, chronic obstructive pulmonary disease, diabetes mellitus, gastrectomy history, and malignancies. This meta-analytical review identified some subtle differences in clinical presentations of older TB patients, when compared with their younger TB counterparts. However, most of these differences can be explained by the already known physiologic changes that occur during aging.

The majority of older TB patients (75%) with *Mtb* disease manifest active disease in their lungs (Yoshikawa, 1992). Extrapulmonary TB in the elderly is similar to younger persons and may involve the meninges, bone and joint, and genitourinary systems, or disseminate in a miliary pattern (Mert *et al.*, 2001; Kalita and Misra, 2004; Shah *et al.*, 2001; Malaviya, 2003; Lenk and Schroeder, 2001). Infection of

lymph nodes, pleura, pericardium, peritoneum, gall bladder, small and large bowel, the middle ear, and carpal tunnel have been described in the literature. Because TB can involve virtually any organ in the body, this infection must be kept in the differential diagnosis of unusual presentations of diseases, especially in the elderly. Thus, TB has been aptly described as "the great masquerader".

DIAGNOSIS

Clinicians caring for the elderly must maintain a high index of suspicion for TB when possible, in order to promptly recognize and treat infected individuals.

Tuberculin Skin Testing

The Mantoux method of tuberculin skin testing using the Tween-stabilized PPD antigen is one of the diagnostic modalities readily available to screen for TB infection, despite its potential for false-negative results (Markowitz *et al.*, 1993). In the elderly, because of the increase in anergy to cutaneous antigens, the two-step tuberculin test is suggested as part of the initial geriatric assessment to avoid overlooking potentially false-negative reactions (Tort *et al.*, 1995). The American Geriatrics Society routinely recommends two-step tuberculin testing as part of the baseline information for all institutionalized elderly (American Geriatrics Society, 1993). The two-step tuberculin skin test involves initial intradermal placement of five tuberculin units of PPD, and the results are read at 48 to 72 hours. Patients are retested within two weeks after a negative response (induration of less than 10 mm). A positive "booster effect", and therefore a positive tuberculin skin test reaction, is a skin test of 10 mm or more and an increase of 6 mm or more over the first skin test reaction. It is important to distinguish the booster phenomenon from a true tuberculin conversion. The booster effect occurs in a person previously infected with *Mtb* but who has a false-negative skin test; repeat skin test elicits a truly positive test. Conversion (not to be confused with the booster phenomenon) occurs in persons previously uninfected with *Mtb* and who have had a true negative tuberculin skin test, but who become infected within 2 years as demonstrated by a repeat skin test induration that is a positive 10 mm or more during this period. Several factors influence the results and interpretation of the PPD skin test. Decreased skin test reactivity is associated with waning DTH with time, disseminated TB, corticosteroids and other drugs, and other diseases as well as the elimination of TB infection. False-positive PPD results occur with cross-reactions with nontuberculous mycobacteria and in persons receiving the Bacillus Calmette-Guerin (BCG) vaccine, the latter having been administered to some foreign-born elderly persons, which has an unpredictable effect on the PPD skin test reactivity and is presumed to wane after 10 years. The use of anergy testing has been debated because of lack of a standardized protocol for selection of the number and type of antigens to be used, the criteria for defining positive and negative reactions, and administration and interpretation techniques (Slovis *et al.*, 2000).

QuantiFERON-TB (QFT) Testing

In 2001, the QuantiFERON-TB (QFT) test was approved by the US Food and Drug Administration (FDA) to aid in the detection of LTBI. This *in vitro* test measures by an enzyme-linked immunosorbent assay (ELISA), the concentration of interferon-gamma (IFN-γ) released from tuberculin PPD-sensitized lymphocytes in heparinized whole blood incubated for 16 to 24 hours. Interpretation of QFT results is stratified by estimated risk for *Mtb* infection in a manner similar to the tuberculin skin test using different induration cut-off values as shown in Tables 1(A) and (B) (Centers for Disease Control and Prevention, 2003a). The role for QFT in targeted testing has not yet been clearly defined and may be a useful alternative to tuberculin skin testing in the future for all infected individuals including the elderly.

Chest Radiography

Chest radiography is indicated in all individuals with suspected TB infection, regardless of the primary site of infection. In the elderly, 75% of all TB disease occurs in the respiratory tract and largely represents reactivation disease; 10 to 20% of cases may be as a result of primary infection (Woodring *et al.*, 1986). Although reactivation TB disease characteristically involves the apical and posterior segments of the upper lobes of the lungs, several studies have shown that many elderly patients manifest their pulmonary infection in either the middle or lower lobes or the pleura, as well as present with interstitial, patchy, or cavitary infiltrates that may be bilateral. Primary TB can involve any lung segment, but more often tends to involve the middle or lower lobes as well as mediastinal or hilar lymph nodes. Thus, caution must be exercised in dismissing the radiographic diagnosis of pulmonary TB in the elderly because of the atypical location of the infection in the lung fields.

Laboratory Diagnosis

Sputum samples must be collected from all patients, regardless of age, with pulmonary symptoms or chest radiographic changes compatible with TB disease and who have not been previously treated with antituberculous agents. In elderly patients unable to expectorate sputum, other diagnostic techniques such as sputum induction or bronchoscopy should be considered. Flexible bronchoscopy to obtain bronchial washings and to perform bronchial biopsies has been shown to be of diagnostic value for TB disease in the elderly; however, in the frail and very old patient, the risk of such a procedure must be carefully balanced against the

Table 1A Interim recommendations for applying and interpreting QuantiFERON-TB (Centers for Disease Control and Prevention. Guidelines for using the QuantiFERON-TB test for diagnosing latent *Mycobacterium tuberculosis* infection. *Morbidity and Mortality Weekly Report* 2003a; **52** (RR02): 15–8)

Reason for testing	Population	Initial screening	Positive results	Evaluation
Tuberculosis (TB suspect)	Persons with symptoms of active TB	Tuberculin skin testing (TST) might be useful; QFT not recommended	Induration $\geq$5 mm	Chest radiograph, smears, and cultures, regardless of test results
Increased risk for progression to active TB, if infected	Persons with recent contact with TB, changes on chest radiograph consistent with prior TB, organ transplants, or human-immunodeficiency virus infection, and those receiving immunosuppressing drugs equivalent of $\geq$15 mg day^{-1} of prednisone for $\geq$1 month[a]	TST; QFT not recommended	Induration $\geq$5 mm	Chest radiograph if TST is positive; treat for LTBI after active TB disease is ruled out
	Persons with diabetes, silicosis, chronic renal failure, leukemia, lymphoma, carcinoma of the head, neck, or lung, and persons with weight loss of $\geq$10% of ideal body weight, gastrectomy, or jejunoileal bypass[a]	TST; QFT not recommended	Induration $\geq$10 mm	
Increased risk for LTBI	Recent immigrants, injection-drug users, and residents, and employees of high-risk congregate settings (e.g. prisons, jails, homeless shelters, and certain health-care facilities)[b]	TST or QFT	Induration $\geq$10 mm; percentage tuberculin response $\geq$15 %	Chest radiograph if either test is positive; confirmatory TST is optional if QFT is positive; treat for LTBI after active TB disease is ruled out; LTBI treatment when only QFT is positive should be based on clinical judgment and estimated risk
Other reasons for testing among persons at low risk for LTBI	Military personnel, hospital staff, and health-care workers whose risk of prior exposure to TB patients is low, and US-born students at certain colleges and universities	TST or QFT	Induration $\geq$15 mm; percentage tuberculin response $\geq$30 %	Chest radiograph if either test is positive; confirmatory TST if QFT is positive; treatment for LTBI (if QFT and TST are positive and after active TB disease is ruled out) on the basis of assessment of risk for drug toxicity, TB transmission, and patient preference

[a]QFT has not been adequately evaluated among persons with these conditions; it is not recommended for such populations.

Table 1B QuantiFERON-TB testing: results and interpretation (Centers for Disease Control and Prevention. Guidelines for using the QuantiFERON-TB test for diagnosing latent *Mycobacterium tuberculosis* infection. *Morbidity and Mortality Weekly Report* 2003a; **52** (RR02): 15–8)

M–N[a] (IUmL)	T–N[b] (IUmL)	Avian difference (%)	Tuberculin response (%)[c]	Report and interpretation	Interpretation
$\leq$1.5	All other response profiles	All other response profiles	All other response profiles	Interferon-gamma (INY-γ) response to mitogen is inadequate	Indeterminate
$\geq$1.5	All other response profiles	All other response profiles	$\leq$15	Percentage tuberculin response is <15 or not significant	Negative: *M. tuberculosis* infection unlikely
$\geq$1.5	$\geq$1.5	$\leq$10	$\geq$15 but <30	Percentage tuberculin response is 15–30	Conditionally positive: *M. tuberculosis* infection likely if risk is identified, but unlikely for persons who are at low risk
$\geq$1.5	$\geq$1.5	$\leq$10	$\geq$30	Percentage tuberculin response is $\geq$30	Positive: *M. tuberculosis* infection likely

[a]M–N is the IFN-γ responses to mitogen minus the IFN-γ responses to nil antigen. [b]T–N is the IFN-γ responses to purified protein derivative from *M. tuberculosis* infection. If T–N is <1.5 IUmL, the persons are deemed negative for *M. tuberculosis* infection, regardless of their percentage tuberculin response and percentage avian difference results. [c]A percentage tuberculin response cutoff of 15% is used for persons with identified risk for tuberculosis infection, whereas a cutoff of 30% is used for persons with no identified risk factors.

benefits of potentially making a definite diagnosis of TB (Patel *et al.*, 1993). In the case of pulmonary and genitourinary TB, three consecutive early morning sputum or urine specimens, respectively, are recommended for routine mycobacteriologic studies (Hanna, 1996; American Thoracic Society, 2000a). Sputum samples are examined initially by smear before and after concentration and then cultured for *Mtb*. Because routine mycobacterial culture methods may require up to 6 weeks for growth of *Mtb*, many laboratories now use radiometric procedures for the isolation and susceptibility testing of this organism; this method may identify the organisms as early as after 8 days. Sterile body fluids

and tissues can be inoculated into liquid media, which also allow the growth and detection of *Mtb* 7 to 10 days earlier than in the solid media techniques. Histological examination of tissue from various sites such as the liver, lymph nodes, bone marrow, pleura, or synovium may show the characteristic tissue reaction (caseous necrosis with granuloma formation) with or without AFB, which would also strongly support the diagnosis of TB disease. Other diagnostic methods for TB that have been clinically evaluated include serology and nucleic acid amplification (NAA) tests such as polymerase chain reaction (PCR) and other methods for amplifying DNA and RNA (Centers for Disease Control and Prevention, 2000). The latter may facilitate rapid detection of *Mtb* from respiratory specimens; the interpretation and use of the NAA test results has been updated by the CDC. Similar techniques using DNA probes can be used to track the spread of the organism in epidemiologic studies and may be used to predict drug resistance prior to the availability of standard results; such methods are currently being used in some laboratories. The rapid diagnosis of TB is especially important in elderly patients, as well as HIV-infected persons, and patients with multidrug-resistant (MDR)-TB.

TREATMENT

Treatment of TB Disease

The recommended treatment regimens are for the most part based on evidence from clinical trials and are rated on the basis of a system developed by the United States Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA). There are four recommended regimens for treating patients with TB caused by drug-susceptible organisms. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances, which are described subsequently. Each regimen has an initial phase of 2 months followed by a choice of several options for the continuation phase of either 4 or 7 months. The recommended treatment algorithm and regimens are shown in Figure 1 and Table 2 (Centers for Disease Control and Prevention, 2003b).

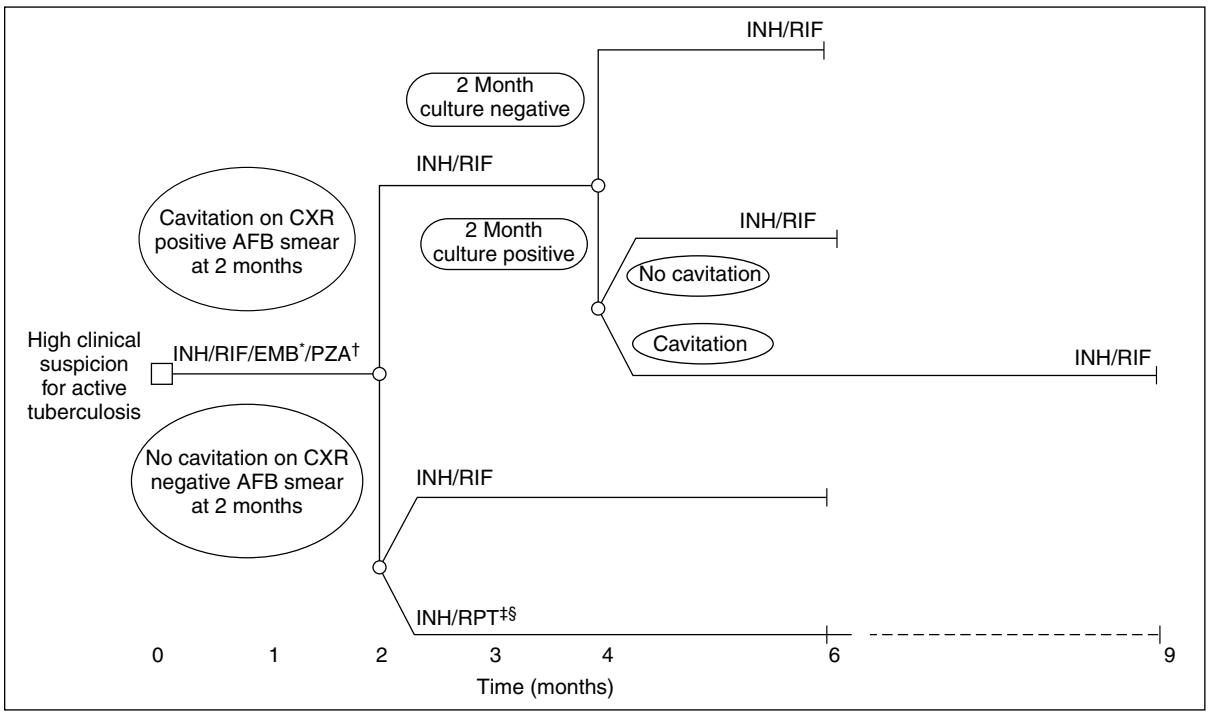
Because of the relatively high proportion of adult patients with TB caused by organisms that are resistant to isoniazid (INH), four drugs are necessary in the initial phase for the 6-month regimen to be maximally effective. Thus, in most circumstances, the treatment regimen for all adults including the elderly with previously untreated TB should consist of a 2-month initial phase of INH, rifampin (RIF), pyrazinamide (PZA), and Ethambutol (EMB). If (when) drug susceptibility test results are known and the organisms are fully susceptible, EMB need not be included. If PZA cannot be included in the initial phase of treatment, or if the isolate is resistant to PZA alone (an unusual circumstance), the initial phase should consist of INH, RIF, and EMB given daily for 2 months. However, since most TB in the elderly is due to reactivation (from infection acquired prior to 1950), the organism will generally be sensitive to INH and other antituberculous drugs.

Treatment of MDR-TB is complex and often needs to be individualized, requiring the addition of a minimum of two additional antituberculous agents to which the organism is presumably susceptible, preferably in consultation with a TB expert who is familiar with *Mtb* drug resistance. Alternate drugs such as capreomycin, kanamycin, amikacin, ethionamide, and cycloserine, as well as the newer quinolones, may have to be used for treatment in such cases.

Monitoring of Response to Drug Therapy

Patients with active pulmonary TB should be monitored on a monthly basis with sputum examination until conversion to negative by culture is achieved; this usually occurs within 3 months in 90% of cases. Continued positive sputum cultures for *Mtb* beyond three months of initiation of therapy should raise the suspicion for drug resistance or noncompliance (if not on DOT); such patients should have sputum culture and susceptibility repeated and started on DOT pending results of these data. Follow-up chest radiography is indicated 2 to 3 months after initiation of drug therapy. Older patients are at greater risk for hepatic toxicity from INH. Although INH therapy poses a small but significant risk for hepatitis, the hepatitis is relatively low in frequency and mild in severity. It would appear, therefore, that with careful monitoring of the older patient, antituberculous chemotherapy is a relatively safe intervention in this population. It is recommended that clinical assessments as well as baseline liver function tests be performed before the administration of INH and RIF (and PZA) in older patients.

Monthly clinical evaluations and periodic measurements of the serum aminotransferase (SGOT) level should be performed in the elderly. If the SGOT rises to 5 times above normal or if the patient exhibits symptoms or signs of hepatitis, INH (as well as other hepatotoxic drugs) should be discontinued. After clinical symptoms improve or the SGOT level normalizes, or both, INH may be resumed at a lower dose (e.g. $50\,mg\,kg^{-1}\,day^{-1}$) and gradually increased to a full dose if symptoms and the SGOT level remain stable. In case of relapse of the hepatitis with the INH challenge, the drug should be replaced with an alternative regimen. There is some disagreement among clinicians regarding the monitoring of liver function tests in older patients on INH. Because frail, elderly patients may often be asymptomatic in the presence of worsening hepatitis and may not be able to communicate symptoms, laboratory monitoring seems prudent. The frequency of such monitoring (e.g. monthly or every 2 to 3 months) remains less clear. RIF, in addition to hepatitis, is also associated with orange discoloration of body fluids. EMB may cause loss of color discrimination, diminished visual acuity, and central scotomata; older patients receiving this drug should have frequent evaluation of visual acuity and color discrimination. Streptomycin is associated with irreversible auditory and vestibular damage and generally should



Patients in whom tuberculosis is proved or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide, and ethambutol for the initial 2 months. A repeat smear and culture should be performed when 2 months of treatment has been completed. If cavities were seen on the initial chest radiograph or the acid-fast smear is positive at completion of 2 months of treatment, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment. If cavitation was present on the initial chest radiograph and the culture at the time of completion of 2 months of therapy is positive, the continuation phase should be lengthened to 7 months (total of 9 months of treatment). If the patient has HIV infection and the $CD4^+$ cell count is <100/ml, the continuation phase should consist of daily or three times weekly isoniazid and rifampin. In HIV-uninfected patients having no cavitation on chest radiograph and negative acid-fast smears at completion of 2 months of treatment, the continuation phase may consist of either once weekly isoniazid and rifapentine, or daily or twice weekly isoniazid and rifampin,to complete a total of 6 months (bottom). Patients receiving isoniazid and rifapentine,and whose 2-month cultures are positive, should have treatment extended by an additional 3 months (total of 9 months).

* EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance.
† PZA may be discontinued after it has been taken for 2 months (56 doses).
‡ RPT should not be used in HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis.
§ Therapy should be extended to 9 months if 2-month culture is positive.
CXR = chest radiograph; EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.

Figure 1 Treatment algorithm for tuberculosis (Centers for Disease Control, American Thoracic Society & Infectious Disease Society of America, 2003b)

not be prescribed in the elderly. Adverse effects of PZA include hyperuricemia, hepatitis, and flushing. Dose adjustment of antituberculous drugs is necessary with streptomycin, when used in the presence of renal impairment; however, no adjustment is needed for INH, RIF, or PZA in most elderly patients.

Treatment of Latent TB Infection

Table 3 outlines the revised criteria for positive tuberculin skin test reactivity by size of induration requiring drug treatment (American Thoracic Society, 2000b). Drug therapy for latent TB (based on tuberculin skin test reactivity) considerably decreases the risk of progression of TB infection to TB disease. The recently revised recommended drug treatment of LTBI in adults including the elderly, is shown in Table 4 (Centers for Disease Control and Prevention, 2001). Since the LTBI treatment recommendations address adults in general, targeted skin testing and treatment of high-risk populations can be applied to the elderly. The INH daily regimen for 9 months has recently replaced the previously recommended 6-month schedule for treatment of LTBI. Randomized, prospective trials in HIV-negative persons have indicated that a 12-month regimen is more effective than 6 months of treatment; subgroup analyses of several trials indicate that the maximal beneficial effect of INH is likely to be achieved in 9 months, with minimal additional benefit gained by extending therapy to 12 months. Although the 9-month regimen of INH is preferred for the treatment of LTBI, the 6-month LTBI treatment course also provides substantial protection and has been shown to be superior to

Table 2 Drug treatment regimens of tuberculosis (Centers for Disease Control and Prevention. American Thoracic Society & Infectious Disease Society of America. CDC-ATS-IDSA Treatment of Tuberculosis. *Morbidity and Mortality Weekly Report* 2003b; **52** (RR11): 1–77)

	Initial phase		Continuation phase				
Regimen	Drugs	Intervals and doses[c] (minimal duration)	Regimen	Drugs	Interval and doses[c,d] (minimal duration)	Range of total doses (minimal duration)	Rating[a] (evidence) [b] HIV–HIV[b]
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 weeks) or days/week for 40 doses (8 weeks)	1a	INH/RIF	Seven days per week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)[e]	182–130 (26 weeks)	A(I) A(II)
			1b	INH/RIF	Twice weekly for 36 doses (18 weeks)	92–76 (26 weeks)	A(I) A(II)[f]
			1c[g]	INH/RPT	Once weekly for 18 doses (18 weeks)	44–58 (26 weeks)	B(I) E(I)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks) or 5 days/week for 10 doses (2 weeks) then twice weekly for 12 doses (6 weeks)	2a	INH/RIF	Twice weekly for 36 doses (18 weeks)	62–58 (26 weeks)	A(II) B(II)[f]
			2b[g]	INH/RPT	Once weekly for 18 doses (18 weeks)	44–40 (26 weeks)	B(I) E(I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 weeks)	3a	INH/RIF	Three times weekly for 54 doses (18 weeks)	78 (26 weeks)	B(I) B(I)
4	INH RIF EMB	Seven days per week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)	4a	INH/RIF	Seven days per week for 217 doses (31 weeks) or 5 days/week for 155 doses (31 week)[e]	273–195 (39 weeks)	C(I) C(I)
			4b	INH/RIF	Twice weekly for 62 doses (31 weeks)	118–102 (39 weeks)	C(I) C(II)

Definition of abbreviations: EMB, Ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine.
[a]Definitions of evidence ratings: A, preferred; B, acceptable alternative; C, when A and B cannot be given; E, should never be given. [b]Definitions of evidence ratings: I, randomized clinical trial; II, data from clinical trials that were not randomized or were conducted in other populations; III, expert opinion. [c]When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies comparing five with seven daily doses, extensive experience indicates this would be an effective practice. [d]Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 weeks); either 217 doses [daily] or 62 doses [twice weekly] continuation phase. [e]Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is AIII. [f]Not recommended for HIV-infected patients with CD4 cell counts <100 cells/μl. [g]Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

Table 3 Skin test criteria for positive tuberculin reaction (mm induration) (American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. *American Journal of Respiratory and Critical Care Medicine* 2000a; **161:** 1376–95)

≥5 mm
1. HIV[a] positive persons
2. Recent contacts of person(s) with infectious tuberculosis
3. Persons with chest radiographs consistent with tuberculosis (e.g. fibrotic changes)
4. Patients with organ transplants and other immunosuppressed hosts receiving the equivalent of $>15\,mg\,day^{-1}$ prednisone for >1 month

≥10 mm
1. Recent arrivals (<5 years) from high-prevalence countries
2. Injection-drug users
3. Residents and employees of high-risk congregate settings: prisons, jails, nursing homes, other health-care facilities, residential facilities for AIDS[b] patients, and homeless shelters
4. Mycobacteriology laboratory personnel
5. High-risk clinical conditions: silicosis; gastrectomy; jejunoileal bypass; ≥10% below ideal body weight; chronic renal failure; diabetes mellitus; hematological malignancies (e.g. lymphomas, leukemias); other specific malignancies (carcinoma of the head or neck, and lung) (alcoholics are also considered high risk)

≥15 mm
1. Persons with no risk factors for TB

Chemoprophylaxis recommended for all high-risk persons, regardless of age. Persons otherwise low-risk tested at entry into employment, ≥15 mm induration is positive.
[a]HIV, Human-Immunodeficiency Virus; [b]AIDS, Acquired Immunodeficiency Syndrome.

Table 4 Revised drug regimens for treatment of latent tuberculosis infection in adults (including the elderly) (American Thoracic Society. Targeted skin testing and treatment of latent tuberculosis infection. *American Journal of Respiratory and Critical Care Medicine*; **161:** S221–47 (Adapted from CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. 2000; **49**(RR06). Interactions with human-immunodeficiency virus (HIV) – related drugs are updated frequently and are available at http/www.aidsinfr.nih.gov/guidelines). (Centers for Disease Control and Prevention. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/Centers for Disease Control and Prevention – recommendations – United States. *Morbidity and Mortality Weekly Report* 2001; August 31, 2001; **50** (34): 733–5)

Drug	Interval and duration	Comments	Ratings HIV-negative	(Evidence) HIV-infected
Isoniazid	Daily for 9 months	In HIV-infected persons, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or, nonnucleoside reverse transcriptase inhibitors (NNRTIs)	A (II)	A (II)
Isoniazid	Twice weekly for 9 months**	Directly observed therapy (DOT) must be used with twice-weekly dosing	B (II)	B (II)
	Daily for 6 months	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children.	B (I)	C (I)
Rifampin	Twice weekly for 6 months	DOT must be used with twice-weekly dosing.	B (II)	C (I)
	Daily for 4 months	Used for persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB In HIV-infected persons, most protease inhibitors or delavirdine should not be administered concurrently with rifampin. Rifabutin with appropriate dose adjustments can be used with protease inhibitors (saquinavir should be augmented with ritonavir) and NNRTIs (except delavirdine). Clinicians should consult web-based updates for the latest specific recommendations	B (II)	B (III)
Rifampin plus pyrazinamide (RZ)	Daily for 2 months	RZ generally should not be offered for treatment of LTBI for HIV-infected or HIV-negative persons	D (II)	D (II)
	Twice weekly for 2–3 months		D (III)	D (III)

Strength of the recommendation: A. Both strong evidence of efficacy and substantial clinical benefit support recommendation for use. Should always be offered; B. Moderate evidence for efficacy or strong evidence for efficacy, but only limited clinical benefit supports recommendation for use. Should generally be offered; C. Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g. drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional; D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered; E. Good evidence for lack of efficacy or for adverse outcome support a recommendation against use. Should never be offered.
Quality of evidence supporting the recommendation: I. Evidence from at least one properly randomized controlled trial; II. Evidence from at least one well-designed clinical trial without randomization for cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results from uncontrolled experiments; III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.
The substitution of rifapentine for rifampin not recommended as rifapentine's safety and effectiveness not established for LTBI.

placebo in both HIV-positive and -negative persons. Hence, clinical judgment must be exercised based on local conditions, health departments or providers' experience, cost, and compliance issues. In a community-based study conducted in Bethel, Alaska, persons who took <25% of the prescribed annual dose had a threefold higher risk for TB than those who took more than 50% of the annual dose. A more recent analysis of study data indicated that the efficacy decreased significantly if less than 9 months of INH was taken (Comstock, 1999). In instances of known exposure to drug-resistant organisms, alternative preventive therapy regimens may be recommended. In addition, because of recent reports in 2001 of fatal and severe hepatitis associated with the 2-month RIF and PZA (R-Z) treatment regimen for LTBI, this regimen must be used with caution, especially in patients concurrently taking other medications associated with liver injury and in those with mild liver compromise (Centers for Disease Control and Prevention, 2001). R-Z is not recommended for persons with known underlying liver disease or for those who have had INH-associated liver injury. Persons being considered for treatment with R-Z should be informed about the potential hepatotoxicity and screened for liver disease or adverse effects from INH. To reduce the risk of liver injury associated with R-Z therapy, the American Thoracic Society (ATS) and CDC, with the endorsement of the IDSA, have prepared recommendations that supercede previous guidelines (Centers for Disease Control and Prevention, 2001).

Although these new recommendations do not specifically address aging adults, the concept of targeted skin testing and revised LTBI treatment guidelines for high-risk populations to include the elderly can be applied. Elderly persons receiving isoniazid should continue to be monitored for hepatitis and peripheral neuropathy induced by the drug.

INFECTION CONTROL ISSUES

The primary goal of an infection control program is to detect TB disease early and to isolate and promptly treat persons with infectious TB. Prevention of transmission of TB in any health-care environment is of utmost importance, both for patients and health-care workers. Enhanced awareness of drug-resistant TB has prompted public health agencies to institute strict TB identification, isolation, treatment, and prevention guidelines. The TB infection control program in

most acute care as well as long-term care facilities should consist of three types of control measures: administrative actions (i.e. prompt detection of suspected cases, isolation of infectious patients, and rapid institution of appropriate treatment), engineering control (negative-pressure ventilation rooms, high efficiency particulate air [HEPA] filtration, and ultraviolet germicidal irradiation [UVGI]), and personal respiratory protection requirements (masks). The Advisory Committee for the Elimination of Tuberculosis of the CDC has established recommendations for surveillance, containment, assessment, and reporting of TB infection and disease in long-term care facilities; health-care professionals, administrators, and staff of such extended care programs should be made aware of these recommendations (Centers for Disease Control and Prevention, 1990).

KEY POINTS

- Tuberculosis (TB) is a significant infectious disease in the elderly that causes increased morbidity and mortality.
- Age-related decrease in adaptive immune responses in addition to underlying comorbid illnesses (diabetes, cancer, immunosuppression) may enhance susceptibility to TB.
- Frail older persons may not exhibit the classical symptoms and signs of TB, that is, fever, night sweats, weight loss, cough, and hemoptysis. TB must be treated as the "great masquerader" and considered in the differential diagnosis of unexplained malaise, anorexia and low-grade fevers, and nonspecific clinical manifestations of illness.
- Screening for TB utilizing the two-step tuberculin skin testing is routinely recommended in the initial assessment of elderly patients admitted to long-term care facilities (the utility of the QFT as an alternative for latent TB diagnosis in this setting needs to be further evaluated). Increased efficiency of transmission of TB between elderly residents of such facilities has been reported.
- Diagnosis and management of TB in the geriatric population is similar to younger patients; close monitoring for adverse reactions to drug therapy is important, particularly in patients taking multiple medications.

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Infective Endocarditis in the Elderly

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INTRODUCTION

The proportion of elderly people is increasing worldwide. In Switzerland, the percentage of people aged >65 years was below 2.5% in 1900, as compared to ca. 15% in 2000 (http://www.statistik.admin.ch). More global projections indicate that people of over 65 years will represent ca. 20% of the population in North America and Western Europe by 2030 (Lloyd-Sherlock, 2002). By this time, people over 65 years will represent 5–10% of the population in developing countries (Lloyd-Sherlock, 2002).

Elderly people are more prone to infections than younger adults. Thus, knowledge of infection in these people is important. This chapter addresses infective endocarditis (IE), focusing on relevant commonalities and differences between elderly and younger patients.

INCIDENCE

Despite continuous improvements in health care, the overall incidence of IE (2–6 per 100 000 population per year) has not changed over the past two decades (Bouza *et al.*, 2001; Hoen *et al.*, 2002; Moreillon and Que, 2004). This apparent paradox results from a progressive change in risk factors. Chronic rheumatic heart disease, which was a prime risk factor in the preantibiotic era, is now rare in industrialized countries (Normand *et al.*, 1995). This group of at-risk patients, which predominated in children and young adults, has been replaced by new at-risk groups, including intravenous drug users (IVDU), elderly people with valve sclerosis, patients with intravascular prostheses, patients exposed to nosocomial diseases and hemodialysis patients (Durack *et al.*, 1994; Bouza *et al.*, 2001; Abbott and Agodoa, 2002; Hoen *et al.*, 2002; Moreillon and Que, 2004). IVDU involve mostly young individuals (mean age 30–40 years) (Wilson *et al.*, 2002), whereas the other risk factors are more frequent in the elderly. As a result, the mean age of patients with IE has increased. It was 30 years in the 1950s, 50 years in the 1980s, and 55 to >60 years since the 1990s (von Reyn *et al.*, 1981; van der Meer *et al.*, 1992b; van der Meer *et al.*, 1992a; Hoen *et al.*, 2002; Moreillon and Que, 2004). In a literature review totalizing 3784 episodes of IE between 1993 and 2003, the incidence of IE was varied from <5 to >15 per 100 000 patients per year in individuals younger and older than 65 years, respectively (Hoen *et al.*, 2002; Moreillon and Que, 2004). Thus, the clustering of risk factors in elderly patients correlates with a >3-times increased incidence of IE.

DEMOGRAPHY

Several studies compared the characteristics of IE in elderly (age >65 years) and younger patients (Robbins *et al.*, 1980; Poupet *et al.*, 1984; Terpenning *et al.*, 1987; Werner *et al.*, 1996; Selton-Suty *et al.*, 1997; Gagliardi *et al.*, 1998; Netzer *et al.*, 1999). Besides the increased incidence in the elderly, demographic characteristics were not strikingly different. The reported predominance of IE in males over females persisted over age (ratio between 2/1–3/1) (Werner *et al.*, 1996; Selton-Suty *et al.*, 1997; Gagliardi *et al.*, 1998; Netzer *et al.*, 1999; Hoen *et al.*, 2002; Moreillon and Que, 2004), identifying the male gender as an independent risk factor.

Predisposing cardiac conditions and comorbidities varied somewhat. Preexisting cardiac conditions were less frequently known in older than in younger patients. In two studies, they were reported to be 20% versus 36% (Selton-Suty *et al.*, 1997), and 45% versus 62% (Poupet *et al.*, 1984) in older and younger patients, respectively. However, combining the results of several studies together indicates that this difference may not be generalized (Table 1).

Comorbidities were more frequent in older patients, but only to a minor extent. Diabetes was more frequent in one

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Table 1 Clinical features of infective endocarditis in elderly (≥65 years) and younger (<65 years) patients. Data compiled from the literature

Clinical features	≥65 years[a,b]	<65 years[a,b]	Compiled from[a,c]
Symptoms			
– Fever	217/264 (82%)	360/404 (89%)	(1, 2, 3, 5, 6, 7)
– Asthenia	25/33 (75%)	34/68 (50%)	(1)
– Weight loss	40/86 (46%)	52/169 (31%)	(1, 5)
– Pleuritic pain	9/53 (17%)	22/101 (21%)	(5)
– Arthralgias	19/86 (22%)	43/169 (25%)	(1, 5)
Clinical signs			
– Cardiac murmur	120/167 (72%)	191/258 (74%)	(1, 2, 3, 5)
– Cutaneous signs and peripheral emboli	24/167 (14%)	51/258 (20%)	(1, 2, 3, 5)
– Palpable spleen	39/240 (16%)	131/418 (31%)	(1, 2, 3, 4, 5, 7)
– Neurologic signs	79/206 (38%)	73/247 (29%)	(2, 5, 6, 7)
Predisposing cardiac conditions	103/184 (56%)	250/426 (59%)	(1, 3, 4, 5, 6, 7)
Valve involved			
– Aortic	47/122 (38%)	99/254 (39%)	(4, 5, 6)
– Mitral	59/122 (48%)	98/254 (38.5%)	(4, 5, 6)
– Aortic and mitral	3/69 (4%)	24/153 (15%)	(4, 6)
– Other	18/122 (14%)	43/254 (17%)	(4, 5, 6)

[a]Only studies providing appropriate details were used. Vertical addition of patient numbers and percentages does not apply in the table. [b]Upper age limit varied between 65 and 70 years in some studies. [c]References used: 1, (Poupet *et al.*, 1984); 2, (Robbins *et al.*, 1980); 3, (Selton-Suty *et al.*, 1997); 4, (Werner *et al.*, 1996); 5, (Terpenning *et al.*, 1987); 6, (Gagliardi *et al.*, 1998); 7, (Netzer *et al.*, 1999).

study (Terpenning *et al.*, 1987; Selton-Suty *et al.*, 1997), but not in two others (Gagliardi *et al.*, 1998; Netzer *et al.*, 1999). Renal failure at admission was more frequent in two studies (Terpenning *et al.*, 1987; Netzer *et al.*, 1999), but not in a third one (Gagliardi *et al.*, 1998). On the other hand, the presence of an accompanying malignancy was uniformly more frequent in elderly than younger patients (Terpenning *et al.*, 1987; Gagliardi *et al.*, 1998; Netzer *et al.*, 1999).

How such patient characteristics may impact therapeutic decisions is unclear. A recent study attempted to establish a prognostic score for IE (Hasbun *et al.*, 2003). Parameters predicting mortality included alteration of the mental status, increased number of comorbidities, heart failure, bacterial pathogens (oral streptococci being associated to a better prognosis and *Staphylococcus aureus* to a worst prognosis), and absence of surgery. Neurological complications were one of the major predictors of mortality (Hasbun *et al.*, 2003; Poupet *et al.*, 1984). Age was not considered as a determinant.

Thus, age is only part of the prognostic evaluation. It should be considered in the patient's global context, including valve status and comorbidities.

RISK FACTORS

The key issues are preexisting valve lesions and transient bacteremia due to IE pathogens (see the section on Pathogenesis). On this basis, IE is commonly classified into four categories: (i) native valve IE, (ii) prosthetic valve IE, (iii) IE in IVDU, and (iv) nosocomial IE. In addition, the increasing incidence of IE in hemodialysis (Abbott and Agodoa, 2002) suggests that new categories may arise.

Classical risk factors include congenital heart disease and chronic rheumatic heart disease (Normand *et al.*, 1995). Most of these are primary features of children and young adults. Aortic bicuspid valves and congenital heart defects are more prevalent in younger than older patients with IE (Poupet *et al.*, 1984). On the other hand, the frequency of mitral valve prolapse is similar in both groups (Terpenning *et al.*, 1987; Selton-Suty *et al.*, 1997; Netzer *et al.*, 1999). Mitral valve prolapse is a relatively common (2–4% of the population) inheritable condition, which is linked to a dominant marker on chromosome 16. Only patients with valve regurgitation have an increased risk of IE.

Prosthetic valve endocarditis (PVE) occurs in 1–5% of cases, or 0.3–0.6% per patient-year (Sidhu *et al.*, 2001). A preexisting prosthesis is up to two times more frequent in elderly than in younger patients with IE (Poupet *et al.*, 1984; Terpenning *et al.*, 1987; Selton-Suty *et al.*, 1997). The issue of whether mechanical or bioprosthetic valves are more prone to infection remains unresolved (Sidhu *et al.*, 2001). PVE is classified as either early infection or late infection, depending on whether the symptoms of infection occur within 60 days after surgery or later. PVE peaks during the first 2 months after valve implantation and is often due to *Staphylococcus epidermidis*, and less frequently due to *S. aureus*. Progressive endothelialization of the prosthetic material over 2 to 6 months reduces the susceptibility of the implanted valve to infection. Late PVE is often due to other organisms including streptococci and sometimes gram-negative bacteria of the so-called HACEK group, including *Haemophilus* spp., *Actinobacillus actinomycetem comitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

Intravenous drug users and HIV patients are at-risk groups constituted of relatively younger people. However, they may progressively increase in elderly patients in the coming years. In IVDUs, the tricuspid valve is infected in more that 50% of the cases, followed by the aortic valve in 25% and the mitral valve in 20%, with mixed right-sided

and left-sided IE in a few cases (Wilson *et al.*, 2002). Most (60–80%) patients have no known preexisting valve lesions. The pathogens usually originate from the skin, which explains the predominance of *S. aureus* infections. *Pseudomonas aeruginosa* and fungi may also occur, and often produce severe forms of IE. In HIV patients, the mortality rate augments inversely to the CD4 counts. The risk is unaffected in patients with >500 CD4 cells mm^3, but increases by 4 times in those with <200 CD4 counts.

MICROBIAL ETIOLOGY

In the studies reviewed, *Staphylococcus* spp. and *Streptococcus* spp. were responsible for ≥80% of cases, and were rather similarly represented in both age-groups (Figure 1 and Table 2) (Robbins *et al.*, 1980; Poupet *et al.*, 1984; Werner *et al.*, 1996; Gagliardi *et al.*, 1998; Netzer *et al.*, 1999). Some studies reported an increase in the frequency of IE due to enteric streptococci, especially *S. bovis* biotype 1 (recently renamed *S. gallolyticus*), and *Enterococcus* spp. in elderly patients (Poupet *et al.*, 1984; Selton-Suty *et al.*, 1997; Hoen *et al.*, 2002). Figure 1 and Table 2 support this epidemiological profile.

One study reported that the increase in *S. gallolyticus* (formerly *bovis*) represented a shift from oral streptococci to enteric streptococci in the elderly, rather than an addition of the enteric species overall (Hoen *et al.*, 2002). Since *S. gallolyticus* IE is often connected to digestive neoplasia (Hoen *et al.*, 1994; Waisberg *et al.*, 2002), the association could mirror the greater frequency of tumors in elderly people (*see* **Chapter 128, Cancer and Aging**). Another intriguing fact is that several of the studies reporting an increase in IE due to *S. gallolyticus* in the elderly were from France (Selton-Suty *et al.*, 1997; Hoen *et al.*, 2002), suggesting the possibility of a local epidemiological feature. However, a recent review of the English literature confirmed the relation between IE due to *S. gallolyticus* and aging (Figure 1) (Moreillon and Que, 2004).

The frequency of negative culture IE varied between 5–15% and was equivalent in elderly and younger adults (Table 2) (Terpenning *et al.*, 1987; Selton-Suty *et al.*, 1997). Only one study reported a greater frequency of negative culture IE in elderly patients (ca. 20% vs 15% in younger patients) (Poupet *et al.*, 1984). Negative culture IE may occur

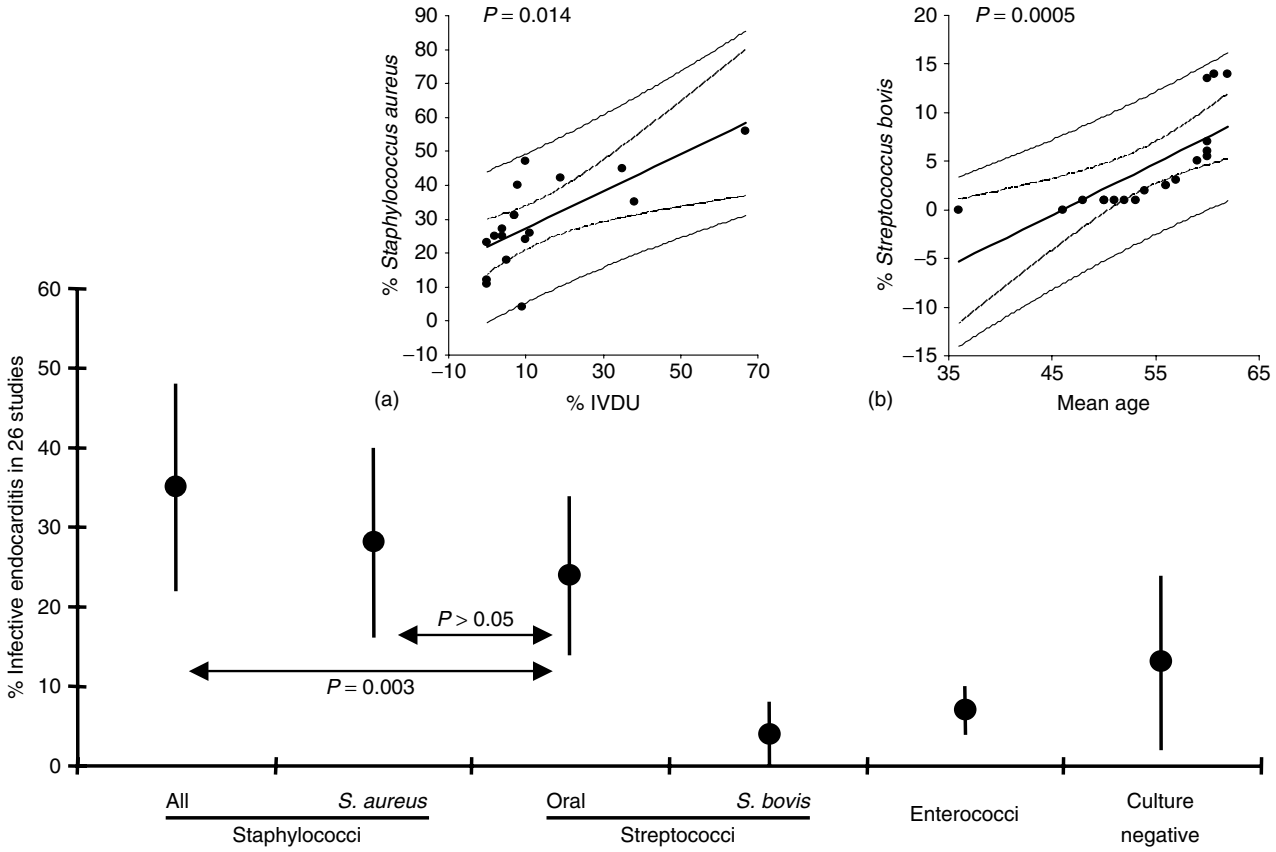

Figure 1 Percent of IE in 3784 episodes compiled from 26 studies published between 1993 and 2003 (Moreillon and Que, 2004). Insets present the linear regressions between the percent of *S. aureus* endocarditis and the percent of IVDU patients reported (a) and the percent of *S. bovis* (recently renamed *S. gallolyticus*) IE and the mean age of the study (b) plotted from 17/26 of the selected publications. Nine publications did not provide enough information to be included in this analysis. The *t*-test and linear regressions were used for statistical comparisons in the figure and the insets, respectively. $P < 0.05$ was considered significant (Reprinted with permission from Elsevier (*The Lancet*, 2004, **363**, 139–149))

Table 2 Microbiology of infective endocarditis in elderly (≥65 years) and younger (<65 years) patients. Data compiled from the literature

Microbial pathogens	≥65 years[a,b]	<65 years[a,b]	Compiled from[a,c]
Staphylococcus spp.	69/227 (30.5%)	139/396 (35%)	(1, 2, 3, 4, 5, 6)
−% *S. aureus*	48/64 (75%)	92/124 (74%)	(2, 3, 4, 5, 6)
−% Coagulase-negative	16/64 (25%)	32/124 (26%)	(2, 3, 4, 5, 6)
Streptococcus spp.	84/227 (37%)	119/396 (30.5%)	(1, 2, 3, 4, 5, 6)
Enterococcus spp.	26/151 (17%)	29/310 (9.5%)	(1, 3, 5, 6)
Gram-negative bacteria	12/186 (6.5%)	19/223 (8.5%)	(1, 2, 5, 6)
Others and Culture-negative	18/227 (8%)	30/396 (7.5%)	(1, 2, 3, 4, 5, 6)

[a]Only studies providing appropriate details were used to compare group of organisms. Vertical addition of patient numbers and percentages does not apply. [b]Upper age limit varied between 65 and 70 years in some studies. [c]References used: 1, (Poupet *et al.*, 1984); 2, (Robbins *et al.*, 1980); 3, (Selton-Suty *et al.*, 1997); 4, (Werner *et al.*, 1996); 5, (Terpenning *et al.*, 1987); 6, (Gagliardi *et al.*, 1998).

Table 3 Rare causes of infective endocarditis associated with negative blood cultures (Adapted from references (Brouqui and Raoult, 2001) and (Moreillon and Que, 2004))

Pathogens	Diagnostic procedure	Proposed therapy[a]
Brucella spp.	• Blood cultures • Serology • Culture, immunohistology, and PCR of surgical material	• Doxycycline plus rifampin or cotrimoxazole. (treatment for >3 months)[b]
Coxiella burnetii (Agent of Q fever)	• Serology: IgG phase 1 >1/800 • Tissue culture, immunohistology, and PCR of surgical material	• Doxycycline plus hydroxychloroquine[c] • Doxycycline plus quinolone (>18 months treatment)
Bartonella spp.	• Blood cultures • Serology • Culture, immunohistology, and PCR of surgical material	• β-lactams or doxycycline plus aminoglycoside[d] (>6 weeks treatment)
Chlamydia spp.	• Serology[e] • Culture, immunohistology, and PCR of surgical material	• Doxycycline • Newer fluoroquinolones[f] (Long-term treatment, optimal duration unknown)
Mycoplasma spp.	• Serology • Culture, immunohistology, and PCR of surgical material	• Doxycycline • Newer fluoroquinolones[f] (>12 weeks treatment)
Legionella spp.	• Blood cultures • Serology • Culture, immunohistology, and PCR of surgical material	• Macrolides plus rifampin • Newer fluoroquinolones[f] (>6 months treatment)
Tropheryma whipplei (Agent of Whipple's disease)	• Histology and PCR of surgical material	• Cotrimoxazole[g] • β-lactam plus aminoglycoside (Long-term treatment, optimal duration unknown)

[a]Owing to the lack of large series on IE due to these pathogens, optimal-treatment duration is mostly unknown. Treatment durations in the figure are indicative, and based on selected case reports. [b]According to reference (Hadjinikolaou *et al.*, 2001). [c]Doxycycline 100 mg orally twice a day and hydroxychloroquine 200 mg orally 3 times a day (hydroxychloroquine levels in the serum were monitored) was significantly superior than doxycycline (Raoult *et al.*, 1999). [d]Several therapeutic regimens were reported, including aminopenicillins and cephalosporins combined with aminoglycosides, doxycycline, vancomycin, and quinolones (reviewed in (Brouqui and Raoult, 2001)). [e]Beware of serologic cross-reaction with the more common IE pathogen *Bartonella* spp. [f]Newer fluoroquinolones are more potent than ciprofloxacin against intracellular pathogens such as *Mycoplasma* spp., *Legionella* spp., and *Chlamydia* spp. [g]Treatment of Whipple IE remains highly empirical. Successes were reported with long-term (>1 year) cotrimoxazole therapy. γ-interferon plays a protective role in intracellular infections. It was proposed as adjuvant therapy in Whipple's disease (Dutly and Altwegg, 2001).

when antibiotics have been prescribed prior to blood cultures, or in the case of fastidious organisms such as those presented in Table 3. Although specific studies are lacking, IE due to fastidious organisms does not seem to differ in elderly and younger people (Brouqui and Raoult, 2001).

Thus, except for an increased frequency of *S. gallolyticus* in the elderly, the microbial etiology of IE is quite comparable in older and younger patients. The prediction of a plausible pathogen depends on the patient's underlying conditions rather than on age. For example, coagulase-negative staphylococci are more frequent on prosthetic valve than on native valves. Antibiotic-resistant staphylococci are more frequent in health-care associated infections than in community-acquired diseases. *Streptococcus gallolyticus* is more prevalent in older patients and should prompt specific colon investigation, because it is suggestive of an underlying colonic neoplasia (Hoen *et al.*, 1994; Waisberg *et al.*, 2002).

MORTALITY

Mortality has been reported as being either much higher in elderly than younger patients (up to 45% vs 10–25%,

Table 4 Complications of infective endocarditis in elderly (≥65 years) and younger (<65 years) patients. Data compiled from the literature

Complications	≥65 years[a,b]	<65 years[a,b]	Compiled from[a,c]
Cardiac failure	65/130 (50%)	89/214 (42%)	(1, 6, 7)
Neurological symptoms	10/86 (11.5%)	13/150 (8.5%)	(1, 7)
Renal insufficiency	23/77 (30%)	19/132 (14%)	(1, 6)
Pulmonary complications	3/53 (6%)	17/101 (16%)	(5)
Arterial emboli	10/86 (12%)	14/277 (5%)	(1, 5)

[a]Only studies providing appropriate details were used to compare group of organisms. Vertical addition of patient numbers and percentages does not apply. [b]Upper age limit varied between 65 and 70 years in some studies. [c]References used: 1, (Poupet *et al.*, 1984); 2, (Robbins *et al.*, 1980); 3, (Selton-Suty *et al.*, 1997); 4, (Werner *et al.*, 1996); 5, (Terpenning *et al.*, 1987); 6, (Gagliardi *et al.*, 1998); 7, (Netzer *et al.*, 1999).

respectively) (Robbins *et al.*, 1980; Poupet *et al.*, 1984; Terpenning *et al.*, 1987), or rather similar (around 20%) in different age-groups (Werner *et al.*, 1996; Selton-Suty *et al.*, 1997; Gagliardi *et al.*, 1998; Netzer *et al.*, 1999). At least two variables might explain these differences. First, the heterogeneity of the cohorts studied, and second, the differences in diagnostic tools and diagnostic standards before and after the introduction of the validated "Duke" criteria for diagnosis of IE (Table 4) (Durack *et al.*, 1994; Li *et al.*, 2000).

Studies reporting a higher mortality included cases comprising notoriously severe prosthetic valve and nosocomial-acquired IE, which are more prevalent in elderly people (Robbins *et al.*, 1980; Terpenning *et al.*, 1987). In contrast, studies reporting equivalent mortalities included less severe cases of native valve and right-sided IE. Nevertheless, in one study, the increased mortality persisted after correction for the patient's heterogeneity (Terpenning *et al.*, 1987). Moreover, two recent studies including heterogeneous patients also reported quasi-comparable mortalities between different age-groups (Werner *et al.*, 1996; Selton-Suty *et al.*, 1997). Eventually, studies in which the patients were carefully matched, for example, for left-sided native valve IE, reported similar mortality rates in various age-groups as well (Gagliardi *et al.*, 1998; Netzer *et al.*, 1999). Thus, the reported variations in mortality may be due to additional factors.

Indeed, all the studies reporting a high mortality in older patients were completed before the application of the "Duke" diagnostic criteria, which were first introduced in 1994 (Durack *et al.*, 1994; Li *et al.*, 2000), and before echocardiography became routinely used for the purpose of IE diagnosis. In symmetry, all the studies reporting quasi-similar mortalities in all age-groups were performed after the introduction of these modern diagnostic tools. Diseased elderly patients may present confounding symptoms. Therefore, clinical diagnosis of infection may be difficult. In one earlier report, elderly patients with IE were mostly identified after secondary complications such as embolic stroke (Poupet *et al.*, 1984). Since stroke is associated with a poor prognosis (Gagliardi *et al.*, 1998; Netzer *et al.*, 1999; Hasbun *et al.*, 2003), earlier diagnosis and therapy might have improved the evolution of these patients. This may be particularly relevant in acute conditions such as *S. aureus* PVE in which a mortality rate of up to 47.5% was recently reported (Chirouze *et al.*, 2004). In consequence, prompt diagnosis, rather than age, emerges as a major determinant for IE prognosis.

PATHOGENESIS

The Valve Endothelium

The pathogenesis of IE has been reviewed (Moreillon *et al.*, 2002). The normal valve endothelium is very resistant to colonization and infection by circulating bacteria. On the other hand, mechanical lesions of this endothelium result in exposure of the underlying extracellular matrix proteins, the production of tissue factor, and the deposition of fibrin and platelets as a normal healing process. Such nonbacterial thrombotic endocarditis (NBTE) is an ideal *nidus* for bacterial adherence and colonization during transient bacteremia.

Endothelial damage may occur in several ways. Congenital cardiac abnormalities may cause turbulent blood flow, which in turn may provoke peeling of the endothelium. Valve scarring and calcification following rheumatic carditis or in the sclerotic valves of elderly patients result in endothelial lesions. Extrinsic intervention, such as prosthetic valve replacement or indwelling electrodes or catheters, also promote endothelial lesions. Recently, the presence of *Chlamydia pneumoniae* or cytomegalovirus in endovascular locations has been linked to atherosclerosis. Whether these organisms also trigger endothelial lesions that promote IE remains to be demonstrated.

Infective endocarditis can also occur without known or identifiable preexisting valve lesions. This is particularly true for *S. aureus*, which has emerged as the leading cause of IE in several recent surveys (Bouza *et al.*, 2001; Moreillon and Que, 2004). Local inflammation, which may occur in some circumstances (see the following text), triggers endothelial cells to express a variety of molecules, including integrins of the $\beta 1$ family (very late antigen or VLA) (Hemler *et al.*, 1990). Integrins are transmembrane proteins that can connect extracellular determinants to the cellular cytoskeleton. Integrins of the $\beta 1$ family bind circulating fibronectin to the endothelial surface. On their side, *S. aureus* and a few other IE pathogens carry fibronectin-binding proteins anchored to their walls. Hence, when activated endothelial cells bind fibronectin, they provide an adhesive surface to circulating staphylococci. Once adherent, *S. aureus* can trigger their active internalization by the host cells, in which they can either persist and escape host defenses and antibacterial agents, or multiply and spread to distant organs. This behavior is orchestrated by global regulators such as *agr* (for accessory gene regulator) and *sar* (for staphylococcal accessory regulator), which sense bacterial density and may trigger the secretion of hemolysins and toxins for the purpose of tissue invasion (Novick and Muir, 1999).

Thus, there might be at least two scenarios for primary valve colonization: one requiring a physically damaged

endothelium, or NBTE, favoring infection by most types of organisms including viridans group streptococci, and one occurring on physically undamaged endothelia, caused by organisms capable of invading (e.g. *S. aureus*) and parasitizing (e.g. *Coxiella burnetii*, the agent of Q fever) the endothelium.

Infection of Presumably Undamaged Valve

It was believed that preexisting valve lesions were less frequently present in elderly than in younger patients with IE (Poupet *et al.*, 1984). This impression has not been confirmed in recent studies (Table 1). It relied on the detection of preexisting valve abnormalities by auscultation, as exemplified by an audible heart murmur. However, subtle valve abnormalities such as early degenerative valve lesions may pass undetected by auscultation.

Degenerative valve lesions are present in up to 50% of patients over 60 years with IE (Stehbens *et al.*, 2000) (*see* **Chapter 44, Cardiac Aging and Systemic Disorders**; **Chapter 46, Ischemic Heart Disease in Elderly Persons**). This condition involves local inflammation, microulcers, and microthrombi of the endothelium, which are quite similar to atherosclerosis (Stehbens *et al.*, 2000) (*see* **Chapter 53, Pathogenesis of Atherosclerosis**). An age-related increase in predisposing valve conditions was recently highlighted in a large (100 patients) echocardiography study (Croft *et al.*, 2004). The authors identified valve abnormalities that qualified for endocarditis prophylaxis (Dajani *et al.*, 1997; Moreillon, 2000) in up to 50% of patients aged more than 60 years. This may explain, at least in part, the increased risk of IE in the elderly.

The Role of Transient Bacteremia

Medical and surgical procedures in nonsterile anatomic sites may provoke transient bacteremia. Transient bacteremia also occurs spontaneously during normal activities such as chewing and toothbrushing. These bacteremia are usually of low grade and short duration (1–100 CFU/ml of blood for less than 10 minutes in the case of dental extraction). However, they may put patients with preexisting cardiac lesions at an increased risk of developing IE.

The fact that transient bacteremia occurs during normal activities probably explains why most cases of IE are not preceded by medico-surgical procedures (van der Meer *et al.*, 1992b; van der Meer *et al.*, 1992a; Strom *et al.*, 1998). Hence, even if antibiotic prophylaxis during procedures were effective, it would only prevent a limited number of IE cases. Good handling of potential portals of entry is primordial. These include at least the oral sphere (risk of *Streptococcus* spp.), the skin (risk of *Staphylococcus* spp.), the urinary tract (risk of *Enterococcus* spp.), and the related interventions (e.g. indwelling catheters).

Two increasingly frequent "health-care associated" bacteremia are of special concern: bacteremia in dialysis patients (especially hemodialysis) and nosocomial bacteremia. Elderly people are particularly exposed to such occurrences. IE is up to 3 times more frequent in hemodialysis patients than in the general population (Abbott and Agodoa, 2002). Moreover, >50% of the cases are due to *S. aureus*, which are often resistant to methicillin and multiple other drugs. Nosocomial IE accounted for 22% of 109 cases in one study (Bouza *et al.*, 2001). Many patients had debilitating conditions, but <50% had known cardiac predisposing factors. The predominant pathogens were staphylococci and enterococci, and were frequently associated with catheters and/or medico-surgical procedures (Bouza *et al.*, 2001). Another study estimated that up to 13% of nosocomial *S. aureus* bacteremia were responsible for subsequent IE (Fowler *et al.*, 1999). Mortality was greater than 50% (Bouza *et al.*, 2001). Therefore, recognition of such cases is important.

Microbial Pathogens and Host Defenses

Classical IE pathogens include *S. aureus, Streptococcus* spp. (primarily viridans group streptococci and *S. gallolyticus*), and *Enterococcus* spp. (primarily *E. faecalis*) (Figure 1, Table 2). These organisms share the ability to adhere to damaged valves, trigger local procoagulant activity, and nurture infected vegetations in which they can survive (reviewed in (Moreillon *et al.*, 2002)). They are equipped with numerous surface determinants that mediate adherence to host matrix molecules present on damaged valves (e.g. fibrinogen, fibronectin, platelet proteins). These determinants are mutually referred to as *MSCRAMM*, for microbial surface components recognizing adhesive matrix molecules. Damaged or inflamed endothelia carry multiple extracellular matrix molecules acting as specific ligands for MSCRAMMs.

After valve colonization, adherent bacteria escape host defenses. Complement is highly active against gram-negative bacteria, but not against gram-positive bacteria such as staphylococci and streptococci. In gram-negative bacteria, the final C5b-C9 membrane attack complex (MAC) of complement can perforate the lipopolysaccharide outermembrane and kill the bacterium. Gram-positive bacteria do not have an outermost membrane. Instead, they have a thick peptidoglycan, which protects their inner plasma membrane from attack by MAC. This may explain the wide predominance of gram-positive over gram-negative bacteria in IE.

Although gram-positive bacteria are resistant to complement, they may be the target of platelet microbicidal proteins (PMPs). PMPs are peptides produced by activated thrombocytes that kill bacteria by a mechanism that is as yet incompletely understood. Microorganisms recovered from patients with IE are consistently resistant to PMP-induced killing, whereas similar bacteria recovered from patients with other types of infection were susceptible to PMP (Fowler *et al.*, 2000). Thus, escaping PMP-induced killing is a typical feature of successful IE pathogens.

Further infection involves promoting vegetation growth. Valve-adherent bacteria attract and activate circulating monocytes. Although activated, these monocytes fail to engulf their target organisms, a phenomenon referred to as *frustrated*

phagocytosis. On the other hand, they produce cytokines that trigger local inflammation – and local deposition of fibronectin – as well as the production of tissue factor both by themselves and by neighboring endothelial cells.

Tissue factor is a 47 kDa integral membrane glycoprotein that activates coagulation by combining with factor VII and factor X, as well as platelets (Camerer *et al.*, 1996). Tissue factor is not produced by unperturbed endothelial cells or monocytes. However, it can be induced by various agonists including cytokines (IL-1) and bacterial components, and contributes to the vegetation's growth (Moreillon *et al.*, 2002) and thus, bacteria can encourage vegetation growth by subverting monocytes and endothelial cells to produce tissue factor.

A clear role for other host defenses remains uncertain. Experiment on immunization gave contradictory results and administration of granulocyte colony-stimulating factor did not influence the course of infection (reviewed in Moreillon *et al.*, 2002). Moreover, IE is not noticeably more frequent in immunocompromised patients than in those without immune defects. In established infection, bacteria are clustered in the amorphous platelet–fibrin vegetations. This explains why successful treatment of IE relies primarily on the ability of antibiotics to kill the bacteria *in situ*.

PROPHYLAXIS

Because of its severity, it is agreed upon that IE should be prevented whenever possible. Determining adequate prophylaxis implies establishing (i) the patients at risk, (ii) the procedures that might provoke bacteremia, (iii) the most effective prophylactic regimen, and (iv) a balance between the risks of the side effects of prophylaxis and of developing IE. Patients at risk and procedures inducing bacteremia have been identified by clinical studies (Strom *et al.*, 1998), and recommendations for prophylaxis have been proposed in several countries (Dajani *et al.*, 1997; Moreillon, 2000). On the other hand, the efficacy of prophylactic antibiotics is based on animal experimentation. Randomized, placebo-controlled studies do not exist in humans, because they would require too large a patient number and would raise ethical issues because of the severity of the disease. Case-control studies have suggested that IE prophylaxis was effective, but prevented only a limited number of cases (Strom *et al.*, 1998). Indeed, most cases of IE are not preceded by medical procedures (van der Meer *et al.*, 1992b; van der Meer *et al.*, 1992a; Strom *et al.*, 1998). Therefore, the primary prevention of IE should target infected foci responsible for spontaneous bacteremia (e.g. poor dental hygiene). Recommendations for IE prophylaxis are similar in elderly and younger people (Dajani *et al.*, 1997; Moreillon, 2000).

CLINICAL FEATURES

Infective endocarditis may follow an acute or subacute course. Clinical features reported in elderly and younger patients are reported in Tables 1 and 4. Although few differences exist, they are not large enough to portray a specific clinical profile of one or the other group.

Acute Infective Endocarditis

Acute IE is most frequently caused by *S. aureus*, followed by enterococci and certain streptococci, such as *Streptococcus milleri*. IE caused by *S. aureus* and other invasive pathogens can be devastating. Bacterial production of proteases and other exoproteins contributes to rapid destruction of valve leaflets and the development of abscesses located in the valve ring and the myocardium. Myocarditis and pericardial effusions are frequent. Patients are prostrated and have a high fever. Hypotension and shock may occur, caused both by the septic state and by cardiac failure. Cardiac vegetations may vary from a few millimeters in diameter to more than 1 cm. Large vegetations are frequent in acute staphylococcal and fungal IE and are more likely to detach and give rise to septic emboli. Complications in peripheral organs mainly result from embolic lesions; these may include skin abscesses (Janeway lesions), retinal emboli, cerebral abscesses, and splenic abscesses.

Major indications for urgent valve replacement include refractory cardiac failure due to valve destruction and persistent sepsis related to myocardial abscesses. A defect in atrioventricular conduction is often an early sign of septal invasion by a contiguous valve ring abscess, which usually requires urgent surgery.

Subacute Infective Endocarditis

Subacute IE is not usually due to *S. aureus*, but it may be due to any of the organisms listed in Figure 1 and Table 2. The course of subacute IE can mimic chronic wasting diseases. The duration between an identifiable event producing bacteremia (e.g. dental procedure) and the diagnosis of IE can vary from a few days to 5 weeks or more. Fever is almost always present (Table 1). Physical signs reflect the existence of cardiac or peripheral complications. These include a new or changing heart murmur and evidence of embolic events.

Immunologic stimulation during subacute IE causes hyperproduction of gammaglobulin. Rheumatoid factor is present in up to 50% of patients after 6 weeks of subacute infection; its level decreases after effective treatment. Immune phenomena may be the cause of petechiae, splinter hemorrhages, Osler nodes and Roth spots, arthritis, and glomerulonephritis. Osler nodes are small and painful nodular lesions on the pads of the fingers or toes or on the thenar or hypothenar eminences. They are caused by an allergic vasculitis. Although classic, they are not pathognomonic of subacute IE. Roth spots are rounded retinal hemorrhages with a white center. Focal or diffuse glomerulonephritis is present in most of the cases. Because these phenomena follow stimulation of the immune system, they are less common in acute IE.

Vascular Complications

Embolic lesions result from vegetation fragments breaking off the valve and lodging in arteries serving peripheral organs. Other types of vascular manifestations are the consequence of immune-related vasculitis. Mycotic aneurysms are found in up to 15% of cases, and are especially common in staphylococcal IE. They may arise either from direct invasion of the arterial wall by the infecting organisms, from septic embolization of the vasa vasorum, or from the deposition of immune complexes that may trigger local inflammation and weaken the arterial wall. Mycotic aneurysms tend to be located at the bifurcation points of vessels. They may either heal during antibiotic therapy or become clinically evident later, even months after the clinical cure of the disease. Therefore, the true incidence of mycotic aneurysms during IE is probably underestimated. In right-sided IE, embolization occurs in the pulmonary circulation and gives rise to pulmonary infiltrates and lung abscesses.

Neurologic Complications

Neurologic manifestations may occur in up to 40% of cases (Bouza *et al.*, 2001) (*see* **Chapter 72, Secondary Stroke**). However, because patients without neurologic symptoms do not undergo specific investigations, the true incidence of neurologic events during IE may be underestimated. Anatomic alterations include cerebral infarction, arteritis, abscesses, mycotic aneurysms, intracerebral or subarachnoid hemorrhage, encephalomalacia, cerebritis, and meningitis. Such complications occur most often in staphylococcal or streptococcal IE, but they are not restricted to IE caused by these pathogens. The frequency of stroke is similar between native valve and prosthetic valve IE (Cabell *et al.*, 2001). However, the frequency of both vegetations and stroke is significantly greater in patients with mitral valve IE than patients with aortic valve IE.

Controlling the infection is essential. Embolization sharply decreases within 1–2 weeks of effective therapy (Vuille *et al.*, 1994). Recurrent embolization may necessitate urgent valve replacement. This decision is difficult because anticoagulation during extracorporeal circulation and after valve replacement put the patients at an increased risk of secondary intracerebral hemorrhage. Therefore, the tendency is often to postpone emergency surgery and wait for the patient to stabilize. On the other hand, ongoing studies suggest that earlier intervention, within the first 72 hours of stroke, may be beneficial in selected patients (Piper *et al.*, 2001). The best approach to these challenging issues needs continuing investigation.

DIAGNOSIS

Infective endocarditis classically combines fever (Table 1), persistent bacteremia, and anatomic lesions of the valves. However, fever may be variable in elderly people (Norman, 2000), and blood cultures may remain negative in up to 10% of cases (Figure 1 and Table 2), often due to prior consumption of antibiotics. Clinical and microbiologic diagnosis of IE is difficult in such circumstances, or when changes in the valve status cannot be assessed owing to the lack of information on preexisting cardiac lesions (Durack *et al.*, 1994; Li *et al.*, 2000).

Fever

Fever may be present in $\geq$80% of both elderly and younger patients (Table 1), suggesting that the absence of fever in elderly patients is not an issue for IE. On the other hand, up to 20–30% of elderly patients have a blunted febrile response in the case of severe infection such as pneumonia and bacteremia (for review see (Norman, 2000)). The reason for the poorer febrile response in elderly patients is not entirely clear. Experimental models suggest that they both secrete less cytokines in response to infection, and respond less sharply to endogenous and exogenous pyogenes. The poor febrile response is a problem because it may both delay the diagnosis and give a false impression of security. Thus, other signs associated with infection, such as unexplained alteration of mental status, must be followed with scrutiny in elderly patients (Norman, 2000).

The Duke Criteria

In 1994, new diagnostic criteria based on both microbiologic data and echocardiographic imaging were proposed (Durack *et al.*, 1994). These so-called *Duke criteria* were validated worldwide, and were recently refined to more accurately detect IE in the case of negative blood cultures and *S. aureus* bacteremia (Table 5) (Li *et al.*, 2000). Today, all patients suspected of having IE should undergo at least one echocardiographic evaluation, including transesophageal echo in selected cases. However, a negative echo does not rule out IE when other criteria are positive.

Blood Cultures

The importance of blood culture cannot be overemphasized. It remains the best identification method and provides live bacteria for susceptibility testing. For the main etiologic agents, the first two blood cultures (drawn $\geq$30 minutes apart) will be positive in more than 90% of cases. Culture-negative IE is often associated with antibiotic consumption within the 2 previous weeks. It may also be due to fastidious or intracellular pathogens that are not easily detected by standard culture conditions. The diagnostic laboratory should be made aware of such possibilities, in order to take appropriate measures.

Culture-negative Infective Endocarditis

Identifying the pathogen in culture-negative IE requires special procedures. They comprise inactivating antibiotics in

Table 5 Modified "Duke" criteria for diagnosis of infective endocarditis (Adapted with modifications from references (Durack *et al.*, 1994; Li *et al.*, 2000) and (Moreillon and Que, 2004))[a]

Definition terminology used in the criteria
Major criteria
1. Blood culture
– Positive blood cultures (≥2/2) with typical IE microorganisms (viridans streptococci, *S. bovis*, HACEK[b] group, ***S. aureus*, or community-acquired enterococci in the absence of primary focus**)[c]
– Persistently positive blood cultures defined as 2 culture sets drawn >12 hours apart, or 3 or the majority of 4 culture sets with the first and last separated at least by 1 hour
– **Single positive culture for *Coxiella burnetii* or anti-phase I antibody titer >1 : 800**
2. Endocardial involvement
– Positive echocardiogram for IE (**transesophageal echo recommended in patients with prosthetic valves, patients rated as "possible" IE by clinical criteria, or complicated IE [paravalvular abscess]; transthoracic echo as first in other patients**):
(i) Oscillating intracardiac mass on valve or supporting structure, *or* in the path of regurgitant jets, *or* on implanted material, in the absence of an alternative anatomic explanation, *or*
(ii) Abscess, *or*
(iii) New partial dehiscence of prosthetic valve
– New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
Minor criteria
1. Predisposing cardiac condition or intravenous drug use
2. Fever: ≥38 °C (100.4 °F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarct, mycotic aneurysms, intracranial hemorrhage, conjonctival hemorrhage, Janeway's lesions
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
5. Microbiology: positive blood cultures, but not meeting major criteria as mentioned above, serologic evidence of active infection with plausible microorganisms[d]
6. Echocardiogram consistent with IE but not meeting the major criterion noted above[e]
Diagnosis
Definite
• Pathology or bacteriology of vegetations, major emboli or intracardiac abscess specimen, *or*
• 2 major criteria, *or*
• 1 major and 3 minor criteria, *or*
• 5 minor criteria
Possible[f]
• **1 major and 1 minor criterion, *or* 3 minor criteria**
Rejected
• Firm alternative diagnosis, *or*
• Resolution of IE syndrome after ≤4 days of antibiotherapy, *or*
• No pathologic evidence at surgery or autopsy after ≤4 days of antibiotherapy
• Does not meet criteria mentioned above

[a]Modifications of the Duke criteria proposed by Li *et al.* (Li *et al.*, 2000) are highlighted in bold in the table. The revised criteria were validated against a retrospective cohort of pathologically demonstrated and/or prospectively followed endocarditis cases. The revision was intended to increase both the diagnostic specificity (diagnostic threshold) and the sensitivity for endocarditis due to *S. aureus* and difficult to cultivate organisms. [b]Includes *Haemophilus* spp., *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella Kingae*. [c]Original Duke criteria state: "or community-acquired *S. aureus* or enterococci in the absence of primary focus" (Durack *et al.*, 1994). [d]Excludes single positive cultures of coagulase-negative staphylococci and organisms that do not cause endocarditis. [e]Appears in the original Duke criteria (Durack *et al.*, 1994), abandoned in the revised criteria (Li *et al.*, 2000). [f]Original Duke criteria state: "findings consistent with IE that fall short "Definite", but not "Rejected" (Durack *et al.*, 1994).

the culture media, prolonging incubation (≥2 weeks), serology, agglutination, indirect fluorescence, ELISA, complement fixation, and polymerase-chain-reaction (PCR) amplification of genes that are specific for bacteria, such as the genes of the 16S ribosomal RNA (Brouqui and Raoult, 2001; Houpikian and Raoult, 2002). PCR is useful to identify bacterial DNA in tissue samples, including valves, and peripheral emboli (Goldenberger *et al.*, 1997). It proved invaluable to detect poorly or noncultivable bacteria such as *Tropheryma whipplei* (Dutly and Altwegg, 2001). However, it may remain positive in spite of clinical cure even after prolonged antibiotic treatment. Thus, specific knowledge and careful interpretation is required to avoid erroneous conclusions.

Undiagnosed culture-negative IE is a problem because unusual pathogens may not respond to empirical β-lactam and aminoglycoside therapy. Table 3 lists the principal organisms of this group, and the proposed diagnostic procedures, and tentative therapy (Brouqui and Raoult, 2001).

MANAGEMENT

Treatment of IE involves several medical specialists including infectious disease experts, cardiologists, cardiovascular surgeons, and sometimes neurologists. In spite of this wide interest, no large-size and/or blinded studies exist on IE treatment. Most recommended therapies are based on

Table 6 Suggested treatment for native valve endocarditis due to streptococci, enterococci, and HACEK microorganisms (Adapted from references (Francioli *et al.*, 1995; Wilson *et al.*, 1995) and (Moreillon and Que, 2004))

Antibiotic	Dosage and route	Duration (week)	Comments
Penicillin-susceptible viridans streptococci and *Streptococcus bovis*:			
Penicillin G	$6 \times 2-3$ million U day^{-1} IV	4	Preferred in patients older than 65 years or with impaired renal function
Ceftriaxone[a]	$1 \times 2\,g\,day^{-1}$ day IV or IM	4	
Penicillin G with gentamicin	$6 \times 2-8$ million U day^{-1} IV	2	Studies suggest that gentamicin 1 x/day might be adequate
	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	2	
Ceftriaxone[a] with netilmicin	$1 \times 2\,g\,day^{-1}$ IV or IM	2	
	$1 \times 4\,mg\,kg^{-1}\,day^{-1}$ IV	2	
Vancomycin	$2 \times 15\,mg\,kg^{-1}\,day^{-1}$ IV	4	Recommended for β-lactam allergic patients
Intermediate penicillin-resistant (MIC $0.1-1\,mg\,l^{-1}$) viridans streptococci and *Streptococcus bovis*:			
Penicillin G with gentamicin	6×3 million U day^{-1} IV	4	Studies suggest that gentamicin 1 x/day might be adequate
	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	2	
Vancomycin	$2 \times 15\,mg\,kg^{-1}\,day^{-1}$ IV	4	Recommended against highly resistant strains or for β-lactam allergic patients
Enterococcus spp.[b]:			
Penicillin G with gentamicin	$6 \times 3-5$ million U day^{-1} IV	4–6	6-weeks therapy recommended for patients with >3 months symptoms
	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	4–6	
Ampicillin with gentamicin	$6 \times 2\,g\,day^{-1}$ IV	4–6	Studies suggest that gentamicin 1 x/day might be adequate
	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	4–6	
Vancomycin with gentamicin	$2 \times 15\,mg\,kg^{-1}\,day^{-1}$ IV	4–6	Monitor drug serum levels and renal function
	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	4–6	
Microorganisms of the HACEK group[c]:			
Ceftriaxone[†]	$1 \times 2\,g\,day^{-1}$ day IV or IM	4	
Ampicillin with gentamicin	$6 \times 2\,g\,day^{-1}$ IV	4	Studies suggest that gentamicin 1 x/day might be adequate
	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	4	

[a]Preferred for outpatient treatment. [b]Treatment of endocarditis due to vancomycin-resistant enterococci requires a careful assessment of susceptibility to alternative antibiotics, including the new streptogramin combination quinupristin/dalfopristin. [c]Includes *Haemophilus* spp., *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella Kingae*.

experimental works, expert opinions, or small case-control studies (Francioli *et al.*, 1995; Wilson *et al.*, 1995; Moreillon and Que, 2004).

Bactericidal antibiotics are a cornerstone of therapy. Therapeutic schemes recommended for the most common pathogens are presented in Table 6 and Table 7 (Francioli *et al.*, 1995; Wilson *et al.*, 1995). High concentrations of antibiotic in the serum are desirable to ensure diffusion into the vegetations. Prolonged treatment is mandatory to kill dormant bacteria clustered in the infected foci. Outpatient and oral therapy is sometimes proposed (Rehm, 1998), but prolonged parenteral therapy is usually recommended.

The choice of an optimal regimen is based on antibiotic susceptibility testing. Minimal inhibitory concentrations of the principal drugs for the infecting pathogens should be determined. Resistant pathogens and culture-negative IE may fail to respond to standard treatment and this is discussed in the following text.

Penicillin-resistant Streptococci

Streptococci are becoming increasingly resistant to penicillin and other β-lactams, owing to a decreased β-lactam affinity of their membrane-bound penicillin-binding proteins (PBPs). Penicillin-resistant streptococci are classified as having either intermediate resistance (MIC of $0.1-1\,mg\,l^{-1}$) or high resistance (MIC over $1\,mg\,l^{-1}$).

Intermediately resistant streptococci may respond to standard therapy because β-lactam concentrations in the serum are much greater than the MIC for these bacteria. Peak serum levels of penicillin G, amoxicillin, or ceftriaxone are in the order of $100\,mg\,l^{-1}$, that is, 100–1000 times greater than the MIC of intermediately resistant streptococci (MIC = $0.1-1\,mg\,l^{-1}$). Nonetheless, potentiating the β-lactam activity by combining it with an aminoglycoside is recommended in such situations.

Alternative drugs must be considered against highly resistant streptococci. These include vancomycin, to which streptococci are still widely susceptible. In the future, newer quinolones with anti-gram-positive activity and quinupristin–dalfopristin may prove useful (Entenza *et al.*, 1995; Entenza *et al.*, 1999). Oxazolidinones are an alternative, but they are poor bactericides. Upcoming daptomycin and tigecycline require further experimental evaluation.

Methicillin-resistant and Vancomycin-resistant Staphylococci

All methicillin-resistant staphylococci carry a new, low-affinity PBP, called *PBP2A* that confers cross-resistance to most β-lactam drugs. In addition, methicillin-resistant staphylococci are usually resistant to most other drugs, leaving only vancomycin to treat severe infections.

Table 7 Suggested treatment for native valve and prosthetic valve endocarditis due to staphylococci (Adapted with modifications from references (Wilson *et al.*, 1995) and (Moreillon and Que, 2004))

Antibiotic	Dosage and route	Duration (week)	Comments
Native valves			
Methicillin-susceptible staphylococci			
Flucloxacillin, or oxacillin, or nafcillin	$6 \times 2\,g\,day$ IV	4–6	The benefit of gentamicin addition is not
with gentamicin (optional)	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	3–5 days	demonstrated
Cefazolin (or other first generation	$3 \times 2\,g\,day^{-1}$ IV	4–6	Alternative for patients allergic to penicillins (not in
cephalosporins) with gentamicin (optional)	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	3–5 days	case of immediate type penicillin hypersensitivity)
Vancomycin	$2 \times 15\,mg\,kg^{-1}\,day^{-1}$ IV	4–6	Recommended for β-lactam allergic patients
Methicillin-resistant staphylococci			
Vancomycin	$2 \times 15\,mg\,kg^{-1}\,day^{-1}$ IV	4–6	Recommended for β-lactam allergic patients
Prosthetic valves			
Methicillin-susceptible staphylococci[a]			
Flucloxacillin, or oxacillin, or nafcillin	$6 \times 2\,g\,day^{-1}$ IV	≥ 6	Rifampin increases the hepatic metabolism of
with rifampin and gentamicin	$3 \times 300\,mg\,day^{-1}$ orally	≥ 6	numerous drugs, including warfarin
	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	2	
Vancomycin with rifampin and gentamicin	$2 \times 15\,mg\,kg^{-1}\,day^{-1}$ IV	≥ 6	Recommended for β-lactam allergic patients
	$3 \times 300\,mg\,day^{-1}$ orally	≥ 6	
	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	2	
Methicillin-resistant staphylococci			
Vancomycin with rifampin and gentamicin	$2 \times 15\,mg\,kg^{-1}\,day^{-1}$ IV	≥ 6	
	$3 \times 300\,mg\,day^{-1}$ orally	≥ 6	
	$3 \times 1\,mg\,kg^{-1}\,day^{-1}$ IV or IM	2	

[a]Rifampin plays a special role in prosthetic device infection, because it helps kill bacteria attached to foreign material. Rifampin should never be used alone, because it selects for resistance at a high frequency (ca. 10^{-6}).

Yet, vancomycin-resistance is developing. *S. aureus* and coagulase-negative staphylococci with intermediate resistance to vancomycin have emerged worldwide. The mechanism of intermediate resistance is mediated by chromosomal mutations affecting the synthesis of the cell wall (Hiramatsu, 2001). High vancomycin-resistance had emerged 15 years ago in enterococci, and could be transferred experimentally into *S. aureus* (Noble *et al.*, 1992). Recently, few highly vancomycin-resistant *S. aureus* were isolated in the clinics. Their vancomycin-resistant genes were also acquired from enterococci (Rep, 2002).

Treatment of IE caused by vancomycin-resistant staphylococci will require new approaches. At present, a few unconventional alternatives are available, including old and new β-lactams with relatively good affinity to PBP2A (Entenza *et al.*, 2002), quinupristin–dalfopristin combined with or without β-lactams (Entenza *et al.*, 1995; Vouillamoz *et al.*, 2000), antibiotic combination including cotrimoxazole (de Gorgolas *et al.*, 1995), and maybe oxazolidinones (Jacqueline *et al.*, 2002). Methicillin-resistant staphylococci are usually resistant to newer quinolones. Promising future drugs include daptomycin (Sakoulas *et al.*, 2003).

Multiple-drug-resistant Enterococci

These organisms are resistant to most available drugs, including vancomycin. Treatment of such bacteria relies on the combination of multiple drugs and the use of experimental antibiotics. It requires precise determination of antibiotic susceptibilities, testing for bactericidal activity, maybe determining the serum inhibitory and bactericidal titers, and monitoring drug levels in the serum. Although aminoglycoside-resistance is often present, these drugs may still synergize with cell-wall inhibitors, provided that the aminoglycosides MIC is $\leq 1000\,mg\,l^{-1}$. Streptomycin is worth testing because it may be active against enterococci that are resistant to other aminoglycosides. Salvage regimens suggested to combat highly aminoglycoside-resistant, but ampicillin-susceptible, enterococci include continuous infusion of high-dose ampicillin, alone or in combination with ceftriaxone, other β-lactam combinations, or oxazolidinones. Whenever envisioned, such an approach should be based on expert opinion. As for streptococci, upcoming daptomycin, and tigecycline require further studies (Kennedy and Chambers, 1989; Lefort *et al.*, 2003).

Culture-negative Endocarditis

Table 3 summarizes the treatment of IE due to rare pathogens. *Brucella* spp. IE responds to ≥ 3 months treatment with doxycycline (100–200 mg every 12 hours) plus cotrimoxazole (960 mg every 12 hours) or rifampin (300–600 mg day^{-1}) combined with or without streptomycin ($16\,mg\,kg^{-1}\,day^{-1}$). Surgery may be required (Hadjinikolaou *et al.*, 2001). Cure is considered by an antibody titer returning to $<1:160$.

Coxiella burnetii IE is often treated with doxycycline combined with a fluoroquinolone for up to 3 years. Recurrences are common. Recently, a combination of doxycycline and hydroxychloroquine appeared more effective (Raoult *et al.*,

1999). Treatment success is considered when the anti−phase I antigen IgG titer is $<1:800$, and IgM and IgA titers are $<1:50$ (Raoult *et al.*, 1999).

Bartonella spp. IE responds to β-lactams (amoxicillin or ceftriaxone) combined with aminoglycosides (netilmicin or gentamicin) for at least 2 weeks, or β-lactams combined with other drugs (e.g. doxycycline) for a total of $\geq$6 weeks (Fournier *et al.*, 2001). Combination with surgery is reported in $\geq$90% of cases.

Treatment of IE due to *Chlamydia* spp., *Mycoplasma* spp., and *Legionella* spp., is unknown. These organisms are highly susceptible to newer fluoroquinolones *in vitro*. Therefore, fluoroquinolones should probably be part of the treatment.

IE due to *T. whipplei* is very rare. In non-IE Whipple's disease, cotrimoxazole (960 mg every 12 hours) given for $\geq$1 year is recommended (Dutly and Altwegg, 2001). Some authors recommend sequential treatment starting with penicillin plus streptomycin, or ceftriaxone plus gentamicin, for 2 to 6 weeks, followed by long-term cotrimoxazole. A recent review of 35 cases of Whipple IE supports this approach and suggests that surgical valve replacement might be a prerequisite for successful therapy (Fenollar *et al.*, 2001).

Surgery (*see* Chapter 51, Management of Acute Cardiac Emergencies and Cardiac Surgery; Chapter 52, Cardiac Surgery in the Elderly)

A detailed overview of surgical techniques is beyond the scope of this review. However, surgery is increasingly becoming important in the management of IE and was even associated with a better outcome in the prognosis scoring proposed overall (Hasbun *et al.*, 2003; Vikram *et al.*, 2003). Surgery encompasses both radical valve replacement and more conservative vegetectomy and valve repairs.

Surgery is necessary in 25 to 30% of cases during acute infection, and in 20 to 40% in later phases (Jault *et al.*, 1997; Alexiou *et al.*, 2000). The final outcome has little relation to the duration of prior antibiotic therapy. The principal indications comprise (i) refractory cardiac failure caused by valvular insufficiency, (ii) persistent sepsis caused by a surgically removable focus or a valvular ring or myocardial abscess, and (iii) persistent life-threatening embolization. The decision is multidisciplinary, and age is not a discriminatory feature (Hasbun *et al.*, 2003). Studies on the surgery of active IE report mortality rates of 8 to 16%, with actuarial survival at 5 years of 75 to 76% and at 10 years of 61% (Alexiou *et al.*, 2000).

CONCLUSION

The mean age of IE is increasing (Bouza *et al.*, 2001, Hoen *et al.*, 2002, Moreillon and Que, 2004). This correlates with an increase in risk factors that are more common in elderly ($\geq$65 years) than in younger people. As a result, elderly people have a $\geq$3-times greater risk of acquiring IE than younger persons (Moreillon and Que, 2004). In spite of this evolution, demographic features, bacterial pathogens, and life prognosis appear not much different in both age-groups. Most patients have predisposing valve conditions as detected by echocardiography (Croft *et al.*, 2004). The major pathogens are *Staphylococcus* spp. and *Streptococcus* spp. (in ca. 80% of cases) and are similarly distributed in older and younger adults. One difference involves the partitioning of oral and enteric streptococci in older and younger patients (Hoen *et al.*, 2002). Elderly patients have an increased prevalence of IE due to *S. gallolyticus,* in relation with colon neoplasia, and a parallel decrease in IE due to oral streptococci (Hoen *et al.*, 2002; Moreillon and Que, 2004). This highlights that a genuine age-related modification of epidemiology. Aging has often been considered as an aggravating factor for life prognosis. However, recent reports suggest that this might not be true. Age-independent clinical and laboratory parameters are more predictive (Hasbun *et al.*, 2003). Moreover, prompt diagnosis and therapy is critical for clinical outcome. Thus, life prognosis should be considered in the patient's global context, rather than on age alone. On the other hand, studies on functional outcome are still missing.

KEY POINTS

- Age is not a primary determinant for life prognosis. Patients who are comparable for mental status, comorbidities, bacterial pathogen, cardiac conditions, and surgery have a similar chance of survival (Hasbun *et al.*, 2003, #613).
- The prognosis of IE depends on prompt diagnosis and therapy. Applying the modern Duke diagnostic criteria is critical (Durack *et al.*, 1994, #390; Li *et al.*, 2000, #1007).
- Degenerative valve sclerosis is a frequent predisposing condition in elderly people. It may be detected by echocardiography, while passing unnoticed in cardiac auscultation (Croft *et al.*, 2004, #867).
- *Staphylococcus* spp. and *Streptococcus* spp. are the principal pathogens of IE (in $>$80% of cases), and are similarly distributed in both elderly and younger patients.
- *S. gallolyticus* is more prevalent in elderly IE patients. It is frequently associated with a colon neoplasia and should prompt digestive investigations.

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Infections of the Central Nervous System

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MENINGITIS

Meningitis is defined as the inflammation of the meninges that is manifested by an increase in the number of white blood cells in cerebrospinal fluid (CSF), and may be a result of a wide variety of infectious and noninfectious etiologies. The following is an overview of the most common infectious causes of meningitis in the elderly, with emphasis on the epidemiology, etiology, clinical presentation, diagnosis, and management of these disorders.

Viral Meningitis

Epidemiology and Etiology

Viruses are the major causes of the aseptic meningitis syndrome, which has been defined as any meningitis (infectious or noninfectious) for which a cause is not apparent after initial evaluation and routine stains and cultures of CSF (Connolly and Hammer, 1990). The most common etiologic agents of the aseptic meningitis syndrome are the nonpolio enteroviruses (specifically Coxsackie and echoviruses), which accounts for 85–90% of cases in which a pathogen is identified (Connolly and Hammer, 1990). These viruses are worldwide in distribution and occur with a peak incidence in the summer and early fall. Other viral causes of the aseptic meningitis syndrome include arboviruses (e.g. St Louis encephalitis virus, the California encephalitis group of viruses, West Nile encephalitis virus, and the agent of Colorado tick fever), mumps virus, the herpesviruses (herpes simplex viruses types 1 and 2, varicella zoster virus (VZV), cytomegalovirus, Epstein–Barr virus, and the human herpesviruses 6 and 7), lymphocytic choriomeningitis virus, and the human immunodeficiency virus (HIV).

Clinical Presentation

Patients with viral meningitis often present with typical symptoms and signs of meningitis, including headache, meningismus, fever, and photophobia (Connolly and Hammer, 1990; Rotbart, 1995; Sawyer and Rotbart, 2004). Symptoms associated with the causative virus may also be present, such as vomiting and diarrhea with the enteroviruses, vesicular rash with herpes simplex virus (HSV), and a mononucleosis-like syndrome with primary HIV infection. The duration of illness in enteroviral meningitis is usually less than 1 week, with many patients reporting improvement after lumbar puncture, probably as a result of reduction of intracranial pressure.

Diagnosis

In enteroviral meningitis, lumbar puncture usually reveals a lymphocytic pleocytosis (100–1000 cells mm^{-3}), although there may be a predominance of neutrophils early in the course of infection; however, this quickly gives way to a lymphocytic predominance over the first 6–48 hours (Connolly and Hammer, 1990; Rotbart, 1995; Sawyer and Rotbart, 2004; Romero, 2002). However, in a recent retrospective chart review, 51% of 53 patients with aseptic meningitis and duration of symptoms for more than 24 hours had a neutrophil predominance in CSF, suggesting that a CSF neutrophil predominance is not useful as a sole criterion in distinguishing between aseptic and bacterial meningitis (Negrini *et al.*, 2000). CSF protein is elevated, while glucose may be normal or low, although these abnormalities, if present, are usually mild. Similar CSF abnormalities are usually observed in other causes of viral meningitis.

Viral cultures are rarely helpful in the etiologic diagnosis of the aseptic meningitis syndrome, except in cases of HSV meningitis. Acute and convalescent serum titers may be obtained to identify specific etiologic agents but are not helpful in acute diagnosis and management. The isolation of a nonpolio enterovirus from the throat or gastrointestinal tract is supportive evidence for the diagnosis of meningitis in the appropriate clinical setting, although viral shedding may occur for several weeks after initial infection, making it difficult to rule out past infection. Furthermore, the time

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required for identifying an enterovirus from CSF using cell cultures is too long to be of clinical utility in establishing the diagnosis.

The polymerase chain reaction (PCR) has been shown to be useful in the diagnosis of meningitis due to HSV type 2 (Tedder *et al.*, 1994; Kojima *et al.*, 2002), and may be helpful in the identification of HIV in the CSF or plasma of patients with meningitis following primary infection. Reverse transcription-polymerase chain reaction (RT-PCR) has also been utilized for detecting enteroviral RNA, with sensitivity ranging from 86 to 100% and specificity from 92 to 100% in the diagnosis of enteroviral meningitis (Sawyer and Rotbart, 2004; Romero, 2002; Rotbart, 1990).

Therapy

Viral meningitis is usually a self-limited illness, and in the majority of cases only supportive therapy is indicated (Connolly and Hammer, 1990; Rotbart, 1995; Sawyer and Rotbart, 2004). However, this may change in the future. Pleconaril, a novel compound that integrates into the hydrophobic pocket of picornaviruses, has recently been shown to have beneficial effects on the clinical, virologic, laboratory, and radiologic parameters in patients with severe enterovirus infections (Romero, 2002; Rotbart and Webster, 2001). In cases associated with HSV infection (most often an initial infection with HSV type 2), treatment of the genital infection with acyclovir often results in resolution of the meningitis.

Bacterial Meningitis

Epidemiology and Etiology

Although numerous bacterial pathogens have been reported to cause meningitis in the elderly, certain agents are isolated more frequently.

Streptococcus pneumoniae is the most common cause of bacterial meningitis in the elderly. A contiguous (e.g. sinusitis, otitis media, or mastoiditis) or distant (e.g. endocarditis or pneumonia) site of infection is often identified. More serious pneumococcal infections occur in elderly patients and in those with underlying conditions such as asplenia, multiple myeloma, alcoholism, malnutrition, diabetes mellitus, and hepatic or renal disease (Musher, 1992). *S. pneumoniae* is also the most common etiologic agent of meningitis in patients with basilar skull fracture and CSF leak (Kaufman *et al.*, 1990). In the United States, the overall mortality rates for pneumococcal meningitis have ranged from 19 to 26% (Schlech *et al.*, 1985; Wenger *et al.*, 1990; Schuchat *et al.*, 1997). For this reason, the 23-valent pneumococcal vaccine is recommended for all patients over the age of 65 and for those in high-risk groups for serious pneumococcal infection.

Persons at risk for infection (including meningitis) with *Listeria monocytogenes* are the elderly ($\geq$50 years of age), those with underlying malignancy, alcoholics, those receiving corticosteroids, immunosuppressed adults (e.g. transplant recipients), and patients with diabetes mellitus and iron overload disorders (Lorber, 1997; Mylonakis *et al.*, 1998). Although *L. monocytogenes* is an unusual cause of bacterial meningitis in the United States, it is associated with high mortality rates (15–29%) (Schlech *et al.*, 1985; Wenger *et al.*, 1990; Schuchat *et al.*, 1997). Outbreaks of *Listeria* infection have been associated with the consumption of contaminated coleslaw, raw vegetables and milk, with sporadic cases traced to contaminated cheese turkey franks, alfalfa tablets, and processed meats; this points to the intestinal tract as the usual portal of entry.

Bacterial meningitis caused by aerobic gram-negative bacilli (e.g. *Klebsiella* species, *Escherichia coli*, *Serratia marcescens*, and *Pseudomonas aeruginosa*) is found in the elderly, occurring after head trauma or neurosurgical procedures, and in patients with gram-negative bacteremia (Tunkel and Scheld, 2005). Some cases have been associated with disseminated strongyloidiasis in the hyperinfection syndrome, in which meningitis caused by enteric bacteria occurs secondary to seeding of the meninges during persistent or recurrent bacteremias associated with migration of infective larvae; alternatively, the larvae may carry enteric organisms on their surfaces or within their own gastrointestinal tracts as they exit the intestine and subsequently invade the meninges.

Other bacterial species are less common causes of bacterial meningitis in the elderly (Tunkel and Scheld, 2005). *Neisseria meningitidis* may cause meningitis during epidemics (caused by serogroups A and C) or in sporadic outbreaks (serogroup B), although meningitis caused by this microorganism is more common in children and adults. Respiratory tract infections, with viruses such as influenza virus, may play a role in the pathogenesis of invasive meningococcal disease. There is an increased incidence of neisserial infections, including that caused by *N. meningitidis*, in persons with deficiencies of the terminal complement components (C5, C6, C7, C8, and perhaps C9), although the case fatality rates in these patients are lower than in those with an intact complement system (Ross and Densen, 1984). *Hemophilus influenzae* meningitis in elderly adults is associated with concurrent infections such as sinusitis, otitis media, and pneumonia, and underlying conditions such as chronic obstructive pulmonary disease, asplenia, diabetes mellitus, immunosuppression, and head trauma with CSF leak (Farley *et al.*, 1992). Meningitis caused by *Staphylococcus aureus* is usually found in the early postneurosurgical period or after head trauma, or in patients with CSF shunts; other underlying conditions include diabetes mellitus, alcoholism, chronic renal failure requiring hemodialysis, injection drug use, and malignancies (Schlessinger *et al.*, 1987). *Staphylococcus epidermidis* is the most common cause of meningitis in patients with CSF shunts (Kojima *et al.*, 2002). The group B streptococcus (*Streptococcus agalactiae*) may cause meningitis in adults (Domingo *et al.*, 1997; Dunne and Quagliarello, 1993); risk factors include age greater than 60, diabetes mellitus, cardiac disease, collagen vascular disorders, malignancy, alcoholism, hepatic failure, renal failure, and corticosteroid therapy, although no underlying disease was found in 43% of patients in one study (Dunne and Quagliarello, 1993).

Clinical Presentation

The classic symptoms and signs in patients with bacterial meningitis include headache, fever, and meningismus; these are seen in more than 85% of patients (Tunkel and Scheld, 2005; Tunkel, 2001). In a review of community-acquired meningitis in adults (Durand *et al.*, 1993), the classic triad of fever, nuchal rigidity, and change in mental status was found in only two-thirds of patients. Another review found the absence of fever, neck stiffness, and altered mental status effectively eliminated the likelihood of acute meningitis in adults (sensitivity of 99–100% for the presence of one finding in the diagnosis of acute meningitis) (Attia *et al.*, 1999). Other findings include cranial nerve palsies (~10–20%), seizures (~30%), and Kernig's and/or Brudzinski's signs. However, in a recent prospective study that examined the diagnostic accuracy of meningeal signs in adults with suspected meningitis, the sensitivity of Kernig's sign was 5%, Brudzinski's sign, 5%, and nuchal rigidity, 30% (Thomas *et al.*, 2002), indicating that the presence of these signs did not accurately distinguish patients with meningitis from those without meningitis. With disease progression, patients may develop signs of increased intracranial pressure such as hypertension, bradycardia, oculomotor nerve palsy, and coma.

However, elderly patients with bacterial meningitis, especially those with underlying conditions (e.g. diabetes mellitus or cardiopulmonary disease), may present insidiously with lethargy, confusion, anorexia, no fever, and variable signs of meningeal inflammation (Tunkel, 2001). In one review (Gorse *et al.*, 1989), confusion was very common in elderly patients on initial examination and occurred in 92 and 78% of those with pneumococcal and gram-negative bacillary meningitis, respectively. There may be a history of an antecedent or concurrent illness such as sinusitis, otitis media, or pneumonia. In the elderly patient, an altered or changed mental status should not be ascribed to other causes until bacterial meningitis has been excluded by CSF examination.

Clues to the causative agent in a patient with bacterial meningitis include the presence of a petechial or purpuric rash (*N. meningitidis*), rhinorrhea or otorrhea after a basilar skull fracture (*S. pneumoniae*), following neurosurgery or head trauma (staphylococcal spp. or aerobic gram-negative bacilli), or seizures, focal neurological deficits, ataxia, and cranial nerve palsies (*L. monocytogenes*) (Tunkel and Scheld, 2005; Tunkel, 2001).

Diagnosis

The diagnosis of bacterial meningitis rests with CSF examination following lumbar puncture (Tunkel and Scheld, 2005; Tunkel, 2001). CSF characteristics of bacterial meningitis include an elevated opening pressure in virtually all patients; values over 600 mmH_2O suggest the presence of cerebral edema, intracranial suppurative foci, or communicating hydrocephalus. The white blood cell count is elevated in untreated bacterial meningitis (usually 1000–5000 cells mm^{-3}) with a neutrophilic predominance, although lymphocytes may predominate in *L. monocytogenes* meningitis (~30% of cases). A CSF white blood cell count of <20 cells mm^{-3}, along with a high concentration of organisms, is indicative of a poor prognosis. An elevated protein (100–500 mg dl^{-1}) and decreased glucose (<40 mg dl^{-1}) are also typically observed; a CSF: serum glucose of ≤0.4 is found in the majority of patients with acute bacterial meningitis.

The CSF Gram stain provides rapid and accurate identification of the causative organism in 60–90% of patients with bacterial meningitis, with a specificity of almost 100%. Bacteria are observed in 90% of cases of meningitis caused by *S. pneumoniae*, but in only about one-third of patients with *L. monocytogenes* meningitis (Gray and Fedorko, 1992). CSF cultures are positive in 70–85% of patients overall. The probability of identifying the organism in CSF cultures may decrease in patients who have received prior antimicrobial therapy.

Several rapid diagnostic tests are available to aid in the etiologic diagnosis of bacterial meningitis (Tunkel and Scheld, 2005; Tunkel, 2001; Gray and Fedorko, 1992). Initial tests utilized counterimmunoelectrophoresis, although newer tests (staphylococcal coagglutination or latex agglutination) are rapid (≤15 minutes) and more sensitive than counterimmunoelectrophoresis. Current latex agglutination tests detect the antigens of *H. influenzae* type b, *S. pneumoniae, N. meningitidis, E. coli* K1, and *S. agalactiae*. The overall sensitivity ranges from 50 to 100% (somewhat lower for *N. meningitidis* because of the limited immunogenicity of the group B meningococcal polysaccharide), although these tests are highly specific. However, the routine use of latex agglutination for the etiologic diagnosis of bacterial meningitis has recently been questioned, because results do not appear to modify the decision to administer appropriate antimicrobial therapy and false-positive tests have been reported (Tunkel *et al.*, 2004). Therefore, use of CSF latex agglutination is no longer routinely recommended in the determination of the microbial etiology in a patient with bacterial meningitis. Latex agglutination may be most useful for the patient who has been pretreated with antimicrobial therapy and whose CSF Gram stain and cultures are negative, although it must be emphasized that a negative test does not rule out infection by a specific meningeal pathogen.

PCR has also been studied on CSF specimens from patients with meningococcal meningitis, with a sensitivity and specificity of 91% in one study (Ni *et al.*, 1992). In another study, broad-based PCR demonstrated a sensitivity of 100%, a specificity of 98.2%, a positive predictive value of 98.2%, and a negative predictive value of 100% (Saravolatz *et al.*, 2003). Further refinements in PCR may demonstrate its usefulness in the diagnosis of bacterial meningitis in patients who already received antibiotics and when the CSF Gram stain, bacterial antigen tests and cultures are negative.

Antimicrobial Therapy

In patients suspected of having bacterial meningitis, blood cultures should be obtained and a lumbar puncture done

immediately. If purulent meningitis is present, targeted antimicrobial therapy should be initiated on the basis of results of Gram staining (e.g. vancomycin and a third-generation cephalosporin if gram-positive diplococci are seen). However, if no etiologic agent can be identified or if there is a delay in the performance of the lumbar puncture, empiric antimicrobial therapy should be initiated on the basis of the patient's age and the underlying disease status (Tunkel and Scheld, 2005; Tunkel, 2001; Tunkel *et al.*, 2004). In patients who are immunosuppressed and have a history of central nervous system (CNS) disease, focal neurologic deficits, seizures or if papilledema is found on funduscopic examination, computed tomographic (CT) scan is recommended prior to lumbar puncture, with empiric antimicrobial therapy initiated before scanning. Empiric therapy for elderly patients with suspected community-acquired bacterial meningitis should include vancomycin, ampicillin, and a third-generation cephalosporin (see following text for specific recommendations). Once the meningeal pathogen is identified, antimicrobial therapy can be modified for optimal treatment (Table 1); recommended dosages for CNS infections are shown in Table 2.

For treatment of bacterial meningitis in elderly persons, choices of antimicrobial therapy should be based on prevalent trends in antimicrobial susceptibility. For meningitis caused by *S. pneumoniae*, therapy in recent years has been significantly altered by changes in pneumococcal susceptibility patterns (Tunkel and Scheld, 2005; Tunkel, 2001; Tunkel *et al.*, 2004). Numerous reports from around the world have documented strains of pneumococci that are of intermediate susceptibility (minimal inhibitory concentration (MIC) range of 0.1 to 1.0 $\mu g\,ml^{-1}$) and highly (MIC $\geq 2.0\,\mu g\,ml^{-1}$) resistant to penicillin G; susceptible strains have MICs $\leq 0.06\,\mu g\,ml^{-1}$. On the basis of these trends and because achievable CSF concentrations of penicillin are inadequate to treat these resistant isolates, penicillin can never be recommended as empiric therapy for patients with suspected or proven pneumococcal meningitis, pending results of susceptibility testing. As an empiric regimen, we recommend the combination of vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone). If the isolate is susceptible to penicillin, high-dose intravenous penicillin G or ampicillin is adequate. If the isolate is relatively resistant to penicillin, only the third-generation cephalosporin needs to be continued. However, if the pneumococcal isolate is highly resistant to penicillin, the combination of vancomycin and the third-generation cephalosporin should be continued, because vancomycin therapy alone

Table 1 Specific antimicrobial therapy for meningitis

Microorganism	Standard therapy	Alternative therapies
Bacteria		
Streptococcus pneumoniae		
Penicillin MIC $<0.1\,\mu g\,ml^{-1}$	Penicillin G or ampicillin	Third-generation cephalosporin[a]; vancomycin
Penicillin MIC $0.1-1.0\,\mu g\,ml^{-1}$	Third-generation cephalosporin[a]	Meropenem; vancomycin
Penicillin MIC $\geq 2.0\,\mu g\,ml^{-1}$	Vancomycin plus a third-generation cephalosporin[a,b]	Third-generation cephalosporin plus a fluoroquinolone[c]
Enterobacteriaceae	Third-generation cephalosporin[a]	Aztreonam; fluoroquinolone; trimethoprim–sulfamethoxazole; meropenem
Pseudomonas aeruginosa	Ceftazidime[d] or cefepime[d]	Aztreonam[d]; fluoroquinolone[d]; meropenem[d]
Listeria monocytogenes	Ampicillin or penicillin G[d]	Trimethoprim–sulfamethoxazole
Hemophilus influenzae		
β-lactamase-negative	Ampicillin	Third-generation cephalosporin[a]; cefepime; chloramphenicol; aztreonam
β-lactamase-positive	Third-generation cephalosporin[a]	Cefepime, chloramphenicol; aztreonam; fluoroquinolone
Neisseria meningitidis	Penicillin G or ampicillin	Third-generation cephalosporin[a]; chloramphenicol; fluoroquinolone
Streptococcus agalactiae	Ampicillin or penicillin G[d]	Third-generation cephalosporin[a]; vancomycin
Staphylococcus aureus		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin
Methicillin-resistant	Vancomycin	
Staphylococcus epidermidis	Vancomycin[b]	
Myobacteria		
Mycobacterium tuberculosis	Isoniazid plus rifampin plus pyrazinamide	Ethambutol[e]; streptomycin[e]; ciprofloxacin[e]
Spirochetes		
Treponema pallidum	Penicillin G	Doxycycline[f]; ceftriaxone[f]
Borrelia burgdorferi	Third-generation cephalosporin[a]	Penicillin; doxycycline
Fungi		
Cryptococcus neoformans	Amphotericin B[g]	Fluconazole
Candida species	Amphotericin B[g]	Fluconazole[f]
Coccidioides immitis	Fluconazole	Amphotericin B[h]

[a]Cefotaxime or ceftriaxone. [b]Addition of rifampin should be considered. [c]Fluoroquinolones with activity against *S. pneumoniae* should be used; see text for details. [d]Addition of an aminoglycoside should be considered. [e]Add to standard therapy in cases of suspected drug resistance; see text for details. [f]Value of these antimicrobial agents has not been established. [g]Addition of 5-flucytosine should be considered. [h]Intravenous and intraventricular administration.

Table 2 Maximal recommended dosages of antimicrobial agents for central nervous system infections in adults with normal renal and hepatic function[a]

Antimicrobial agent	Total daily dose	Dosing interval (hours)
Acyclovir	30 mg kg^{-1}	8
Amikacin[b]	15 mg kg^{-1}	8
Amphotericin B[c]	0.6–1.0 mg kg^{-1}	24
Amphotericin B lipid formulation	5 mg kg^{-1}	24
Ampicillin	12 g	4
Aztreonam	6–8 g	6–8
Cefepime	6 g	8
Cefotaxime	8–12 g	4–6
Ceftazidime	6 g	8
Ceftriaxone	4 g	12–24
Chloramphenicol[d]	4–6 g	6
Ciprofloxacin	800–1200 mg	8–12
Doxycycline	200–400 mg	12
Ethambutol[e,f]	15 mg kg^{-1}	24
Fluconazole	400–800 mg	24
Flucytosine[e,g]	100 mg kg^{-1}	6
Gentamicin[b]	5 mg kg^{-1}	8
Imipenem	2 g	6
Isoniazid[e,h]	300 mg	24
Liposomal amphotericin B (AmBisome)	5 mg kg^{-1}	24
Meropenem	6 g	8
Metronidazole	30 mg kg^{-1}	6
Nafcillin	9–12 g	4
Oxacillin	9–12 g	4
Penicillin G	24 million units	4
Pyrazinamide[e,i]	15–30 mg kg^{-1}	24
Rifampicin (rifampin)[e]	600 mg	24
Streptomycin[j,k]	15 mg kg^{-1}	24
Tobramycin[b]	5 mg kg^{-1}	8
Trimethoprim–sulfamethoxazole[l]	10–20 mg kg^{-1}	6–12
Vancomycin[b,m]	30–45 mg kg^{-1}	8–12
Voriconazole[n]	8 mg kg^{-1}	12

[a]Unless indicated, therapy is administered intravenously. [b]Need to monitor peak and trough serum concentrations. [c]Can increase dosage to 1.5 mg kg^{-1} per day in severely ill patients. [d]Higher dose recommended for pneumococcal meningitis. [e]Oral administration. [f]Maximum daily dosage of 2.5 g. [g]Maintain serum concentrations from 50 to 100 μg ml^{-1}. [h]Initiate therapy at a dosage of 10 mg kg^{-1} per day. [i]Maximum daily dosage of 2 g. [j]Intramuscular administration. [k]Maximal daily dosage of 1 g. [l]Dosage based on trimethoprim component. [m]May need to monitor cerebrospinal fluid concentrations in severely ill patients. [n]Load with 6 mg kg^{-1} IV every 12 hours for two doses.

may not be optimal therapy for patients with pneumococcal meningitis. Any patient who is not improving as expected, or has a pneumococcal isolate for which the cefotaxime/ceftriaxone MIC is $\geq$2.0 μg ml^{-1} should undergo a repeat lumbar puncture to document sterility of CSF after 36–48 hours of therapy (Tunkel *et al.*, 2004); this may be especially important for patients who are also receiving adjunctive dexamethasone therapy (see following text). Some experts have also recommended the addition of rifampin for these highly resistant strains, although there are no clinical data to support this recommendation. In patients not responding, administration of vancomycin by the intraventricular of intrathecal route is a reasonable adjunct. Newer fluoroquinolones (e.g. moxifloxacin, gatifloxacin, gemafloxacin, garenoxacin) that have *in vitro* activity against *S. pneumoniae* may have utility in the treatment of pneumococcal meningitis (Tunkel *et al.*, 2004; Cottagnoud and Tauber, 2003). Trovafloxacin has been compared to ceftriaxone with or without vancomycin in children with bacterial meningitis (Saez-Llorens *et al.*, 2002), and both treatment groups had similar outcomes in terms of CSF sterilization and clinical success. Although trovafloxacin is no longer used because of concerns of liver toxicity, these data suggest the benefit of the newer fluoroquinolones in the treatment of bacterial meningitis. However, further clinical trials are needed before these agents can be recommended.

Adjunctive Therapy

Despite the availability of effective antimicrobial therapy, the mortality and morbidity from bacterial meningitis has not significantly changed over the past 20 years. Studies in experimental animal models of infection have demonstrated that a major factor contributing to increased morbidity and mortality is the generation of a subarachnoid space inflammatory response following antimicrobial-induced bacterial lysis (Tunkel, 2001). Administration of the anti-inflammatory agent dexamethasone was effective in attenuation of this inflammatory response, and led to several clinical trials examining the use of adjunctive dexamethasone in the therapy of bacterial meningitis. Most of these studies were conducted in infants and children with predominantly *H. influenzae* type b meningitis and supported the routine use of adjunctive dexamethasone in this patient population (Tunkel and Scheld, 2005; Tunkel, 2001).

Until recently, the use of adjunctive dexamethasone was not recommended in adults with bacterial meningitis. In a recently published prospective, randomized, double-blind trial in 301 adults with bacterial meningitis, adjunctive dexamethasone was associated with a reduction in the proportion of patients who had unfavorable outcomes and in the proportion of patients who died (de Gans and van de Beek, 2002); the benefits were most striking in the subgroup of patients with pneumococcal meningitis and in those with moderate-to-severe disease as assessed by the admission Glasgow Coma Scale score.

On the basis of these data and the apparent absence of serious adverse outcomes in the patients who received dexamethasone, the routine use of adjunctive dexamethasone (0.15 mg kg^{-1} every 6 hours for 2–4 days, given concomitant with or just prior to the first dose of an antimicrobial agent for maximal attenuation of the subarachnoid space inflammatory response) is warranted in adults with suspected or proven pneumococcal meningitis (Tunkel *et al.*, 2004; Tunkel and Scheld, 2002a). Adjunctive dexamethasone should not be used in patients who have already received antimicrobial therapy; if the meningitis is subsequently found not to be caused by *S. pneumoniae*, dexamethasone should be discontinued. However, the use of adjunctive dexamethasone is of particular concern in patients with pneumococcal meningitis caused by highly penicillin-resistant strains, since a diminished inflammatory response may significantly impair

CSF vancomycin penetration. In an experimental model of *S. pneumoniae* meningitis in rabbits, the concurrent use of dexamethasone with vancomycin decreased the penetration of vancomycin into the CSF and also decreased the rate of bactericidal activity of vancomycin. In patients with pneumococcal meningitis caused by strains that are highly resistant to penicillin or cephalosporins, careful observation and follow-up are critical to determine whether the use of adjunctive dexamethasone is associated with adverse clinical outcome in these patients.

Tuberculous Meningitis

Epidemiology and Etiology

Almost all cases of tuberculous meningitis are caused by *Mycobacterium tuberculosis*. Risk factors for the development of tuberculous meningitis include a history of prior tuberculous disease, advanced age, homelessness, alcoholism, gastrectomy, diabetes mellitus, and immunosuppression (Leonard and Des Prez, 1990). HIV infection has influenced the epidemiology of tuberculosis, in which extrapulmonary disease occurs in more than 70% of patients with AIDS, but in only 24–45% of patients with tuberculosis and less advanced HIV infection (Barnes *et al.*, 1991).

Clinical Presentation

Tuberculous meningitis often has a subacute, indolent presentation with a prodrome characterized by malaise, low-grade fever, headache, and personality changes (Leonard and Des Prez, 1990; Kent *et al.*, 1993); this is followed by a meningitic phase with worsening headache, meningismus, nausea, vomiting, and waxing-and-waning mental status. A history of prior clinical tuberculosis is obtained in fewer than 20% of cases. Up to 30% of patients have focal neurologic signs on presentation, usually consisting of unilateral or, less commonly, bilateral cranial nerve palsies (cranial nerve (CN) VI is the most frequently affected). Hemiparesis may result from ischemic infarction, most commonly in the distribution of the territory of the middle cerebral artery.

Diagnosis

CSF examination in patients with tuberculous meningitis often reveals a lymphocytic pleocytosis (5–500 cells mm^{-3}), although early in the course of disease there may be a mix of both lymphocytes and neutrophils (Leonard and Des Prez, 1990; Ogawa *et al.*, 1987). Following treatment with antituberculous drugs, a so-called "therapeutic paradox" may develop with a change in the white blood cell differential from a lymphocytic to a neutrophilic predominance. There is usually an elevated CSF protein (median of 150–200 mg dl^{-1}) and often a very low glucose (<20 mg dl^{-1}, although the median value is 40 mg dl^{-1}).

Because of the low number of organisms present in the CSF, acid-fast bacilli (AFB) smears are often negative (fewer than 25% of smears are positive). The sensitivity of smears of CSF was improved to 86% in one study by examination of up to four concentrated CSF specimens from repeated lumbar punctures (Kennedy and Fallon, 1979), although these results have not been duplicated.

On the basis of these poor results, several rapid diagnostic tests are under development to aid in the diagnosis of tuberculous meningitis. The most promising appears to be PCR, which can detect *M. tuberculosis* DNA in CSF specimens (Sinner and Tunkel, 2002; Zugar, 2004).

CT and magnetic resonance (MR) scanning may be useful to support the diagnosis of tuberculous meningitis (Leonard and Des Prez, 1990; Zugar, 2004). Hydrocephalus is frequently present at diagnosis or develops during the course of infection. The presence of basal cistern enhancement is also supportive evidence for the diagnosis. MR may be superior to CT in the identification of basilar meningeal inflammation and small tuberculoma formation.

Antimicrobial Therapy

Therapy for tuberculous meningitis is often initiated on the basis of the patient's clinical presentation, as cultures may take weeks to become positive and may remain negative in up to 20% of patients. In areas where drug resistance is not a problem, therapy with isoniazid, rifampin, and pyrazinamide for 2 months, followed by isoniazid and rifampin, should be adequate (Leonard and Des Prez, 1990; Sinner and Tunkel, 2002; Zugar, 2004). However, in areas with >4% isoniazid resistance, ethambutol or streptomycin should be added to the above regimen, and all four drugs continued until susceptibility results are available. Six months of therapy are used in most patients, although some authorities recommend a total treatment duration of 9 months for patients with tuberculous meningitis. In HIV-infected patients, therapy is continued for at least 12 months. For patients with suspected tuberculous meningitis caused by multidrug-resistant strains, at least five drugs should be used pending susceptibility testing. The fluoroquinolones (e.g. ciprofloxacin, ofloxacin) penetrate well into CSF and have good *in vitro* activity against *M. tuberculosis.* Most authorities recommend continuing therapy for a total of 18–24 months in patients with multidrug-resistant tuberculous meningitis.

Adjunctive Therapy

Corticosteroids have been shown to be of value as adjunctive therapy in tuberculous meningitis with resolution of fevers, improved mental status, and most importantly, the ability to treat or avert the development of spinal block (Leonard and Des Prez, 1990; Sinner and Tunkel, 2002; Zugar, 2004). Despite some controversy, most authorities recommend the use of corticosteroids in patients with tuberculous meningitis with extreme neurologic compromise, elevated intracranial pressure, impending herniation, or impending or established spinal block; some authors also recommend their use in patients with CT evidence of either hydrocephalus or basilar

meningitis. Recommended therapy is prednisone $1\,mg\,kg^{-1}$ per day slowly tapered over 1 month, although varying doses of dexamethasone or hydrocortisone have also been used. In a recent randomized, double-blind, placebo-controlled trial in Vietnam in patients with tuberculous meningitis, adjunctive dexamethasone improved survival in patients over 14 years of age (Thwaites *et al.*, 2004), although probably did not prevent severe disability.

Spirochetal Meningitis

Epidemiology and Etiology

Treponema pallidum (the etiologic agent of syphilis) disseminates to the CNS early during infection, with CSF abnormalities detected in 5–9% of patients with seronegative primary syphilis (Hook and Marra, 1992). The overall incidence of neurosyphilis has recently increased in association with HIV infection; in one report (Musher *et al.*, 1990), 44% of all patients with neurosyphilis had AIDS and 1.5% of AIDS patients were found to have neurosyphilis at some point during the course of their illness.

Approximately 10–15% of patients with Lyme disease will develop signs and symptoms of meningitis, usually early in the course of infection (Cadavid, 2004; Steere, 1989). Infection with *Borrelia burgdorferi* should be suspected in a patient with meningitis in association with other symptoms of Lyme disease, such as erythema migrans, malaise, myalgias, and arthralgias. Meningitis usually follows erythema migrans by 2–10 weeks, although only about 40% (range of 10–90%) of cases of Lyme meningitis are preceded by this characteristic rash. Illness occurs from May to November, with a peak incidence during the summer months.

Clinical Presentation

There are four categories of CNS involvement with *T. pallidum* (Hook and Marra, 1992; Marra, 2004). Syphilitic meningitis occurs within the first two years of infection, with symptoms of headache, nausea, vomiting, and less frequently fevers, meningismus, and mental status changes. Meningovascular syphilis (found in 10–12% of individuals with CNS involvement), occurring months to years after infection, results in focal neurologic findings as a result of focal syphilitic arteritis, which almost always occurs in association with meningeal inflammation; focal deficits may progress to a stroke syndrome with attendant irreversible neurologic deficits. Parenchymatous neurosyphilis (10–20 years after infection) manifests as general paresis and tabes dorsalis. Gummatous disease is very rare, and generally occurs more than 30 years following initial infection. Coinfection with HIV may alter the clinical course of syphilis, in which patients may be more likely to progress to neurosyphilis and show accelerated disease courses.

Symptoms of CNS infection with *B. burgdorferi* include headache, fever, meningismus, nausea, and vomiting (Cadavid, 2004; Steere, 1989). Up to 50% of patients will develop cranial nerve palsies, most commonly involving CN VII; facial nerve palsy is bilateral in 30–70% of patients, although the two sides are affected asynchronously in most cases. In untreated patients the duration of symptoms is 1–9 months and patients typically experience recurrent attacks of meningeal symptoms lasting several weeks, alternating with similar periods of milder symptoms. About half of the patients with Lyme meningitis have mild cerebral symptoms, consisting of somnolence, emotional lability, depression, impaired memory and concentration, and behavioral symptoms.

Diagnosis

CSF findings in patients with CNS syphilis are nonspecific, revealing a mononuclear pleocytosis ($>10\,cells\,mm^{-3}$ in most patients), elevated protein, and a normal or slightly decreased glucose (Hook and Marra, 1992; Marra, 2004). A reactive VDRL (venereal disease research laboratory) slide test in the CSF has a sensitivity of only 30–70% for the diagnosis of neurosyphilis (although the specificity is high), so treatment for neurosyphilis is indicated in the presence of any of the above abnormalities in association with the appropriate clinical setting. The fluorescent treponemal antibody absorption test (FTA-ABS), in the CSF has been examined as a possible diagnostic test for neurosyphilis; a nonreactive test effectively rules out the likelihood of neurosyphilis, although a positive test may result from the leakage of small amounts of antibody absorption from the serum into CSF, making it less specific than the CSF VDRL.

The best currently available laboratory test for the diagnosis of Lyme disease is the demonstration of specific serum antibody to *B. burgdorferi*, in which a positive test in a patient with a compatible neurologic abnormality is strong evidence for the diagnosis (Cadavid, 2004; Steere, 1989). It is currently recommended that when the pretest probability of Lyme disease is 0.20–0.80, sequential testing with enzyme-linked immunosorbent assay (ELISA) and Western blot is the most accurate method for ruling in or out the possibility of Lyme disease (American College of Physicians, 1997). A lymphocytic pleocytosis (usually $<500\,cells\,mm^{-3}$) is observed in the CSF, along with an elevated protein and normal glucose in patients with Lyme meningitis. Antibodies and antigens to *B. burgdorferi* may be detected in the CSF by ELISA or Western blot, respectively, although antibody tests are not standardized with marked variability between laboratories. PCR may be a useful tool for the detection of *B. burgdorferi* DNA in CSF (Keller *et al.*, 1992), although PCR must still be considered experimental in the diagnosis of CNS Lyme disease (Connolly and Hammer, 1990).

Antimicrobial Therapy

Treatment for neurosyphilis is intravenous penicillin G 18–24 million units day in divided doses every 4 hours for 10–14 days (Marra, 2004). No large studies have been performed to evaluate alternative antimicrobial agents for the

therapy of neurosyphilis; the tetracyclines, chloramphenicol, and ceftriaxone may have potential clinical utility based on case reports, clinical experience, and extrapolations from experimental animal studies.

Treatment of Lyme meningitis is intravenous ceftriaxone 2 g day for 2–4 weeks; the literature contains no agreement on the duration of therapy or on the minimal adequate dose of the antimicrobial (Cadavid, 2004; Steere, 1989). At present, there is no evidence to support treatment durations of longer than 4 weeks.

Fungal Meningitis

Epidemiology and Etiology

Cryptococcus neoformans is the most common fungal cause of clinically recognized meningitis with most cases seen in immunocompromised patients, including those with AIDS, transplant recipients, and in those receiving chronic corticosteroids (Tunkel and Scheld, 2002b). Other underlying conditions with an increased risk for cryptococcal disease include sarcoidosis, collagen vascular disorders (e.g. systemic lupus erythematosus), chronic renal and hepatic failure, and diabetes mellitus; *C. neoformans* meningitis has also been documented in apparently healthy individuals.

Meningitis due to *Candida* species is relatively rare and is often associated with disseminated disease. Risk factors include malignancy, neutropenia, chronic granulomatous disease, the presence of central venous catheters, diabetes mellitus, hyperalimentation, and corticosteroid therapy (Tunkel and Scheld, 2002b).

Coccidioides immitis is a fungus endemic to the semiarid regions and the desert areas of southwestern US. Lesser than 1% of infected patients develop disseminated disease, although, of those, one-third to one-half has meningeal involvement. Dissemination is associated with extremes of age, male gender, nonwhite race, and immunosuppression (e.g. corticosteroid therapy, organ transplantation, and HIV infection) (Tunkel and Scheld, 2002b; Ampel *et al.*, 1989).

Clinical Presentation

Clinical presentation of cryptococcal meningitis is different in non-AIDS and AIDS patients (Tunkel and Scheld, 2002b). In non-AIDS patients the presentation is typically subacute after days to weeks of infection with symptoms of headache and mental status changes, with or without fevers and meningismus. Ocular abnormalities (e.g. cranial nerve palsies and papilledema) occur in about 40% of patients. In contrast, AIDS patients may present with very minimal symptoms; the only clinical findings may be fever, headache and lethargy, and cranial nerve palsies are often absent.

Patients with *Candida* meningitis may present either abruptly or insidiously (Tunkel and Scheld, 2002b). Symptoms include fever, headache, and meningismus; patients may also have depressed mental status, confusion, cranial nerve palsies, and focal neurologic signs. The presentation is often similar to that observed with bacterial meningitis.

Meningeal infection with *C. immitis* most often follows a subacute or chronic course (Tunkel and Scheld, 2002b; Ampel *et al.*, 1989). Clinical findings include headache, low-grade fever, weight loss and mental status changes; disorientation, lethargy, confusion, or memory loss are seen in about 50% of patients. Signs of meningeal irritation have been reported in as many as one-third of patients.

Diagnosis

In most non-AIDS patients with cryptococcal meningitis, examination of the CSF reveals an elevated opening pressure, lymphocytic pleocytosis (range of 20–500 cells mm^{-3}), elevated protein, and normal or decreased glucose (Tunkel and Scheld, 2002b). AIDS patients with cryptococcal meningitis may have very low or even normal CSF white blood cell counts; 65% of patients have fewer than 5 cells mm^{-3} in CSF. India ink examination is positive in up to 50–75% of patients with cryptococcal meningitis, and the rate of positivity is even higher (~88%) in AIDS patients. As the India ink examination is difficult to perform and rates of positivity are dependent upon the experience of the laboratory, the latex agglutination test for cryptococcal polysaccharide antigen in the CSF should be performed and is both sensitive and specific for the diagnosis of cryptococcal meningitis, as long as samples are heated to eliminate rheumatoid factor. A presumptive diagnosis is indicated by a titer of $\geq 1:8$. The presence of cryptococcal antigen in the serum is also supportive evidence for the diagnosis, and may be detected in severely immunocompromised patients (i.e. those with AIDS); however, the value of the serum cryptococcal polysaccharide antigen for screening patients suspected of having meningeal disease has not been established. Routine and fungal cultures of the CSF are often positive.

Examination of the CSF in patients with *Candida* meningitis typically shows a mixture of neutrophils and lymphocytes, elevated protein, and decreased glucose. Yeast cells are seen on smear in approximately 50% of patients, with fungal cultures positive in most cases.

CSF examination in coccidioidal meningitis reveals a pleocytosis, occasionally showing a prominent eosinophilia (Tunkel and Scheld, 2002b; Ampel *et al.*, 1989). Unfortunately, only about 25–50% of patients have positive CSF cultures. Elevated serum concentrations of complement-fixing antibodies (titers in excess of 1:32–1:64) suggest dissemination. CSF complement-fixing antibodies are present in at least 70% of patients with early meningitis and from virtually all patients as disease progresses, although antibodies may fail to develop in the serum or CSF of patients with immunodeficiencies. When present, the antibody titers appear to parallel the course of meningeal disease.

Antimicrobial Therapy

The treatment of cryptococcal meningitis in non-AIDS patients is amphotericin B with 5-flucytosine for 4–6 weeks (Tunkel and Scheld, 2002b). The 4-week combination regimen can be used in the subset of patients who, at presentation, have no neurologic compromise, no underlying diseases, no immunosuppressive therapy, a pretreatment CSF white cell count $>20\,mm^{-3}$, and a serum cryptococcal antigen titer of $<1:32$; and who, at 4 weeks, have a negative CSF India ink and CSF cryptococcal antigen titer $<1:8$. The optimal use of fluconazole in non-AIDS patients with cryptococcal meningitis is unclear. In a recently published report of 157 non-HIV infected with CNS cryptococcosis (Pappas *et al.*, 2001), patients were more likely to receive an induction regimen with amphotericin B and subsequent fluconazole, suggesting a role for fluconazole for consolidation therapy in this patient population. However, pending further data, non-AIDS patients should receive 4–6 weeks of amphotericin B plus 5-flucytosine.

Although the optimal therapeutic regimen for treating cryptococcal meningitis in AIDS patients has not been determined, the consensus is to use amphotericin B with or without 5-flucytosine for the initial 2 weeks of therapy or until a clinical response is obtained, followed by fluconazole at 400 mg day to complete a 10-week course. Doses of fluconazole up to 800 mg day have benefited some AIDS patients with cryptococcal meningitis who failed primary therapy or who relapsed (Berry *et al.*, 1992). Liposomal formulations of amphotericin B have also shown efficacy in AIDS patients with cryptococcal meningitis (Sharkey *et al.*, 1996; Leendera *et al.*, 1997). Chronic suppressive therapy with fluconazole (200 mg daily) is then continued indefinitely in patients with AIDS to prevent relapse.

Treatment of meningitis caused by *Candida* species is amphotericin B, with or without 5-flucytosine (Slavoski and Tunkel, 1995). Although there are no studies comparing the efficacy of single versus combination therapy, some investigators recommend combination therapy based on more rapid CSF sterilization and possible reduction of long-term neurologic sequelae in newborns. The efficacy of fluconazole in *Candida* meningitis has yet to be proven, but may be an acceptable alternative.

The previously recommended therapeutic regimen for coccidioidal meningitis was amphotericin B, administered both intravenously and intrathecally (Slavoski and Tunkel, 1995). Intrathecal administration may be via the lumbar, cisternal or ventricular route (i.e. through an Ommaya reservoir). The usual dosage is 0.5 mg 3 times weekly for 3 months, although 1.0–1.5 mg combined with hydrocortisone can be used. Antifungal therapy is discontinued once the CSF has been normal for at least 1 year on an intrathecal regimen of once every 6 weeks. Fluconazole has been examined in the therapy of coccidioidal meningitis, with one study revealing a response rate of 79%, although 24% of patients exhibited a persistent CSF pleocytosis despite the relative absence of symptoms (Galgiani *et al.*, 1993). On the basis of these results, fluconazole is recommended as first-line therapy for coccidioidal meningitis; therapy may need to be continued indefinitely.

Adjunctive Therapy

Increased intracranial pressure and hydrocephalus have been noted in AIDS patients with cryptococcal meningitis. Ventriculoperitoneal shunting, frequent high-volume lumbar punctures, acetazolamide, and corticosteroids have been used for these complications (Fessler *et al.*, 1998; Park *et al.*, 1999), although the precise roles of these measures remain to be established. Removal of CSF should be performed in patients with persistent elevated opening pressures after lumbar puncture; shunting procedures can ameliorate the sequelae of elevated intracranial pressure in AIDS patients with cryptococcal meningitis.

FOCAL CENTRAL NERVOUS SYSTEM INFECTIONS

Brain Abscess

Epidemiology and Etiology

Bacterial brain abscesses may be due to a single organism or may be polymicrobial in origin (Tunkel, 2005a; Mathisen and Johnson, 1997; Heilpern and Lorber, 1996). Clues to the likely etiologic agents may be found in the patient's history. Streptococci (aerobic, anaerobic, and microaerophilic) are identified in up to 70% of patients. They are normal inhabitants of the oral cavity, gastrointestinal tract, and female genital tract. Although streptococcal brain abscesses are seen most often in patients with otopharyngeal infections or infective endocarditis, they are isolated after neurosurgical or other medical procedures. Staphylococci are found in 10–15% of patients, usually those with a history of trauma or injection drug use. *Bacteroides fragilis* is identified in 20–40% of patients, often in mixed cultures. Enteric gram-negative bacilli are isolated in 23–33% of patients with brain abscess, often in patients with otitic foci of infection, septicemia, following neurosurgical procedures, or in those who are immunocompromised. Other bacteria (*S. pneumoniae, H. influenzae,* and *L. monocytogenes*) are seen much less frequently (<1% of cases). Patients with defects in cell-mediated immunity (e.g. patients with AIDS, transplant recipients and those receiving corticosteroids) have an increased incidence of brain abscess caused by *Nocardia* species.

Brain abscesses caused by *Aspergillus* species are seen in patients with hematologic malignancies and those with prolonged neutropenia; other risk groups include patients with Cushing's syndrome, diabetes mellitus, and hepatic disease (Tunkel, 2005a; Cortez and Walsh, 2004). Risk factors for development of cerebral mucormycosis include patients with diabetes mellitus (especially in association with

diabetic ketoacidosis), hematologic malignancies, transplant recipients, and corticosteroid or deferoxamine use. Infection caused by either agent may result from direct extension of rhinocerebral disease or from hematogenous spread from a distant focus of infection.

Clinical Presentation

Symptoms in patients with bacterial brain abscess result from the presence of a space-occupying lesion, and include headache (~70% of cases), nausea, vomiting, and seizures (Tunkel, 2005a; Mathisen and Johnson, 1997; Heilpern and Lorber, 1996). Many patients also experience a change in mental status, ranging from lethargy to coma. Fever is found in only 45–50% of patients. The clinical presentation also depends upon the location of the abscess. Frontal lobe involvement may result in headache, drowsiness, inattention, hemiparesis, and/or motor disorders. Ataxia, nystagmus, and vomiting indicate a cerebellar lesion, while an abscess of the temporal lobe produces headache, aphasia, and visual field defects. Involvement of the brainstem may result in cranial nerve palsies, headache, fever, and vomiting.

Fungal brain abscesses often present with symptoms similar to those of bacterial brain abscess (see preceding text) (Tunkel, 2005a; Cortez and Walsh, 2004). However, some differences do exist. *Aspergillus* species have a tendency to invade blood vessels, and patients may present with signs and symptoms of cerebral infarction. In patients with rhinocerebral mucormycosis, symptoms may be referable to the eyes and sinuses in which patients present with headache, diplopia, and nasal discharge. Physical examination may show nasal ulcers or discharge, proptosis, and/or external ophthalmoplegia. Approximately 60% of patients will have orbital involvement, and there is an increased incidence of development of cavernous sinus thrombosis.

Diagnosis

Radiologic techniques, such as CT and MR, have revolutionized the diagnosis of brain abscess (Tunkel, 2005a; Mathisen and Johnson, 1997; Heilpern and Lorber, 1996). CT characteristically reveals a hypodense lesion with peripheral ring enhancement; there may also be a surrounding area of decreased attenuation due to cerebral edema. MR offers significant advantages over CT in the diagnosis of brain abscess, including early detection of cerebritis, detection of cerebral edema with greater contrast between edema and the brain, more conspicuous spread of inflammation into the ventricles and subarachnoid space, and the earlier detection of satellite lesions. Contrast enhancement with the paramagnetic agent gadolinium diethylenetriaminepentaacetic acid provides the added advantage of clearly differentiating the central abscess, surrounding enhancing rim, and cerebral edema surrounding the abscess.

In abscesses caused by *Aspergillus* species, radiographic studies (CT or MR) may show evidence of infarction with surrounding abscess formation. In mucormycosis, there may be bony erosion, sinus opacification, and evidence of cavernous sinus thrombosis.

CT has also been useful to permit stereotactic guided aspiration of brain abscesses to obtain tissue for microbiologic diagnosis (Tunkel, 2005a). Samples should be sent for Gram stain, aerobic and anaerobic culture, and smears and cultures for AFB and fungi. If there is a clinical suspicion of *Nocardia* infection, a modified AFB stain should also be done. Tissue should also be sent for histopathologic examination. Definitive diagnosis in fungal brain abscess is based on biopsy or resection of the lesion, with a characteristic appearance of the causative organism in microbiologic and histopathologic specimens.

Therapy

Empiric antimicrobial therapy for bacterial brain abscess should include agents active against streptococci, anaerobes, the Enterobacteriaceae, and staphylococci, although therapy can usually be chosen on the basis of the likely pathogenic mechanism of brain abscess formation (Table 3) (Tunkel, 2005a; Mathisen and Johnson, 1997; Heilpern and Lorber, 1996). Optimal therapy of brain abscesses includes surgical intervention with either stereotactic CT-guided aspiration, or craniotomy with resection or debridement; all lesions greater

Table 3 Empiric antimicrobial therapy of bacterial brain abscess

Predisposing condition	Usual bacterial isolates	Antimicrobial regimen
Otitis media or mastoiditis	Streptococci (anaerobic or aerobic), *Bacteroides* species, Enterobacteriaceae	Metronidazole + a third-generation cephalosporin[a]
Sinusitis (frontoethmoidal or sphenoidal)	Streptococci, *Bacteroides* species, Enterobacteriaceae, *Staphylococcus aureus, Hemophilus* species	Vancomycin + metronidazole + a third-generation cephalosporin[a]
Dental sepsis	Mixed *Fusobacterium* and *Bacteroides* species, streptococci	Penicillin + metronidazole
Penetrating trauma or postneurosurgical	*Staphylococcus aureus*, streptococci, Enterobacteriaceae, *Clostridium*	Vancomycin + a third-generation cephalosporin[a]
Lung abscess, empyema, bronchiectasis	*Fusobacterium, Actinomyces, Bacteroides* species, streptococci, *Nocardia asteroides*	Penicillin + metronidazole + a sulfonamide[b]
Bacterial endocarditis	*Staphylococcus aureus*, streptococci	Vancomycin + gentamicin

[a]Cefotaxime or ceftriaxone; ceftazidime or cefepime is used if *Pseudomonas aeruginosa* is suspected. [b]Sulfadiazine or trimethoprim–sulfamethoxazole; include if *Nocardia asteroides* is suspected.

Table 4 Antimicrobial therapy of brain abscess

Organism	Standard therapy	Alternative therapies
Actinomyces species	Penicillin G	Clindamycin
Aspergillus species	Voriconazole	Amphotericin B lipid complex, liposomal amphotericin B
Bacteroides fragilis	Metronidazole	Chloramphenicol, clindamycin
Candida species	Amphotericin B[a]	Fluconazole
Cryptococcus neoformans	Amphotericin B[a]	Fluconazole
Enterobacteriaceae	Third-generation cephalosporin[b]	Aztreonam, trimethoprim–sulfamethoxazole, fluoroquinolone, meropenem
Fusobacterium species	Penicillin G	Metronidazole
Mucormycosis	Amphotericin B	
Liposomal amphotericin B		
Amphotericin B lipid complex		
Nocardia asteroides	Trimethoprim–sulfamethoxazole or sulfadiazine	Minocycline, imipenem, meropenem, third-generation cephalosporin[b], amikacin
Pseudomonas aeruginosa	Ceftazidime[c] or cefepime[c]	Aztreonam[c], fluoroquinolone[c], meropenem[c]
Staphylococcus aureus		
Methicillin-sensitive	Nafcillin or oxacillin	Vancomycin
Methicillin-resistant	Vancomycin	
Streptococcus milleri, other streptococci	Penicillin G	Third-generation cephalosporin[b], vancomycin

[a]Addition of flucytosine should be considered. [b]Cefotaxime or ceftriaxone. [c]Addition of an aminoglycoside should be considered.

than 2.5 cm in diameter should be excised or stereotactically aspirated. Certain patients may be treated with medical therapy alone (Tunkel, 2005a; Carpenter, 1994), and these criteria include the presence of multiple abscesses, location in a surgically inaccessible area, clinical improvement with medical therapy alone, and abscess size $\leq$2.5 cm. Once culture results are available, antimicrobial therapy may be adjusted for optimal therapy (Table 4). Six to 8 weeks of intravenous therapy is recommended for treatment of bacterial brain abscess, often followed by several months of oral therapy (although the efficacy and necessity of this approach has not been established). Brain abscess caused by *Nocardia* species should be treated for up to 12 months, in conjunction with surgical resection.

The optimal therapy of fungal brain abscess requires a combined medical and surgical approach (Tunkel, 2005a; Cortez and Walsh, 2004). High-dose amphotericin B ($0.8-1.25\,mg\,kg^{-1}$ per day, with doses up to $1.5\,mg\,kg^{-1}$ per day depending on the clinical response) with surgical resection or debridement is recommended for treatment of fungal brain abscess. The use of triazoles (fluconazole or itraconazole) is not recommended in fungal brain abscess based on the lack of clinical data on their efficacy. Voriconazole has recently been shown to be a useful agent in patients with *Aspergillus* brain abscess, and many authorities now consider this the agent of choice in patients with this infection.

Subdural Empyema

Epidemiology and Etiology

The most common predisposing conditions to cranial subdural empyema are otorhinologic infections; 50–80% of cases begin in the paranasal sinuses (Tunkel, 2005b; Silverberg and DiNubile, 1985). Other predisposing conditions include skull trauma, neurosurgical procedures, and infection of a preexisting subdural empyema; hematogenous dissemination occurs in only about 5% of cases. The bacterial species isolated from cranial subdural empyema include streptococci (~25–45%), staphylococci (~10–15%), and aerobic gram-negative bacilli (~3–10%); anaerobes (e.g. anaerobic and microaerophilic streptococci *Bacteroides fragilis*) have been recovered in up to 100% of cases; polymicrobial infections are common.

Clinical Presentation

Subdural empyema can present as a rapidly progressive, life-threatening infection with symptoms and signs related to the presence of increased intracranial pressure, meningeal irritation, and/or focal cortical inflammation (Tunkel, 2005b; Silverberg and DiNubile, 1985). A prominent complaint is headache, which is initially localized to the infected sinus or ear but becomes generalized as the infection progresses. Other clinical findings include vomiting, altered mental status (with progression to obtundation if treatment is not initiated), fever, and focal neurologic signs (usually within 24–48 hours with rapid progression). About 80% of patients have meningeal irritation, and seizures occur in more than half of cases. Without treatment, there is a rapid neurologic deterioration with signs of increased intracranial pressure and cerebral herniation. However, this fulminant presentation may not be seen in patients with cranial subdural empyema following cranial surgery or trauma, in patients who have received prior antimicrobial therapy, in patients with infected subdural hematomas, or in patients with infections metastatic to the subdural space.

Diagnosis

The diagnostic procedure of choice for cranial subdural empyema is either CT with contrast enhancement or MR

imaging (Tunkel, 2005b). CT typically reveals a crescentic or elliptically shaped area of hypodensity below the cranial vault or adjacent to the falx cerebri; with extensive disease, there is often associated mass effect. Following the administration of contrast material, there is a fine, intense line of enhancement that can be seen between the subdural collection and cerebral cortex. Extensive mass effect, manifested as ventricular compression, sulcal effacement, and midline shift is invariably present. MR provides greater clarity of morphologic detail than CT and is particularly valuable in detecting subdural empyemas located as the base of the brain, along the falx cerebri, or in the posterior fossa. MR can also differentiate empyema from most sterile effusions and chronic hematomas, making it the diagnostic modality of choice for subdural empyema.

Therapy

The therapy of subdural empyema requires a combined medical and surgical approach because antimicrobial agents alone do not reliably sterilize these lesions and surgical decompression is needed to control increased intracranial pressure (Tunkel, 2005b; Silverberg and DiNubile, 1985). Drainage via burr hole placement is usually used in the early stages of subdural empyema when the pus is liquid, although it may not be adequate in 10–20% of patients. For patients requiring craniotomy, a wide exposure should be afforded to allow adequate exploration of all areas of suspected infection. In a recent report (Nathoo *et al.*, 2001), craniotomy appeared to be superior to burr hole and craniectomy drainage, as patients undergoing burr holes or craniectomy drainage not only required more frequent operations to drain recurrent or remaining pus, but also exhibited higher mortality rates and poorer outcomes.

Following the aspiration of purulent material, antimicrobial therapy is based on the results of Gram stain and predisposing condition. If the primary infection is paranasal sinusitis, otitis media or mastoiditis, therapy with vancomycin, metronidazole, and a third-generation cephalosporin (cefotaxime or ceftriaxone; or ceftazidime or cefepime if *P. aeruginosa* is suspected) is recommended pending organism identification. Parenteral therapy should be continued for 3–4 weeks and perhaps longer if an associated osteomyelitis is present (Tunkel, 2005b), although there are no firm data to support a specific duration of antimicrobial therapy in patients with subdural empyema.

Epidural Abscess

Epidemiology and Etiology

Epidural abscess refers to a collection between the dura mater and the overlying skull or vertebral column (Tunkel, 2005b). The etiologies of cranial subdural abscess are usually the same as for subdural empyema (see preceding text), whereas spinal epidural abscess usually follows hematogenous dissemination from foci elsewhere to the epidural space (25–50% of cases) or by extension from a vertebral osteomyelitis, local trauma, or infection (e.g. from penetrating trauma, decubitus ulcers, paraspinal abscess, back surgery, lumbar puncture, or epidural anesthesia). The likely infecting organisms in spinal epidural abscess are staphylococci (50–90%), streptococci (8–17%), and aerobic gram-negative bacilli (12–17%).

Clinical Presentation

Symptoms in patients with cranial epidural abscess are usually insidious with the presentation overshadowed by the primary focus of infection (e.g. sinusitis or otitis media) (Tunkel, 2005b; Danner and Hartman, 1987). Cranial epidural abscesses usually enlarge too slowly to produce sudden major neurologic deficits unless there is deeper intracranial extension. The typical complaint is headache; eventually focal neurologic signs, seizures, papilledema, and other signs of increased intracranial pressure may develop without appropriate therapy.

In contrast, spinal epidural abscess may develop rapidly within hours (following hematogenous dissemination) or pursue a chronic course over months (associated with vertebral osteomyelitis) (Connolly and Hammer, 1990). Initially, patients complain of focal vertebral pain (the most consistent symptom seen in 70–90% of patients), followed by root pain, defects of motor, sensory, or sphincter function, and finally paralysis. These symptoms and signs indicate the need for emergent evaluation, diagnosis, and treatment.

Diagnosis

MR imaging is the diagnostic procedure of choice for both cranial and spinal epidural abscess (Tunkel, 2005b). In cases of spinal epidural abscess, MR is recommended because it can visualize the spinal cord and epidural space in both the sagittal and transverse sections and can also identify accompanying osteomyelitis, intramedullary spinal cord lesions, and joint space infection (Hook and Marra, 1992).

Therapy

Recommendations for antimicrobial therapy for cranial epidural abscess are the same as for subdural empyema (see preceding text). Presumptive therapy for spinal epidural abscess must include an antistaphylococcal agent (i.e. vancomycin); coverage for gram-negative bacilli (e.g. ceftazidime or cefepime) must be included for patients with a history of a spinal procedure or injection drug use (Tunkel, 2005b). Antimicrobial therapy for an uncomplicated spinal epidural abscess should be continued for 3–4 weeks and for 6–8 weeks if osteomyelitis is present.

Surgical therapy for epidural abscess is aimed at drainage of the collection and for patients with neurologic changes to minimize the likelihood of permanent neurologic sequelae. Some patients with spinal epidural abscess have been treated

with antimicrobial therapy alone (i.e. those with an unacceptably high surgical risk or those without neurologic deficits), although these patients must be carefully followed for clinical deterioration and for progression by radiologic studies (Tunkel, 2005b; Wheeler *et al.*, 1992; Baker *et al.*, 1992). Surgical decompression should be performed in patients with increasing neurologic deficit, persistent severe pain, increasing temperature, or peripheral white blood cell count. Surgery is not likely to be a viable therapeutic option in patients who have experienced complete paralysis for more than 24 hours, although some would perform surgical therapy in patients with duration of complete paralysis of less than 72 hours.

ENCEPHALITIS

Encephalitis is characterized by symptoms similar to those seen with acute meningitis, but patients with encephalitis are more likely to experience mental status changes and seizures. Numerous infectious and noninfectious etiologies may produce encephalitis. Most common are the herpesviruses that are also the most treatable. More recently, West Nile encephalitis has been reported in endemic areas and is discussed in the following section.

Herpes Simplex Virus

Epidemiology and Etiology

Herpes simplex virus accounts for approximately 10–20% of viral encephalitides, and occurs sporadically throughout the year, affecting all age-groups (Whitley, 2004); most cases are caused by HSV type 1. The disease is associated with significant morbidity and mortality (as high as 70% if untreated).

Clinical Presentation

Patients with HSV encephalitis often present with diminished levels of consciousness and focal neurologic signs, such as dysphasia, weakness, and paresthesias (Whitley, 2004; Whitley, 1990). Personality changes and fever are uniformly present, and approximately two-thirds of patients develop seizures, often involving the temporal lobes. The clinical course may be slow or progress with alarming rapidity, with progressive loss of consciousness leading to coma.

Diagnosis

CSF examination in HSV encephalitis reveals a lymphocytic pleocytosis in 97% of cases with biopsy-proven disease and an elevated protein (Whitley, 2004; Whitley, 1990). The presence of CSF red blood cells suggests the diagnosis but is not always present. About 5–10% of patients have normal CSF findings on initial evaluation. CSF viral cultures are positive in only ~4% of cases, making a definitive diagnosis difficult without performance of a brain biopsy. However, detection of HSV DNA in the CSF using PCR is both sensitive and specific, and is now the optimal method for the diagnosis of HSV encephalitis (Rowley *et al.*, 1990; Lakeman and Whitley, 1995).

Several noninvasive tests may also support the diagnosis of HSV encephalitis (Whitley, 2004; Cepelowicz and Tunkel, 2003). The electroencephalogram (EEG) may show a characteristic spike-and-slow wave activity with periodic lateralizing epileptiform discharges over the temporal and frontotemporal regions. CT with contrast administration may reveal a hypodense area with mass effect localized to the temporal lobes. MR is more sensitive than CT and is considered by many experts to be the most important and specific imaging technique. With the availability of these diagnostic modalities, brain biopsy is seldom indicated.

Antimicrobial Therapy

On the basis of its ease of administration and good safety profile, treatment with intravenous acyclovir 30 mg kg per day (in patients with normal renal function) in three divided doses for 14–21 days is recommended for patients with suspected HSV encephalitis (Whitley, 2004; Cepelowicz and Tunkel, 2003).

Varicella Zoster Virus

Epidemiology and Etiology

Herpes zoster is a consequence of reactivation of latent VZV, and a direct correlation exists between cutaneous dissemination and visceral involvement (including meningoencephalitis) (Tunkel and Scheld, 2002b; Cepelowicz and Tunkel, 2003). CNS complications associated with recurrent zoster infection result in significantly higher morbidity and mortality than primary varicella infection. This may be due to the advanced age and underlying illnesses of most patients with herpes zoster.

Clinical Presentation

Symptoms associated with CNS infection with VZV include headache, fever, vomiting, seizures, altered sensorium, and focal neurologic deficits (Tunkel and Scheld, 2002b; Cepelowicz and Tunkel, 2003). Encephalitis is the most common abnormality associated with herpes zoster, seen most commonly in patients of advanced age, following immunosuppression, and in those with disseminated cutaneous zoster. Some patients with ophthalmic zoster present with the distinctive CNS process of contralateral hemiplegia that usually occurs several weeks or more after zoster ophthalmicus; this

finding is seen in up to one-third of CNS abnormalities in herpes zoster.

Diagnosis

CSF analysis in patients with herpes zoster encephalitis shows a lymphocytic pleocytosis and elevated protein, although these findings may be seen in up to 40% of zoster patients without CNS involvement (Tunkel and Scheld, 2002b; Cepelowicz and Tunkel, 2003). Viral cultures are rarely helpful diagnostically. In patients with zoster ophthalmicus with contralateral hemiplegia, a unilateral arteritis or thrombosis of involved vessels may be seen on cerebral angiography, and cerebral infarction may be seen on CT.

Antimicrobial Therapy

Although no clinical trials have established the efficacy of antiviral therapy in herpes zoster encephalitis, we believe intravenous acyclovir should be used in this setting.

West Nile Virus

Epidemiology and Etiology

West Nile encephalitis is an infection of the brain caused by West Nile virus (WNV), a flavivirus that is commonly found in Africa, West Asia, and the Middle East. The virus first appeared in the United States in 1999 with an outbreak of meningoencephalitis reported in New York City (Nash *et al.*, 2001). Mosquitos are the primary vectors of WNV, and anyone bitten by an infected mosquito can get the disease. It has been estimated that the risk to a person of getting infected with WNV from the bite of an *infected* mosquito is about 1% (Peterson and Marfin, 2002). Transmission can also occur via transplanted organs and infected blood products (Centers for Disease Control and Prevention, 2002). Most human infections with WNV are asymptomatic, but, in recent outbreaks, 1 in 5 infected persons developed West Nile fever and 1 in 150 developed CNS disease (Mostashari *et al.*, 2001); the elderly are much more likely to develop serious diseases. While the risk of infection with WNV may be small, the disease can be quite serious. Of those patients who develop symptoms serious enough to require hospitalization, 3–15% of cases are fatal.

Clinical Presentation

Patients with WNV encephalitis present with fever, headache, mental status changes, nausea, and vomiting (Campbell *et al.*, 2002; Marfin and Gubler, 2001). Severe generalized muscle weakness was a common feature in cases during the New York City outbreak, as well as in other outbreaks in the United States. Seizures are uncommon. Depressed deep tendon reflexes, diffuse muscle weakness, flaccid paralysis, and respiratory failure may also occur. The disease progresses to coma in about 15% of patients.

Diagnosis

CSF examination in patients with WNV encephalitis typically reveals a moderate lymphocytic pleocytosis (although no cells or neutrophils may be seen), elevated protein, and normal glucose. Testing for patients with encephalitis, meningitis, or other serious CNS infections can be obtained through local or state health departments. Public health laboratories usually perform an IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA). Using this assay, virus-specific IgM can be detected in nearly all CSF and serum specimens received from WNV-infected patients at the time of their clinical presentation (Mostashari *et al.*, 2001). However, the serum IgM antibody may persist for more than a year and physicians must determine whether the detection of antibody is the result of a WNV infection in the previous year and unrelated to the current clinical presentation. The IgM in the CSF is specific for CNS infection, with almost all patients having detectable antibody by the first week of admission.

Treatment

There is no specific treatment for West Nile encephalitis (Peterson and Marfin, 2002; Campbell *et al.*, 2002). In more severe cases, intensive supportive therapy is indicated, often involving hospitalization, intravenous fluids, airway management, respiratory support, prevention of secondary infections (e.g. pneumonia, urinary tract infection), and good nursing care. Ribavirin in high doses and interferon α-2b were found to have some activity against WNV *in vitro*, but no controlled studies have been completed on the use of these agents for therapy of West Nile encephalitis. A multicenter controlled trial of intravenous immunoglobulin in the treatment of West Nile encephalitis is currently under way in the United States.

POSTPOLIO SYNDROME

Epidemiology

Any discussion of CNS infections in the elderly should include the postpolio syndrome. This syndrome does not appear to be because of persistent poliovirus infection, but rather is likely due to an age-related loss of surviving motor neurons, and their inability to innervate the enlarged motor neuron units seen in poliomyelitis patients (Modlin, 2004). In a study of the prevalence and risk factors for postpolio syndrome in a cohort of 551 former poliomyelitis patients in Allegheny County, Pennsylvania, 137 ($\sim$25%) developed symptoms of the postpolio syndrome between 32 and 39 years after the acute illness (Ramlow, 1992). Risk factors for the development of the postpolio syndrome were female

sex, bulbar disease and the degree of postrecovery residual impairment. Despite the relatively high prevalence of this disorder, the majority of patients (80% in this study) did not require the use of new assisted devices to accomplish their activities of daily living, despite a subjective decline in their functional status.

Clinical Presentation

The postpolio syndrome is characterized by muscle weakness, muscle and/or joint pain, fatigue, and a decline in functional status occurring 30–40 years after acute poliomyelitis (Modlin, 2004). Some patients have progressive weakness and wasting in muscles that were not necessarily weak at the onset of poliomyelitis.

Diagnosis

Conventional electromyography (EMG) demonstrates chronic denervation; occasionally there may also be new or ongoing denervation manifested as fasciculations, fibrillations, and positive sharp waves (Modlin, 2004). Enlarged motor units consistent with highly increased fiber density can be demonstrated in 90% of patients on single-fiber EMG. However, the primary role of EMG is to exclude other causes of the patient's presentation.

Therapy

There is no definitive treatment for the postpolio syndrome, but symptomatic improvement may be obtained with analgesics such as paracetamol (acetaminophen) or nonsteroidal anti-inflammatory drugs, local heat application to affected muscles and joints, and a low-impact, nonfatiguing exercise program to prevent the development of muscle atrophy (Modlin, 2004). Patients may also benefit from rest periods, increased sleep time, and other energy conservation methods to overcome fatigue.

CREUTZFELDT–JAKOB DISEASE

Epidemiology

The most common human prion disease is sporadic, or classic, Creutzfeldt–Jakob Disease (CJD), with a worldwide incidence of approximately 1 case per million population (Janka and Maldarelli, 2004); however, among individuals aged 60–74 years, the incidence is 5 cases per million population (Holman *et al.*, 1996). Symptoms generally begin by age 60–70, with a mean age of onset of 60 years.

Clinical Presentation

Sporadic CJD is characterized by a rapidly progressive multifocal neurological dysfunction, myoclonus, and a terminal state of global severe cognitive impairment. About 40% of patients with sporadic CJD present with rapidly progressive cognitive impairment, 40% with cerebellar dysfunction, and the remaining 20% with a combination of both findings. The clinical picture rapidly expands to include behavioral abnormalities, higher cortical dysfunction, cortical visual abnormalities, cerebellar dysfunction, and both pyramidal and extrapyramidal signs (Collins *et al.*, 2004). Almost all patients with sporadic CJD develop myoclonus that involves either the entire body or a limb; myoclonus may be absent at disease onset, but appears with increasing severity as the disease progresses. After a rapidly progressive illness of 3–9 months, death usually occurs with the patient in an akinetic and mute state (Janka and Maldarelli, 2004).

Diagnosis

The clinical presentation, progressive nature, and failure to find any other diagnoses are the hallmarks of sporadic CJD. There are no available, completely reliable diagnostic tests for use before the onset of clinical symptoms in patients with sporadic CJD. During the course of disease, most patients develop a characteristic picture on EEG with periodic paroxysms of sharp waves or spikes on a slow background (Janka and Maldarelli, 2004; Chiofalo *et al.*, 1980). These periodic complexes have a diagnostic sensitivity and specificity of 67% and 87%, respectively, on a single EEG; if repeated recordings are obtained, more than 90% of patients show periodic EEG abnormalities. The triad of myoclonus, dementia, and EEG periodic sharp waves is a characteristic presentation of sporadic CJD.

Therapy

There is no treatment that can cure or control CJD. About 90% of patients die within 1 year (Janka and Maldarelli, 2004). Current treatment is aimed at alleviating symptoms and making the patient as comfortable as possible. Opiate drugs can help relieve pain; clonazepam and sodium valproate may help relieve involuntary myoclonus. Quinidine has been tested in an uncontrolled and unblinded study of patients with sporadic CJD; despite transient improvement in some patients, they reverted to their previous states and died of progressive disease (Follette, 2003).

KEY POINTS

- Empiric antimicrobial therapy, based on the patient's age and underlying disease status, should be initiated as soon as possible in patients with presumed bacterial meningitis; therapy should not be delayed while diagnostic neuroimaging tests are awaited.
- In elderly patients with bacterial meningitis, empiric antimicrobial therapy should consist of vancomycin,

ampicillin, and a third-generation cephalosporin (either cefotaxime or ceftriaxone), pending organism identification, and susceptibility testing.
- Adjunctive dexamethasone has been shown to reduce morbidity and mortality in adults with pneumococcal meningitis; this adjunctive modality should also be utilized in patients with tuberculous meningitis.
- The diagnosis of focal CNS infections (i.e. brain abscess, subdural empyema, epidural abscess) has been revolutionized by the development of neuroimaging studies; MR imaging has been especially useful in better detection of the extent of disease and early detection of cerebral edema.
- The therapeutic approach to focal CNS infections often requires a combined medical and surgical approach, because drainage of infected material can rapidly reverse neurologic symptoms and signs and antimicrobial therapy alone will not reliably sterilize these lesions.

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PART IV

Health Care Systems

Geriatric Medicine Education in Europe

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INTRODUCTION

The Council of Europe includes 45 state members, while the European community, limited until May 2004 to 15 countries, includes today 25 different countries, all with varying degrees of industrialization, economic benefits, and employment. These initial remarks highlight that it is really difficult to consider Europe as a homogeneous group of countries. The wide variation of demographic data is probably the best way of showing the disparity among the European countries (Economic Commission for Europe's Population Activities Unit, 2005):

- Birth rate: the highest is in Turkey (2.4/woman) and the lowest in Latvia (1.1/woman);
- Mortality rate during the first year of life: the highest is in Turkey (35.7/1000) and the lowest in Iceland (2.4/1000);
- Life expectancy at birth for men: the highest is in Iceland (79.9 years) and the lowest in Russia (61.3 years);
- Life expectancy at birth for women: the highest is in San Marino (83 years) and the lowest in Turkey (71 years).

However, in each developed European country, life expectancy at birth continues to increase: there is actually a 3-month "bonus" of life for each year of life (Oeppen and Vaupel, 2002). In 1999, Europe had a total population of 728 million inhabitants, of which 14% were over 65 years. Between 1999 and 2050, the expected increase of the 60+ and 80+ European population should reach 160% and 158%, respectively. In 2050, among 100 European inhabitants, 35 will be older than 65 years and 9 will be older than 80. The number of nonagenarians, centenarians, and supercentenarians (over 110 years) will continue to increase (Robine and Paccaud, in press). While the healthy life expectancy is longer than ever in developed countries, still many older subjects spend the last years of their life suffering from chronic diseases and increasing disability, which explains why a large percentage of patients requiring health care belong to this age-group.

One of the most efficient ways to cope with this programmed overflow of the older sick population with their specific medical and psychosocial needs would be to enhance the geriatric training of all categories of health-care professionals, and particularly medical doctors. It has been recently acknowledged that current medical education is failing to provide the knowledge and skills that are needed to manage chronic diseases that are common in the older population (Holman, 2004). It is unfortunate, therefore, that there is little evidence that European countries are responding adequately to this "Geriatric education imperative" (Besdine, 1989).

In 1994, a Group of European professors of medical gerontology provided an inventory of teaching activities in geriatrics in several European countries (Stähelin *et al.*, 1994). In this chapter, we aim to update this important review discussing the current status of geriatric medicine teaching at the undergraduate and postgraduate levels in various European countries, as well as the continuing medical and professional education activities.

UNDERGRADUATE GERIATRIC MEDICINE EDUCATION

Undergraduate geriatric medicine education remains a major area for development, and curricula have become available only recently in a number of European countries.

As part of a larger survey of geriatric medicine in Europe, the authors received information from 28 geriatricians, trained at the European Academy for Medicine of Aging (EAMA), and working in 14 different European countries. The results of this survey were, in general, difficult to analyze and interpret because of different curricula being taught within the medical schools surveyed. However, it is interesting to present these data because they can give some clues on the current status and also on the new trends in undergraduate geriatric education across Europe.

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Western Europe

In Austria there are three medical schools, but no formal position on academic geriatric medicine exists, and consequently there is an inadequate level of teaching of the subject. In Belgium, among the existing 11 medical schools, only half have well-developed undergraduate geriatric teaching with academic positions in the biology of aging, geriatrics, and psychogeriatrics. Furthermore, Belgium is the first country that has established special interuniversity geriatric teaching activities to cover the training needs in geriatrics for all students in their last year of medical undergraduate study.

In the United Kingdom, every undergraduate medical school has a professorial department of geriatrics or a related subject. There is broad-based teaching in the science of aging, clinical geriatrics, and psychogeriatrics. These programs are well defined, based on both traditional and problem-based learning (PBL) approaches, and are usually integrated throughout the five years of medical course. France appears, today, as being one of the most advanced countries in undergraduate geriatric teaching, although geriatrics is not yet recognized as an independent speciality from internal medicine. However, there is at least one professorship in each French medical school ($N = 40$) with some of them still in the process of being appointed. Undergraduate teaching programs are based on a national core curriculum established by a group of French professors of geriatrics. The teaching activity is both traditional and problem-based, dealing with the geriatric giants as well as comprehensive geriatric assessment. The undergraduate teaching in geriatrics takes part of the last year of the medical course.

In Germany, undergraduate geriatric teaching is very often done under the leadership of internal medicine or other medical specialists who are not trained in geriatric medicine. In a few medical schools, the geriatric program is an independent one, or is sometimes linked with the public health and nursing programs.

In the Netherlands, the number of geriatric academic positions have decreased during the last five years, and unfortunately, the training is often embedded in the internal medicine and neurobiology curricula, although all students are still required to study this discipline. In Switzerland, only one of the five medical schools had a geriatric professorship in 2004. However, undergraduate teaching activities are developed in all the Swiss medical schools because of the involvement of promising nonacademic geriatricians. In Geneva, there is a well-developed and successful problem-based learning program, which takes place from the beginning to the end of medical studies (Table 1).

Table 1 New undergraduate geriatric core curriculum at the Geneva Medical School

The emergence of integrated problem-based undergraduate medical curricula is a real opportunity for the undergraduate teaching of geriatrics. The PBL approach allows integrating geriatrics vertically and longitudinally with the teaching of basic sciences and other clinical disciplines, since geriatrics is an intrinsically multidisciplinary and integrative field.
Most PBL curricula, for example, in Geneva, Switzerland, start with a preclinical curriculum in which the students acquire knowledge in basic sciences and participate in some kind of longitudinal Clinical Skills Program (Vu *et al.*, 1997). Geriatric objectives in basic sciences and clinical disciplines can be integrated in the problems of the PBL units. For instance, a problem in the "Cell growth and aging" unit of the Geneva curriculum describes the story of an old lady who is about to give up driving. This problem allows a discussion of the pathophysiology of cataract, theories of aging, cellular mechanisms of aging, as well as legal issues about evaluating the driving ability of older persons. Similarly, other geriatric objectives in basic sciences and clinical disciplines can be integrated in the problems of other PBL units (Huber *et al.*, 1998).
A longitudinal Clinical Skills Program that runs parallel to the PBL units allows an early and progressive acquisition of clinical skills relevant for geriatrics. For example, basic training in neuropsychological assessment can be coordinated with a problem concerning dementia.
Other types of PBL problems help further integrate basic sciences concepts, and to develop student's clinical knowledge and problem-solving abilities. This approach is especially relevant for addressing frequent clinical problems in older persons (stroke, dizzy spells, falls, malnutrition, dementia). Again, these problems can be coordinated with related seminars that emphasize the acquisition of important aspects of the geriatric assessment, such as functional assessment, evaluation of the social network, mental examination, or assessment of the nutritional status.
During the clinical phase, exposure to the inpatient and outpatient care of frail elderly subjects should be provided in an attempt to foster a positive and multidisciplinary approach to the care of the elderly. Exposure to normal and successful aging should be provided whenever it is possible. Finally, it is very important to stress that undergraduate geriatric curriculum must be mandatory and evaluated to ensure that the students receive geriatric clinical attachments for their daily clinical practice in the future.

Northern Europe

Finland, Norway, and Sweden have academic positions in geriatrics in each medical school, with an undergraduate geriatric program constituted by both traditional and problem-based teaching activities varying from a few hours to 44 hours in the 3rd and the 6th year of medical study. Geriatric patients staying in academic geriatric wards are accessible to every medical student, and this activity is always very well appreciated. The same is not true for the psychogeriatric and the long-term care/nursing home patients.

Southern Europe

In Italy, the majority of medical schools have at least one faculty member who is specialized in geriatric medicine, although in some of them the teaching of geriatrics is provided by nongeriatricians, mainly internal medicine physicians. All students receive a formal education in geriatrics during the last year of medical school, although the practical training is performed mainly within the acute care hospital, and only a few medical schools have implemented training in the community services, that is, in nursing homes.

In Greece, there is only one chair in geriatrics among six different medical schools, with the internal medicine departments providing optional geriatric teaching.

In Spain, geriatric medicine is mandatory for all medical students in the 3rd and 6th year of undergraduate training. However, there is only one medical school that has a professor of geriatric medicine, and in the vast majority of them, physicians, usually from the internal medicine department, with no formal education in geriatrics are in charge of teaching geriatric medicine. The students receive mainly formal lessons with little or no practical training, with the majority of training taking place in hospitals.

Eastern Europe

We have received updated information so far only from Hungary and Poland.

In Hungary, there is not yet any academic position in the biology of aging, geriatrics, or psycho geriatrics. However, an intermedical schools undergraduate geriatric program exists, due to the enthusiasm of a few well-trained (but not yet academic appointed) geriatricians. This 20-hour program takes place at the end of medical studies in each Hungarian medical school.

In Poland, the number of geriatric academic positions has increased considerably during the last few years. In each medical school where a geriatric academic position exists, a 30-hour undergraduate geriatric program has been introduced in the 5th year of study. Geriatric teaching is, however, not mandatory and no geriatric ward exists to train medical students in this speciality.

In summary, undergraduate geriatric training is better organized in Scandinavia, the United Kingdom, Belgium, France, and Italy, while the other countries have a less adequate educational system. In many countries, undergraduate training in gerontology and geriatrics is not well integrated in the medical curricula, particularly with basic and preclinical disciplines, being limited to the last year of training, with the risk of remaining isolated from the core educational contents.

It is interesting to note that a similar conclusion was arrived at by an independent report produced by a collaborative initiative of the World Health Organization and the International Federation of Medical Students' Association, which was released in 2002 (Keller *et al.*, 2002). The overall status of geriatric teaching in Europe is not considered "very promising" in this report, since in the majority of countries, particularly of central and southern Europe, there is a vast lack of structured geriatric teaching. Even in those universities that offer geriatric training, only a 20- to 40-hour course is usually provided, which includes the physiological, psychiatric, pharmacological, and pathological aspects of aging. Moreover, although the European Union of Medical Specialists – geriatric medicine section (GMS-UEMS) has produced an undergraduate curriculum in geriatric medicine in 1999, which has been approved by a number of national geriatric societies, there is no evidence that this curriculum has been implemented in EU countries (Geriatric Medicine Section of the European Union Medical Specialists, 2005).

The most important conclusion we can derive is that the lack of recognition of geriatric medicine as a distinct speciality in a majority of countries represents the most important cause of the unsatisfactory status of geriatric training at the undergraduate level in Europe. The main identified deficiencies were: lack of a sufficient number of academic geriatricians, lack of the adoption of a uniform curriculum, the short time devoted to geriatrics usually at the end of the medical training, and the inadequate organization of clinical training with older patients. The absence of gerontological education in the medical curriculum does not allow students to fully understand the complexity of older patients, while the limitation of practical training with geriatric patients to the acute hospital care undermines their capacity to appreciate the absolute need of interdisciplinary comprehensive assessment and continuity of care.

Another potential difficulty is the indifferent or negative attitude toward the care for older people expressed by medical students, which has been widely documented, particularly in studies from the USA (Coccaro and Miles, 1984; Reuben *et al.*, 1995). Improving knowledge about aging and older people by teaching gerontological and geriatric topics early in the curriculum as well as providing direct personal experience with healthy and active older people have been found to ameliorate the attitude and perception of medical students toward elderly subjects (Alford *et al.*, 2001).

GERIATRIC MEDICINE TEACHING AT THE POSTGRADUATE LEVEL

In many European countries, there are ongoing residency programs in geriatrics, with a well-defined curriculum. In some of them (e.g. Italy, Spain), geriatrics is an independent speciality, meaning that trainees enter a 4 to 5 year postgraduate training in geriatric medicine directly after medical school, while in others (e.g. Austria, Belgium, France, Germany, Netherlands, Switzerland, and United Kingdom), formal training in internal medicine or general practice may be required first, but often runs alongside training in geriatrics. Only in some of these countries, there is the requirement for an accreditation in geriatric medicine (Belgium, France, Ireland, the Netherlands, Switzerland, and United Kingdom). On the other hand there are some countries, such as Greece, Hungary, Luxemburg, and Portugal, which do not have any recognized geriatric training program (Hastie and Duursma, 2003). Although there is now an established geriatric curriculum produced by Geriatric Medicine Section of the European Union Medical Specialists (UEMS), 2005 the geriatric training programs remain extremely heterogeneous even within the same country; this is mainly because the training programs have been historically organized on the basis of the services which were locally available, and were not based primarily on the educational needs of the geriatric specialist. It is still of particular concern that in many countries

geriatric training is hospital-based, and trainees do not have any access to community services, including nursing homes. It is now time that the organization of geriatric training is reconsidered, in order to restructure it with the aim of providing future specialists with the required knowledge and skills to practice twenty-first century geriatric medicine (Phelan *et al.*, 2003).

Concerning the geriatric education of postgraduate trainees in primary care or other specialities, there is evidence that it is nowadays extremely scanty or even completely ignored in the official curricula in many countries. This is certainly worrisome because primary care physicians as well as medical and surgical specialists are treating a large number of older patients, including the oldest, the very sick, and the most complicated and frail patients, but they are not adequately prepared to deal with their complex problems (Duursma *et al.*, 2004; Michel, 1997). Paradoxically, in several countries the geriatric training of nonmedical health-care professionals, especially nurses, is better organized than that of physicians. Finally, there is no well-organized continuous medical education program in geriatric medicine for the large number of physicians who did not get any formal exposure to geriatric medicine during their undergraduate and postgraduate training, and who still account for the majority of practicing medical doctors.

EAMA: A MODEL EXAMPLE OF GERIATRIC CONTINUOUS PROFESSIONAL TRAINING

The European Academy of Medicine of Aging (EAMA) (Stähelin *et al.*, 1994), organizes courses to train many of the future academic teachers of geriatrics in Europe. Part of the course deals with enhancing, updating, and improving the use of scientific knowledge by gathering data, gaining skills in critical interpretation of information, identifying deficiencies, learning how to establish priorities, and expressing important clinical messages. The first EAMA course (four residential 1-week sessions), started in January 1994 at the University Institute Kurt BOESCH (IUKB) in Sion (Switzerland), which significantly contributed to the launch of the course. In 2005, the course still has the same format. Each session includes state-of-the-art lectures by teachers and students, group discussions, and tutorial supervision of all student activities (Michel, 1997).

From 1995 to 2004, the weekly sessions have always addressed different topics and welcomed distinguished colleagues from all over the world, who played a key role in updating scientific knowledge and stimulating research ideas. EAMA recruits students from many European countries (Belgium, France, Germany, The Netherlands, Switzerland, United Kingdom, and several others including Eastern European countries such as Hungary, Poland, Russia), where geriatric societies select promising academic geriatricians, or students are nominated by senior academics in their own country. The Scientific committee also accepts outstanding non-European students (Argentina, Brazil, Israel, Lebanon, Mexico, Senegal, South Africa, and Tunisia) without exceeding a maximum number of 40 students per session to allow better supervision and interaction between students and teachers. This learning environment promotes a rich learning experience with cultural perspectives, multiple socioeconomical differences, and varied health-care organizations enhancing fruitful discussions on care and research issues. Geriatricians with many diverse perspectives interact on ethical issues and establish valuable networks.

The possibilities of exchanges were amplified by the launch of an EAMA virtual classroom located within the "www.healthandage.com/edu/eama" internet site. Since the first session, all the training activities of the teachers and students are evaluated. Students evaluate the performances of the teachers, the experts, and their colleagues, and vice versa. The comparison of evaluation results between students and teachers shows that students are stricter and more severe with their colleagues than the teachers themselves (Michel, 1997). The evaluation of the students' scores between the first and the last session of the third EAMA course showed that the scientific content of their lecture were enhanced, the formulation of taking home messages was more precise, and the techniques of oral presentation were better focused. In total, the score of the overall quality of the student's teaching performance between the first and the fourth session of the third course was increased by 31% (Swine *et al.*, 2004). The most impressive result of EAMA is the fact that 91% of the former students ($n = 167$) acquired professional promotion and 20% obtained an academic position.

The EAMA activities are now organized in close collaboration with the European Union Geriatric Medicine Society (EUGMS) and the International Association of Gerontology and Geriatrics – European Region (IAG-ER), allowing for an excellent and promising networking of the new generation of geriatricians.

The success of EAMA is officially recognized by their recent accreditation (2002) by both the Swiss Medical Federation and the European Union of the Medical Specialists – geriatric section. Another indicator of the success of the EAMA is the launch of similar initiatives in different parts of the world by former students: the "Academia Latino Americana de Medicina del Adulto mayor" (ALMA), the "Middle East Academy for Medicine of Aging" (MEAMA), the "Saint Louis University Geriatric Academy" (SLUGA) and, probably next year, the "European Nursing Academy for the Care of the Older" (ENACO).

CONCLUSION

Undergraduate and postgraduate training programs in geriatric medicine across Europe are varied in content and format and are often poorly developed. Restructuring of the educational process in order to equip future health-care professionals including physicians to provide specialist care to elderly patients is needed. Otherwise, we may see the progressive collapse of European health-care systems under the burden

of the complexity and multiplicity of health-care needs of an increasing sick and disabled older population. It is therefore a priority for nongovernmental and professional organizations, such as EUGMS, UEMS, IAG-ER clinical section, and national geriatric societies, to try to influence the decision makers in both the health-care sector and the academic centers to address this urgent educational imperative.

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KEY POINTS

- The European population is aging: while in 1999 14% of the subjects were older than 65 years, this percentage will increase by about 160% in the next 50 years. Whereas the majority of older people live healthy and independent lives, the risk of morbidity, ill health, and disability increases with age.
- The frail elderly population with its specific medical and psychosocial needs requires high-quality geriatric care: this can be provided only if appropriate geriatric training is guaranteed to all categories of health-care professionals and, particularly, doctors.
- There is little evidence that European countries are responding adequately to this "Geriatric education imperative". There is indeed an extreme heterogeneity in the provision of geriatric education, both at the undergraduate and the postgraduate level not only between different countries but also within the same country.
- In many European countries, undergraduate training in gerontology and geriatrics is not adequately developed and is not integrated into the medical curricula, particularly with basic and preclinical disciplines, being often limited to the last year of training and to the hospital setting.
- Postgraduate training in geriatric medicine is available in several European countries, but not at all in some others. In general, training is still limited to the hospital setting and does not include periods of training in the ambulatory, community and long-term care settings, where the majority of older patients are cured.

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Nursing (UK)

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INTRODUCTION – OVERVIEW OF CHAPTER

This chapter explains the characteristics and principles of older people's nursing and explores the scope of its application across the spectrum of care: from prevention of ill health, through acute illness and rehabilitation to continuing care. Nurses are involved with care provision for older people in a wide range of settings – primary care and community care home, hospital, mental health center, acute and rehabilitation wards, A&E, intermediate-care services, outpatients, day hospital, and nurse-led clinics. While many nurses work within the National Health Service (NHS), within older people's services, many also work in the independent sector. This is a significant care provider and employer, due to the majority provision of long-term care beds now being sited outside the NHS. In 2000, 70 895 qualified nursing staff were working in nursing homes, private hospitals, and clinics, the majority being in general nursing homes (UKCC, 2002). As well as being diverse in application to care settings, nursing older people is characterized by its flexibility, breadth, and overlap with other roles – coordinator, manager, essential caregiver, therapist, specialist carer, and educator are just some of the many aspects of specialist nursing across these areas of practice.

Over recent years, nursing older people has emerged from being a somewhat underrated and stigmatized area of nursing service into a recognized skilled speciality. This chapter examines how this process has been supported by professional articulation, development of nursing curricula and professional qualifications, extended roles and responsibilities, and publication of specialist standards and competencies. New roles such as the older people's specialist nurse, matron, and consultant nurse have provided a boost to clinical leadership and the retention of skilled practitioners within the nursing speciality. It will also be shown how the principles of caring for older people are applicable to nurses in many settings and specialities, not just to those nurses who work in older people's services, or have a title of older people's specialist nurse. It will be concluded that older people's nursing has many future opportunities, as well as challenges ahead, including extension of specialist practice, strengthening of nurses' roles in clinical leadership and research, and involving older people and carers further in care and service development. Underpinning all contemporary and future practice are the fundamental principles of caring for older people: use of a multidisciplinary, person-centered, evidence-based approach, which applies understanding of the impact of the aging process to the individual's wellness, illness, and recovery.

BACKGROUND – THE DEVELOPMENT OF OLDER PEOPLE'S NURSING

Since the work of Dr Marjorie Warren in the 1930s, and the emergence of geriatric medicine as a speciality, a parallel revolution has occurred in older people's nursing.

Nursing older people was once seen by some as an unattractive career option, associated with negative stereotypes of services that warehoused and institutionalized dependent older people. This stereotype was partly reinforced by the prolonged use by the NHS of former workhouse facilities for community hospitals and rehabilitation units, which were a physical reminder of the past for both patients and staff. The perceived unpopularity of work with older people has been found to be associated with these "impoverished environments" in which older people receive care, rather than negative attitudes towards older people themselves. The majority of students and qualified nurses now consider work with older people to be challenging and stimulating, and a highly skilled job (Nolan *et al.*, 2002).

Challenges to development of the speciality have particularly applied in the independent sector. While older people's nursing in the NHS is increasingly recognized and developed, the capacity for specialist nurses to further develop, and lead effective health-care practices in care homes has been limited by lack of investment in access to specialist

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training and development. Nurses in the independent sector have limited opportunity for formal, funded professional development in comparison with that which is available to NHS nurses, yet it is in care homes that many of the most frail and medically complex older people in our society are cared for. The lack of investment is partly reflected in the issues underpinning complaints which arise against practitioners in this sector: the UKCC (2002) identified organizational issues such as low staffing levels, poor skill mix, and lack of leadership or direction that were common to the majority of complaints against nurses working in the independent sector. Professional issues, such as, lack of training and career progression are also a common feature. The introduction in 2001 of NHS-funded nursing for care home residents may be an opportunity for Primary Care Trusts to increase training and support to care homes, and help redress this imbalance and impact on the quality of service delivery. A further challenge to the independent sector is to increase published evidence of good practice and innovation from practitioners who work there, particularly in the nursing homes for older people.

Until fairly recently, there has been a relative lack of national standards, competencies, and research base within the nursing speciality. The skills and value of any speciality can only be recognized if there is an evidence base to support it and the practitioners are sufficiently articulate, empowered, and supported. Through nurse leadership, promotion of positive attitudes to aging, modernization of facilities and developments in nurse education, standards, policy and politics, and any stigma that might have existed of "geriatric nursing" has been gradually eroded.

The significant policy drivers which have recently emerged, the NHS Plan (Department of Health, 2000) and the National Service Framework for Older People (NSF) (Secretary of State for Health, 2001), set out principles and standards which rule out ageist policy and practice in all sectors. With this precedent firmly established, the major challenges and opportunities for older people's nurses lie in further development of specialist education, maintaining an appropriate focus on the essential areas of patient care, and developing and retaining a workforce with the required knowledge and skills. These issues will be more fully explored in the sections that follow.

DEVELOPMENT OF THE SPECIALIST NURSING ROLES

As already noted, nurses care for older people in a wide range of settings, yet many would not necessarily consider themselves to be older people's specialists. With the majority of hospital and primary care patients being aged over 65, it can be argued that most nurses require some knowledge of caring for older people. It is vital that skills are not just learnt in the classroom but that nurses who have contact with this patient group can also learn from experts in practice and then implement what they have learnt, with appropriate support and leadership. This is one reason for development of the specific role of the older people's specialist nurse (and other senior roles such as consultant nurse and matron within the NHS); by strengthening clinical leadership and clinical expertise in caring for older people, good practice will be role modeled and promoted. Clinical leadership helps ensure that knowledge and skills acquired through both pre- and postregistration education and professional development can be implemented and further developed.

The development of the role of older people's specialist nurse (OPSN) in all areas of care delivery has been strongly supported by both the Royal College of Nursing and the British Geriatrics Society, who published a joint statement in 2001 (RCN & BGS, 2001). Their statement points to the increasing complexity of health and social care for older people, and the difficulty in providing smoothly coordinated care focused on older people as individuals. It clearly articulates the potential value that this type of role can contribute to older people's care. This includes:

- expert clinical practitioner working alongside older people and their families;
- key resource to provide leadership for nursing and contribute to cross-boundary working;
- key contribution to implementation of the National Service Framework for Older People and the Single Assessment Process;
- working as part of a specialist multidisciplinary team, sharing a vision and accountability for comprehensive service delivery, and development of good practice.

Some NHS Hospital Trusts and Primary Care Trusts have now started to develop these roles, an example of which, older people's specialist nurse in Care Home support, is summarized in BOX 1.

BOX 1 Role of the OPSN in a Care Homes Support Team

The post of OPSN within a Care Homes Support Team was developed in three South London Primary Care Trusts in 2003.

The OPSNs work within a wider multidisciplinary support team, which includes dedicated sessions from Consultant Geriatricians, a Consultant Old Age Psychiatrist and a pharmacist. Eight posts, at senior nursing grades, were created and subsequently fulfill a variety of roles across primary care and in 40 nursing homes that include:

- undertaking initial determinations of NHS-funded nursing care in care homes (also known as the *RNCC*), and subsequent reviews including full continence assessments;

- holding a case load of selected older people who are resident in nursing homes within the three local boroughs;
- advising care providers on care planning and delivery;
- acting as a specialist skills' resource to care providers;
- identifying and triggering referrals to specialist care services;
- leading on behalf of the specialist interdisciplinary team on issues of clinical governance and monitoring of care.

When undertaking patient reviews, including determination of the RNCC, the OPSNs undertake an assessment of the residents' mental state and falls risk, and collect a range of health outcome measures. They provide advice to the Care Home staff on the resident's care plan, and specific clinical needs such as tissue viability and wound management. They contribute to a review of the resident's medication, in conjunction with the team's full-time pharmacist. The review is conducted when possible, and when wished by the resident, with the resident's family carer so that communication and support may be optimized. Working closely with the consultant members of the team, the OPSNs also contribute to the review of residents who receive fully funded NHS care both in Care Homes and their own homes. Finally, they are engaged in a range of practice development activity, benchmarking, audit and research in the Care Homes across the three boroughs.

The OPSN role described here provides a good example of how appropriately skilled and experienced nurses make skilled independent judgments and provide advice to care providers while contributing to multidisciplinary management of the older person. The roles of these particular nurses have a majority clinical focus, but are broad enough to include elements of activities such as research and audit, which help drive practice forward and develop the speciality.

The development of consultant nurse roles, was set out in the key document, *Making a Difference* (DoH, 1999). This strategy is applicable to nursing in all specialities, and has been highly influential in professional nursing development within the NHS. These leadership roles will help ensure that the standards of care for older people are maintained and developed both within and beyond specialist older people's services.

Consultant nurses' posts have four key role components (NHSE, 1999):

- professional leadership and consultancy
- expert practice
- practice development, research, and evaluation
- education and development.

There are, at the time of writing, 54 consultant nurse posts for older people in England, 23 of which are in acute trusts, 21 in primary care trusts, 8 in mental health trusts and 2 which span both mental health and acute trusts (Sturdy, 2004). The difference between the consultant role and that of specialist nurse is predominantly one of level of working – the consultant role has a greater leadership and strategic component, while retaining a 50% clinical component. Although there are no national criteria for the academic or professional level of a specialist nurse post, the nurse consultants are required to be qualified to at least master's level, and to have substantial experience within the speciality. Both types of roles contribute to the further development and leadership of the nursing speciality, and work well in partnership with each other. In the case of the OPSN team described above, overall clinical leadership and direction, and clinical supervision of the team, are provided by a consultant nurse.

UNDERPINNING PRINCIPLES OF NURSING PRACTICE WITH OLDER PEOPLE

Whether working as part of the multiprofessional team in delivering care for older people during an acute illness or in a period of maintenance of good health, or in any other stage in the continuum of health, the fundamental principle of nursing older people is the same: the use of a person-centered approach. The use of a person-centered approach in nursing means that individuality, choice, and rights are recognized and respected, when making assessments, planning, and delivering care. A prerequisite for person-centered care is also that nurses invest in care-giving out of choice, that they want to work with older people, value interdependence, and respect personhood (Mulrooney, 1997). This approach combines with recognition of the central importance of helping older people to meet their essential care needs, which includes assisting patients with intimate care and comfort. In order to deliver care using these holistic principles, all nurses are trained to use the nursing process. This is a problem-centered approach, which works through the four stages of:

- assessment
- planning
- implementation
- evaluation.

High-quality assessment of older people's needs depends upon good teamwork and the use of valid and reliable assessment tools. Older people's nurses work in an interdisciplinary way to contribute to the overall assessment of the patient, and are familiar with the use of a range of standardized and validated tools to support assessment of the person's physical, psychological, and social status. Some of the areas that nurses need to address when assessing the older person may be described within these three domains:

Physical
Tissue viability
Continence
Constipation and bowels
Pain
Rest and sleep
Foot health
Oral health
Prevention of ill health and promotion of good health
Falls risk and safety needs
Mobility
Eating, drinking, and nutrition
Self-care ability
Hygiene needs
Wound care
Administration of medicines

Social
Carers' needs
Recreation
Social networks and support
Transport
Communication
Appearance
Ethnicity and culture
Education and intellectual needs

Psychological
Mental health problems including dementia, depression, and delirium
Cognitive function
Behavior
Spiritual needs
Sexuality.

While these principles, domains, and processes underpin nursing care of older people in all areas, nurses also utilize specific knowledge and skills to enable them to care effectively for older people with different intensities or acuteness of care need. The older people's nurse is able to distinguish normal from abnormal aging, and recognizes the impact of the aging process upon health, illness, treatment, and recovery. They also understand the management of complex problems, physical, psychological and social, and are prepared to encounter these frequently and work closely with the multiprofessional team to achieve solutions to them. Nurses who are skilled in working with older people also work closely with colleagues from social care and at the interfaces between services, ensuring that transfers of care are managed properly. The next section explores the application of older people's nursing to four care areas: acute care, continuing care in care homes, working with older people and their carers in the community (with the specific example of admiral nurses), and rehabilitation and intermediate care.

Acute Care of Older People

During an acute phase of illness, older people need care by nurses who are not only skilled in the technical aspects of nursing but who can also apply knowledge of the impact of aging process in response to acute treatments and recovery. This particularly includes knowledge of how older people may respond differently to drug treatment, infection, injury, and pain than younger people. A particularly vital concern during acute illness is recognition of delirium, a condition which is often underrecognized by general nurses (Inouye *et al.*, 2001), but which the specialist nurse will understand as a reversible acute confusional state rather than an irreversible dementia, and will also recognize it as a condition that may persist beyond the acute phase of treatment. Patients who are acutely or chronically confused have specific health and safety needs including psychological management, falls and injury prevention, nutrition, and communication. In an acute setting, nurses need to be vigilant for these differences, and the implications for care planning in terms of patient and carer support.

The scope of nursing older people within acute care was described and critiqued in a report in 2001 from the Standing Nursing and Midwifery Advisory Committee (SNMAC). The report "Caring for Older People: a Nursing Priority" (SNMAC, 2001), formulated a number of standards of care for older people and their carers during an acute phase of illness, covering the following care domains:

- respect for older people's dignity;
- promotion of choice, involvement, and independence of older people and carers;
- facilitation of communication with older people and carers;
- individualized care and its management;
- continence;
- dementia;
- mental health;
- mobility;
- nutrition and hydration;
- pain management;
- palliative care;
- pressure damage prevention and management.

These domains offer a useful framework for identifying the fundamental care needs of older people in hospital, and describing the scope of nursing in this setting. The standards may be used to audit care, although in most hospitals, it has been the *Essence of Care* benchmarking (DoH, 2001b), which has been more widely implemented. The *Essence of Care* is relevant to all care areas, and will be described in more depth later.

In hospital care, the SNMAC report also strengthened the case for further development of speciality nursing roles. They identified that when there were obstacles to the delivery of high-quality care, this could be due to lack of clinical leadership, management and role modeling, inadequate training and preparation of nurses for working with older people, and deficiencies in the physical environment and resources (SNMAC, 2001). These are undeniable challenges in ensuring that acute care is appropriately tailored to older people's needs. The publication of the SNMAC report and the NSF helped to drive further improvement in acute care of older

people in hospital, particularly for nursing in terms of leadership and in specific clinical areas of concern such as the feeding, hydration, and nutrition of older patients. Protected mealtimes for hospital patients are one example of this.

Quality improvement initiatives in acute care have particularly been related to the requirements of Standard 4 "General Hospital Care" of the NSF for Older People. This standard is as relevant to nurses as to all other health and social care professionals. The NSF supports the strengthening of clinical nurse leadership within interdisciplinary older people's services in general hospitals, including the role of the specialist nurse. The specialist nurse in an acute hospital may be ward or department based, or have a role in working at the interface with other areas, providing outreach expertise. The value to this type of role has been demonstrated in a recent evaluation of the introduction of OPSNs within an inpatient setting in Nottingham. This study provides evidence that the role can provide rapid assessment and review of patients with appropriate identification of transfer of care, discharge, referrals, and review (Harwood *et al.*, 2002).

The milestones set by the NSF also impact on training and preparation of staff who work with older people in acute settings: NHS Trusts are required to carry out a skills audit of all staff within the organization. Nurses being by far the largest proportion of the workforce has enabled trusts to review the training needs across the organization and put action plans in place to ensure that all staff have at least the minimum knowledge and skills to care for older people.

Continuing Care in Care Homes (*see* Chapter 153, Nursing Home Care)

Continuing care can be interpreted as the delivery of care services in any setting, including the client's own home, care homes, and other long-stay facilities. When older people require continuing care in their own home, NHS nurses provide registered nursing through the community nursing service, unless the older person prefers and has the means to privately employ a registered nurse. Care assistants, and often family caregivers or other informal carers otherwise deliver the majority of care. There is a similar skill mix in Care Homes with Nursing, where independent care providers employ registered nurses and care assistants, but care assistants under supervision from the registered nurses deliver the majority of care.

Masterson (1997) identified the function of nursing in continuing care is to provide

- specialist practice skills,
- assessment and review of needs,
- health promotion and health maintenance,
- partnership working with clients and carers.

Although this guidance (produced for the nursing regulatory body, the United Kingdom Central Council for Nursing, Midwifery & Health Visiting (UKCC)) predates the NSF for older people, the principles it sets out resonate with the NSFs person-centered and proactive approach to health and social care. Nurses have the key role to play in delivery of care and in ensuring that older people's continuing care needs are regularly and appropriately reviewed, reversible health problems are identified, and chronic health problems are appropriately managed so that the remaining function may be optimized. For them, this guidance is highly relevant. There may be only one registered nurse on duty for each shift within a Care Home with Nursing, and the responsibilities upon that practitioner are considerable, requiring them to lead the care team and ensure that care is properly delivered. Unlike acute or many subacute hospital settings, there is reduced access to medical cover and therapy input. Consequently, the skilled practitioner in continuing care manages the maintenance care of clients, while being alert to changes in health and well-being. They understand the implications of these changes, particularly when residents may be at the end of their life or in a condition in which hospital admission may be inappropriate. Particular skills relate to the mental health of nursing home residents, the proportion who have dementia being around 62% (Matthews and Dening, 2002). Safety issues related to wandering and challenging behaviors amongst this group of residents are managed frequently in nursing homes.

Some of the challenges to the development of specialist nursing in Care Home settings in the independent sector were raised at the beginning of this chapter, particularly in relation to investment in training and support for nursing. Some of the underlying reasons for these challenges can be further understood within Masterson's identification of the requirements for an effective nursing contribution to continuing care:

- appropriate education, induction, and clinical supervision;
- an organizational culture which is committed to continuing care;
- positive attitudes expressed by nurses and health visitors toward older people;
- supportive and committed management processes;
- respect for the contribution of other members of the care team;
- appropriate delegation and supervision.

The squeeze on resources within "for-profit" organizations that provide continuing care for older people means that it may be difficult to meet all of these conditions for registered nurses to make an effective contribution. For example, there is no obligation within the legal requirements of the National Minimum Standards for Care Homes for Older People (Secretary of State for Health, 2003) for independent care providers to make provision for clinical supervision for registered nurses. Standard 30 of the Standards does require staff to be trained and competent to do their jobs, and to have a minimum of three paid days training per year, but it does not specify the content of this. The requirement applies to registered nurses and health-care assistants, 50% of the latter group of carers being required to have received training to National Vocational Qualifications (NVQ) level 2 or equivalent – a basic standard which is below that of entry

level to nurse training. In fact, only 42% of registered nurses working in nursing homes receive paid study time from their employers (UKCC, 2002). This suggests that while the employers clearly do have responsibilities for developing and training their staff they may interpret this creatively. Furthermore, there is no requirement for them to take account of specific published standards such as the SNMAC standards or the guidance of the NSF when determining the content or appropriateness of the training provided or supported. Registered nurses also have a professional obligation to ensure that they are fit to practice and to account for this to the Nursing and Midwifery Council when renewing their professional registration on a 3-yearly basis.

There is now a role for NHS nurses to support long-term care, which is delivered by the independent sector, through the requirement for determination of the level of NHS-funded nursing care (RNCC). The guidance on NHS-funded nursing care was issued in June 2001 (Department of Health, 2001). Originally referred to as *free nursing care* it sets out the NHS responsibility for provision of free nursing and health care whether the patient is in hospital, nursing home, or at home. Nursing Home residents must now have a determination of the level of NHS-funded nursing care undertaken by a designated NHS nurse prior to transfer to a Nursing Home, followed by reviews at 3 months and 1 year posttransfer. The NHS is also responsible for provision of continence products, which should only be supplied once a full assessment of the resident's continence has been completed. A registered nurse must carry out both these NHS responsibilities.

The determination of the level of NHS-funded nursing care is a high-level clinical judgment that requires a review of the risk, complexity, predictability and stability, and the resident's care needs (Department of Health, 2001a). To carry out the determination, a high level of knowledge, skill, and experience is required, with a recommendation by the Department of Health (DoH) that the designated nurses should include nurse specialists, nurse consultants, district nurses, discharge liaison nurses, and community psychiatric nurses. This has acted as a major catalyst for the provision of specialist nursing input to care home residents, based on the statutory requirement for the reviews to be carried out.

Working with Older People and their Carers in the Community (*see* Chapter 152, Carers and the Role of the Family)

A majority of older people never need long-term care in a Care Home, and probably would choose not to do so. Indeed only 4% of the population aged over 65 live in residential care settings, and the Royal Commission on Long Term Care recommended that more care should be given to people in their own homes, and more services should be offered to people who have an informal carer (Secretary of State for Health, 1999). While local authorities have responsibility for provision of personal and social care in people's own homes, the nursing needs of older people who live at home are met through community nursing services. This constitutes a high proportion of community practitioner's caseloads. Consequently, community nurses have a large role to play in the management of chronic diseases and have high levels of clinical skills in particular areas such as, continence management and tissue viability. The need for community nurses to have skills in caring for older people is becoming increasingly reflected in district nurse training courses (Ryder, 1994), although this is not a core curriculum requirement.

The introduction of the Single Assessment Process as part of the NSF for Older People (Secretary of State for Health, 2001) has brought a focus on the assessment of older people within health and social care. Primary care nurses' roles in assessment and care of older people in the community have a place at both overview and specialist levels of assessment, including working interprofessionally with both health and social care practitioners in comprehensive old age assessment of people who may need admission to a Care Home.

With the increasing prevalence of dementia with old age, specialist support for patients and their informal carers is a priority if community-based care is to be sustained, although primary care nurses have been found to have low understanding and confidence in identifying dementia and dealing with coexisting behavioral and mental health problems (Bryans *et al.*, 2003). This suggests that there is still progress to be made in the education and training of community nurses. Another approach is the development of specialist supporting nursing roles, such as admiral nurses. These are specialist mental health nurses, who work in the community, with families, carers, and supporters of people with dementia. In contrast to many community mental health teams, the service works primarily with the caregiver, focuses exclusively on dementia and offers continuing involvement including emotional support, information giving, and coordination of practical support. A Competency framework for admiral nurses has been developed (Traynor and Dewing, 2002) and the core competency areas are shown in BOX 2.

BOX 2 Core competency areas of Admiral Nurses

1. Therapeutic work (interventions)
2. Sharing information about dementia and carer issues
3. Advanced assessment skills
4. Prioritizing work
5. Preventative work and health promotion
6. Ethical and person-centered care
7. Balancing the needs of the carer and the person with dementia
8. Promoting best practice.

The identification of a specialist skill set and competencies is important for measuring and maintaining the quality of

the service and ensuring the professional development of the practitioners. An evaluation of the service itself has identified a significant impact on the anxiety and insomnia of carers of people with dementia, although it did not find any difference in the outcomes for the person with dementia, in terms of institutionalization (Woods *et al.*, 2003). This is an example of a specialist competency framework; by contrast, a national competency framework covering older people's care will be discussed later.

Rehabilitation and Intermediate Care

"The nursing role in rehabilitation is key to the government's agenda of modernization of the NHS" and "rehabilitation should be part of every nurse's role" – two quotes from the Royal College of Nursing's Rehabilitation Workbook (RCN, 2000). Although the use of a rehabilitation approach is widely acknowledged, in publications such as this, as being important to the care of older people, definition and clarification of the nursing's role in rehabilitation has still been slow to emerge. It may be suggested that general nursing initially struggled to identify it's specific therapeutic component in rehabilitation, possibly because of an underlying tension between perceptions of the concepts of *caring* and *treating* – although it may be rather simplistic to make this distinction, nurses have conventionally tended to consider themselves as providing the former, while therapists and Doctors carry out the latter. It was not until the 1990s that nursing researchers began to analyze and clarify nursing's role within the multiprofessional rehabilitation team, and explore the overlap between the role of a nurse and a therapist.

Waters (1991), identified three domains of nursing's role in rehabilitation, which she identified as the three constructs of "general maintenance", "specialist" and "carry-on". This implies a caring role that meets essential needs, while adding specific specialist skills and an understudy component to ensure that therapy interventions are continued as part of planned care. Nolan *et al.* (1997) further identified a role for nurses in creating and sustaining a suitable environment for rehabilitation. More recently Long *et al.* (2001) identified six core nursing roles in rehabilitation, which are:

- assessment
- coordination and communication
- technical and physical care
- therapy integration and therapy carry-on
- emotional support
- involving the family.

These roles are closely associated with the 24-hour presence of nurses in inpatient units and the breadth and flexibility of nursing practice in all settings. Although the therapy carry-through, or "understudy" role of rehabilitation nurses, has been identified through the nursing literature, identification of specific therapeutic nursing skills in rehabilitation have been more elusive, but might also be suggested to include pain management, continence promotion and management of incontinence, falls prevention, health education, and the promotion of rest and sleep.

Patient reenablement, choice and empowerment are integral to the rehabilitation process, and nurses have embraced this approach to help older people regain optimum function and independence. A good example of this, allied to a specific aspect of nursing, is the practice in some units of offering older patients the opportunity to participate in patient's self-administration of medicines – a relinquishing of the traditional role of nurses in drug administration in favor of a partnership – an educative approach which is endorsed by the NSF for Older People (Medicines Management). A further example is the involvement of nurses in delivery of exercise programs for older people. Individualized, tailored exercise has an effective contribution to make in improving strength and balance in older people and reducing falls (Day *et al.*, 2002). Research by Robertson *et al.* (2001) has demonstrated a role for nurses in delivery of these programs, and this is another area in which UK nurses are beginning to develop practice and expand their roles in rehabilitation (Nursing Times, 2004).

Recent developments in intermediate-care services have brought more focus to health and social care roles in providing focused, time-limited rehabilitation services that are delivered both in the community and in bed-based services. Some of these services have been developed and led by nurses, particularly in nurse consultant roles. Although at the time of writing, these services are relatively new, some evaluation has been carried out. For example, evaluation of one nurse-led intermediate-care unit found it to be a safe alternative to conventional management (Steiner *et al.*, 2001). Inpatient stay in this type of unit has been found to be longer than on general medical wards (Griffiths *et al.*, 2001). Obviously, nurse-led units require multidisciplinary input and would not be effective in providing a rehabilitation service without the input of other professions including medicine, therapy, and pharmacy.

EDUCATION AND PREPARATION FOR NURSING OLDER PEOPLE

The Nursing and Midwifery Council (NMC) is the regulatory body for Nursing and Midwifery in the United Kingdom that specifies the requirements of preregistration nursing programs (NMC, 2002). The basic qualification of registered nurse in the United Kingdom is awarded on completion of 4600 hours of training within a 3-year course, 50% of which must be in clinical practice. The minimum academic standard of this training program is a diploma in higher education. The required core competencies of registered practitioners include a range of transferable skills within the following domains:

- professional and ethical practice
- care delivery and care management
- personal and professional development.

There are no competencies that explicitly address the care of older people, although multidisciplinary working is specified. Registered nurses are competent to practice with either adult child, or person with mental health or learning disabilities according to the particular branch program they undertook in the second part of the preregistration program. All preregistration nursing courses do include some practice contact with older people, although practice placements are designated as "adult" rather than specifically "older adult". It has been suggested that a positive learning environment is one which ensures that students, staff and patients have a sense of security, belonging, continuity, purpose, achievement, and significance – this framework of "six senses" has been suggested by Professor Mike Nolan (Nolan *et al.*, 2002), who has made significant contribution to the development of postregistration curricula within the speciality of nursing and rehabilitation of older people.

Although there are Standards for Specialist Education and Practice (UKCC, 2001) likewise these do not specify educational requirements or qualifications for working with older people after initial registration. Employers, according to the duties and requirements of the post, determine this locally. Many specialist courses in the care of older people are available at degree and postgraduate level, offered at Universities throughout the United Kingdom. The English National Board (ENB) for Nursing framework for postregistration courses previously specified an outline curriculum for courses on nursing older people including the ENB 941 course, which was well known to practitioners until recently. These courses are no longer run since the Nursing and Midwifery Council absorbed the functions of the ENB in 2001. Postregistration course curricula are now determined and validated locally by education providers. There continue to be calls for greater emphasis on the care and rehabilitation of the older adults in nurse education. Long *et al.* (2001), for example, call for rehabilitation to be an ongoing thread through the preregistration curriculum, and at the postregistration level, a nationally recognized and accredited postregistration qualification in rehabilitation. This type of course should be multiprofessional.

While there is no nationally recognized qualification for the role of the older people's specialist nurse, an outline specification for preparation for the role has been published by the Royal College of Nursing and British Geriatrics Society (RCN & BGS, 2001). Specification for preparation for the role of older people's specialist nurse includes:

- sufficient and sound clinical experience working with older people;
- specialist postregistration development in the distinct and special aspects of older people's health and social needs;
- attributes and competencies which enable the nurse to respond expertly to the needs of the older person and professional colleagues;
- postregistration development in understanding the specific issues of later life, for example, the social and gerontological literature on older people's experiences of later life, the range of living circumstances and personal and social networks.

This provides a basis for development of specific posts within the many care areas in which specialist nurses may practice. A further route by which nurses may develop their skills and competency is through the Nursing and Midwifery Council (NMC) Higher Level Practice standards, which are described in BOX 3. Competency statements were developed around the NMC's seven higher-level practice standards, at each of the three levels of competency. These are generic and offer a framework for individual professional development.

BOX 3 The NMCs seven higher-level practice standards (UKCC, 2002a)

1. Providing effective health care
2. Leading and developing practice
3. Improving quality and health outcomes
4. Innovation and changing practice
5. Evaluation and research
6. Developing self and others
7. Working across professional and organizational boundaries.

The experience that nurses gain in practice with older people is recognized as a vital component of their expertise, although there has been a great increase in expectation of academic achievement of nurses who wish to specialize or work in more senior clinical roles. This is currently taken to its highest level in the requirements for nurse consultants to be qualified to at least masters' degree level.

BENCHMARKING AND MEASURING QUALITY OF NURSING CARE OF OLDER PEOPLE

The work of investigators such as Norton *et al.* (1962, 1975) were formative in raising issues around the care of older people in hospitals and continuing care. Since then, continued awareness of standards of care has been ensured through publications, some of which have already been mentioned, including statutory bodies such as SNMAC, UKCC, and professional organizations such as the RCN. Voluntary organizations such as Help the Aged have also contributed to public and professional awareness of care issues through campaigns such as the "Dignity on the Ward" campaign (Help the Aged, 2000). While the care of older people in hospital is the concern and responsibility of all staff, from porters to the Chief Executive, nurses have a strong contribution to make to ensuring that good practice is achieved and quality of care continuously improved, including in the core, or essential areas of care, such as nutrition, rest and elimination, and particularly in acute settings (SNMAC, 2001). This is why expertise in specialist

older people's nursing has to include expertise in the fundamentals of nursing practice.

In the NHS, quality monitoring and initiatives within nursing practice fit within the broader framework of clinical governance, which has been defined as:

> "A framework through which NHS organisations are accountable for continually improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish."
>
> (Scally and Donaldson, 1998)

One of the key mechanisms that have recently emerged for monitoring and improving quality of nursing care in all care settings is the *Essence of Care* benchmarking (DoH, 2001b). The *Essence of Care* was designed to support the measures to improve quality that were set out in "A First Class Service" (DoH, 1998) and to contribute to clinical governance at a local level. The benchmarking tool has high relevance for nursing older people as it focuses on the fundamental or essential care needs of patients, which form the basis of nursing practice. These are:

- principles of self-care;
- personal and oral hygiene;
- food and nutrition;
- continence and bladder and bowel care;
- pressure ulcers;
- safety of clients/patients with mental health needs in acute mental health and general hospital settings;
- record keeping;
- privacy and dignity.

Standards of care in the independent sector are regulated through the National Minimum Standards for Care Homes for Older People (Secretary of State for Health, 2003). The specific clinical content of these standards covers basic requirements for:

- privacy and dignity;
- death and dying;
- service user plan;
- health care – including personal care, pressure sore prevention, continence management, psychological monitoring, falls prevention, and nutrition;
- medication.

The standards cover a similar range of domains to the *Essence of care*, that is, fundamental patient care. It can be suggested from this observation that in order for care providers to monitor and improve their service delivery effectively, a system such as the *Essence of Care* or equivalent quality improvement framework would complete the circle. The benchmarking process engages frontline staff in exploring and agreeing the level of quality they have achieved, evidencing it, and forming action plans for improvement. The process is, however, time consuming and consequently the same tensions apply to quality assurance in care homes as to the issues of professional development and training.

Competency frameworks are a further tool that can be used to ensure that nurses have the skills to deliver good care. As mentioned earlier, there are general professional competency frameworks through the professional bodies, which apply to all student and registered nurses. When services rely on a high proportion of unqualified care assistants, as is the case in independent sector Care Homes, it is particularly important that there are frameworks to ensure that care assistants demonstrate competence to provide care for older people too, and that the minimum care standards can be met. One approach to guiding this is the use of nationally developed competency frameworks which apply to all formal carers, both qualified and unqualified. For health and social care workers in older people's care, the national occupational standards database now offers this. Developed by the organization Skills for Health (2004), the framework addresses the skills and underpinning knowledge that is needed across a wide range of older people's care, and is being linked to NVQ and the Agenda for Change (a system of pay review within the NHS, implemented in 2004, applies to nurses and other staff although not to medical staff). It has relevance across all sectors of care delivery, and can be linked to staff training, induction, and performance appraisal.

A challenge arising from development of competency frameworks is that they work well at basic levels of practice but because of the reductionist process of defining competence, it can be argued that it is difficult to develop a competency framework that adequately describes the detail of practice at an expert level. Nursing practice is by its nature extremely complex and in the literature it has been theorized that nurses use many sources of knowledge, including intuitive, personal, and ethical knowledge (e.g. Carper, 1978) and deal with multiple tasks and demands when providing care. For example, the older people's specialist nurses in a Care Homes Support Team, which were described earlier, draw on extensive knowledge of both normal and abnormal aging, assessment and evidence-based practice, and interpret this within a setting that is both the person's home and a caregiving environment. They make high-level clinical judgments about resident's care needs and advise residents, carers, GPs, and other multidisciplinary team members. They combine these skills with a leadership role in practice development and clinical governance activity. It may not be possible to explain expert practice in terms of easily understood tasks but there remains a responsibility for practitioners to exercise professional accountability for their actions, and to demonstrate that their actions are effective. This is achieved by expert nurses through a combination of appraisal, peer review, clinical supervision, and collection of appropriate activity data.

THE FUTURE FOR OLDER PEOPLE'S NURSING – FUTURE CHALLENGES AND OPPORTUNITIES

This chapter has had scope to discuss in depth only a few of the issues relating to the present and ongoing development

of older people's nursing. There are particular challenges in continuing care and the independent sector, but now that there is NHS recognition of its responsibility to fund registered nursing in care homes, it is to be hoped that there will be widespread recognition of the related obligation to support nursing development and help promote good practice. Generally, nursing is challenged to ensure sustained development of practice and the nursing contribution to older people's services in all sectors. In particular, evidence-based nursing practice requires a strong research base, and nursing needs to continue to develop its contribution, both into nursing aspects of care and also within multidisciplinary enquiry. With nurses increasingly acquiring graduate and postgraduate qualifications, there has never been a better time for this, although there needs to be access to adequate and substantial research funding, for which there is already intense competition within health care.

Nursing leadership in older people's services is at its strongest yet, but is challenged to champion and lead at all levels from local to international, and to continue to raise the profile of the speciality and ensure that it's value and professionalism are recognized. There is an associated opportunity for further development of nurse-led services and extension of older people's nurses' roles into areas such as prescribing and chronic disease management. Whatever the advances in roles, however, older people's nurses will always need to be experts at partnership working and multidisciplinary practice.

At the center of practice are older people and nurses who have much to learn from patients and clients and informal carers. The person-centered approach of nursing and strong emphasis on psychosocial as well as physical care identifies potential for nurses to further involve service users in developing services and evaluating the quality of care. A major challenge with this is the involvement of people with dementia and to find further ways to ensure that even when their ability to communicate is restricted, their needs, views, and feelings will be recognized and heeded. This particularly applies to care at end of life, and nurses are ideally placed to hear and help patients and carers express their views and choices. Older people's nurses face many ethical and moral issues in their work, and will always be able to offer a strong contribution within the interdisciplinary team, to supporting older people and their carers when these issues arise, and helping to maintain a focus on quality of life.

CONCLUSION

It is to be hoped that this chapter has provided a flavor of the skill and potential of older people's nursing, and the advances that have occurred in leadership and specialist skills development. The discussion has attempted to be realistic, by acknowledging some of the antecedents and challenges to contemporary nursing of older people, particularly those facing continuing care and the independent sector of care provision for older people. The scope of nursing older people, from essential care to expert practice, has nonetheless been illustrated. Issues have been explored around the development of practice in areas such as acute, continuing and primary care, and a number of policy, politics, and professional drivers have been identified. These continue to drive standards, competency development, education and professional development within the speciality, and older people's nurses and their professional leaders have embraced and responded to them. Older people's nurses have much to take professional pride in, and continue to have a tremendous contribution to make to health care in the future. The caveat remains that nursing will always need to stay patient-centered and focused on meeting essential care needs and quality of life, and share with medical and therapy colleagues a multidisciplinary approach to care.

KEY POINTS

- Nursing older people has developed into a skilled speciality.
- New roles such as the older people's specialist nurse and consultant nurse provide professional leadership and expert practice.
- The principles of nursing older people are based on person-centered care, a focus on essential care needs and interdisciplinary working.
- Professional standards, benchmarking, and competencies promote quality of care for older people in all sectors.
- Much nursing care for older people is provided through the independent sector, for whom particular challenges apply.

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Geriatric Occupational Therapy: Focus on Participation in Meaningful Daily Living

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OVERVIEW

Humans as Occupational Beings

The science underlying the occupational therapy profession views humans as *occupational beings* (Clark *et al.*, 1997). In other words, *who we are* is often determined by *what we do*. What we do are the *activities (occupations)* that comprise our lives. Thus, the focus of occupational therapy interventions with and for older adults is to address their unique needs and preferences for *what they need and want to do*, typically in the face of age-related changes and acute and/or chronic conditions. These potential or actual changes in the ability to perform necessary and desired activities *(occupations)* in which they find meaning impact how elders conduct their everyday lives and present a threat to their overall health and identity (Clark *et al.*, 2001; Csikszentmihalyi, 1997). Typically, the identity and sense of well-being of the elders is expressed through their participation in the activities/occupations that comprise their roles, habits, and routines. These patterns of participation represent who they have been throughout their lives, who they are today, and who they may yet become. Participation in society to the extent needed and desired by elders is fundamental to their perception of the quality of personal life, and also a basic component of the World Health Organization's (WHO) latest disability model, the International Classification of Functioning, Disability and Health (ICF) (2001 (*see* **Chapter 10, Social and Community Aspects of Aging**).

Scope of Occupational Therapy Services

Occupational therapy (OT) services are provided at three different levels: (1) directly with individuals and/or family/caregiver(s), (2) consultation and administration with community organizations, and (3) consultation and/or administration with governmental and/or international agencies. Historically, the majority of services have been provided for individual patients and clients, however, a growing number of community level OT services have been established during the past 30 years.

Overall, OT services are designed to sustain or improve the everyday activity related well-being and quality of life of older adults. In addition, services aim to enable families, nongovernmental organizations, and government agencies to mobilize efforts that promote the health of elders, prevent deterioration, restore functions that are impaired by organic disease, impairment or disability, and/or provide compensatory techniques necessitated by age or disability-related changes. In providing services, OT personnel collaborate with older adults and organizations in order to sustain or improve the ability of elders to perform necessary and meaningful activities, taking into consideration their overall health status, personality, lifestyle, family, and other support systems. Thus, whether administered an individual, a group, or a population, OT interventions aim to ensure a quality of life commensurate with the elders' priorities, as well as those of their family members, carers, and their communities (*see* **Chapter 155, Improving Quality of Care**).

OT assessment and intervention services are provided collaboratively with or on behalf of older adults who are at risk for or experience limitations due to disease, acute or chronic illness, injury, developmental disability, and/or the aging process. For example, a person who has sustained a stroke may receive OT services in order to relearn how to dress or to feed herself or himself. These services are provided throughout the continuum of care, to address the full range of daily activity (occupation) and participation needs of older clients or patients, as shown in Figure 1 (*see* **Chapter 160, Geriatric Day Hospitals**).

The levels and forms of OT services span from the needs of older adults living in the community to the

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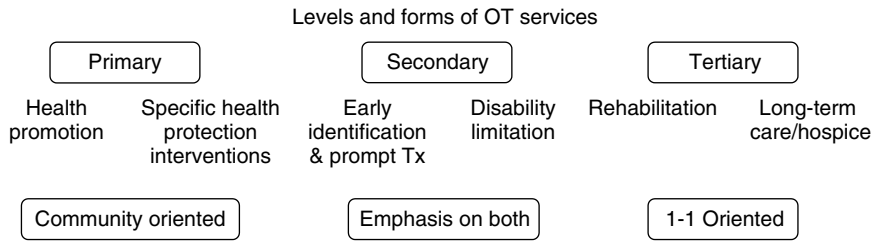

Figure 1 Continuum of geriatric occupational therapy (OT) services

- Retirement planning
- Employment/ reemployment
- Development of leisure activities
- Establishing/ reestablishing occupational (activity participation) balance
- Relationships
- Physical activity/ fitness/exercise
- Sexuality
- Spirituality
- Community service
- Use of technology

- Lifelong learning
- Product development
- Home design and accessibility
- Home management
- Home safety
- Shopping
- Use of public transportation
- Driving skills
- Energy conservation
- Joint protection
- ADL
- IADL
- Care management
- End of life activities

1. Compensatory activity approaches for:
   - Age-related changes including:
     - Presbyopia
     - Presbycusis
   - Tremors
   - Incoordination
   - Weakness
   - Low endurance
   - Arthritis
   - Joint replacements
   - Amputations
   - CVA
   - Spinal cord injuries
   - Traumatic brain injuries
   - Dementias, including Alzheimer's disease
   - Pain
   - Terminal illness
2. Family/carer/staff skills and coping

Figure 2 Geriatric occupational therapy services

needs of those experiencing end-of-life circumstances. Thus, primary, secondary, and/or tertiary settings are included in this continuum of OT services. Primary care OT interventions include provision of health promotion and health protection services within communities. Examples of this type of services include programs on home safety to prevent falls and other injuries and driving retraining as elders experience age-related changes in function. Secondary care OT interventions include individual, group, and/or community approaches for management of health conditions such as arthritis and Alzheimer's disease. Figure 2 displays the categories of services that OTs provide to older adults, their family members, and/or carers:

This topical list depicts typical OT services and is not completely exhaustive. Professional OT services are provided in a range of settings throughout the continuum of care, as shown in Figure 3:

OT services are coordinated with the providers of health care and other services, including physicians, nurses, physical therapists, speech therapists, social workers, community and public health agencies, and others, whenever indicated and available. When services are provided on an individual basis, family members and/or other available support systems often become an integral component of the OT service team, to ensure successful intervention outcomes (*see* **Chapter 152, Carers and the Role of the Family**).

CONCEPTUAL FOUNDATIONS OF GERIATRIC OCCUPATIONAL THERAPY

With a simultaneous focus upon intrinsic and extrinsic factors that impact elders' participation in necessary and meaningful activities, OT personnel work in partnership with the individual or organizational client to promote the enablement of the elders to pursue a meaningful quality of life at all levels of care.

Person–Environment–Occupation–Performance/ Participation

Occupational therapists assess the patient's/client's abilities and occupational performance (enactment of movement, tasks, activities, and routines). These occupational performance abilities relate to the activities (known as *occupations*) that are important to the older individual in the context of their daily lives and environment. OT

- Individual homes/apartments
- Senior centers
- Senior housing
- Retirement centers
- Naturally occurring retirement communities
- Elder continuum of care centers
- Learning centers
- Shopping centers
- Parishes, temples, and congregations
- Private practices
  - Home modification services
  - Care management
  - Lifestyle redesign programs
  - Reemployment services
  - Driving skills
- Local, regional, and/or national private or public agencies

- Acute care
- Sub acute care
- General medicine services
- Rehabilitation
- Adult day services
- Group homes
- Assisted living
- Intermediate care
- Skilled care
- Palliative care
- Hospice care

Figure 3 Geriatric occupational therapy service settings

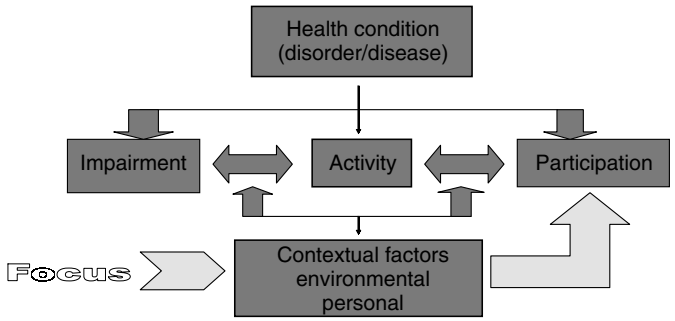

Figure 4 World Health Organization (WHO) International Classification of Function (ICF) model. (Adapted from Figure 1, International Classification of functioning, disability and health, World Health Organization, 2001)

interventions center on enabling elders to pursue the activities, tasks, habits, and routines that are personally important and meaningful to them. All of these activities and occupational components contribute to the elders' perception of their quality of life. Figures 4 and 5 compare the WHO ICF (World Health Organization International Classification of Function) model and the OT person–environment–occupation–performance/participation (PEOP) model (Christiansen *et al.*, 2005).

The WHO ICF is the currently accepted model for systematically grouping consequences associated with health conditions. Level of ability, function, and/or disablement is seen as a dynamic interaction between the individual's health condition and their personal environmental contextual factors. These intrinsic and extrinsic factors affect the individual's ability to pursue the needed and desired activities that comprise their lives and to participate in individual and

Figure 5 Person-environment-occupation-performance/participation (PEOP) model (Christiansen *et al.*, 2005) applied to geriatric OT practice (Copyright Slack, Inc.)

group societal functions. If impairment and contextual factors are incompatible, this set of circumstance in turn affects the individual's overall sense of well-being and personal perceptions of the quality of life (World Health Organization, 2001).

Likewise, the PEOP model depicts well-being and quality of life as a function of the relationship of the personal/intrinsic factors, the environmental/extrinsic factors, occupation/activity, and occupational performance/participation in activity and society (Christiansen *et al.*, 2005). These components are shown as being totally interdependent. Figure 5 and the following model express the *P-E-O-P* relationship:

$$Elder\ Quality\ of\ Life = f(Personal\ Attributes + Environmental\ Factors + Occupations + Participation)$$

Where "elder quality of life" is dependent upon and a function of the *person's* unique health status and functional abilities, plus the degree to which their *environment* supports the *occupations* that they need and want to pursue and allows them to *perform/participate* in society, to the extent they desire.

Person (Intrinsic Factors)

Occupational therapists assess and intervene to enable elders to cope with normal and inherent age-related changes known as *intrinsic factors*. These factors include physiological, cognitive, spiritual, neurobehavioral, and psychological components of human function. The older adult's level of motivation, as well as roles, habits, and routines that comprise her/his lifestyle are an integral part of occupational performance and quality of life. Hence, the capacity for a life-long homemaker to continue cooking and taking pride in her culinary creations may be compromised by diminishing olfactory and gustatory ability. In addition, the elders' individual beliefs about themselves, as well as their life experiences – past, current, and potential – impact their execution of self-maintenance, work, service, leisure, and other activities (*see* **Chapter 98, Geriatric Psychiatry**).

Environment (Extrinsic Factors)

Extrinsic, or environmental/contextual determinants of occupational performance, include social support, social and economic system, culture and values, technology and the built environment, as well as the natural environment (Christiansen *et al.*, 2005; Fougeyrollas, 1995). Typically, intrinsic age-related changes in vision, hearing, olfaction, vestibular functions, musculoskeletal and other systems may alter the individual's ability to cope with any or all of these extrinsic environmental factors. The elder's physical surroundings may not adequately support their performance of necessary and desired activities because of age-related changes that they experience. Thus, in order for elders to continue to live independently and participate as fully as possible, the inherent changes in sensory and other systems, as well as in cognition, may require changes in their physical environment and other external support systems.

Occupation

What we do consists of occupation(s). Occupations, better known as *activities*, including all abstract and observable types, comprise the everyday lives of people of all ages around the world (American Occupational Therapy Association, 2002). They also assist individuals in understanding who they are, as humans often define themselves by what they do. When young adults are asked, "What do you do?" they may respond by stating their role as student, the type of worker/vocation they pursue, or by their role as homemaker, or parent. When elders are asked the same question, they may respond differently, depending upon what is important to their sense of identity at this later point in life. Nevertheless, occupation/activity in all conceivable forms is the fabric of our existence.

Participation

Active involvement in daily life and various life situations comprise *participation*. This concept includes the ability to perform roles at home, work, and in the community. Various factors may hinder an individual's ability to function in one or more of these environments, due to lack of support, attitudes, physical, social, or societal barriers (Fougeyrollas, 1995; Whiteneck & Holicky, 2000). Through their life span individuals encounter different forms of access to participate in activities that are necessary and meaningful to them (Antonovsky, 1979, 1987; Frankl, 1963, 1997; World Health Organization, 2001). Elders may encounter limits to their participation due to decline in age-related or functional abilities, ageism, or policies that limit continuation of involvement in activities such as employment or driving (*see* **Chapter 13, Transportation, Driving, and Older Adults**).

OCCUPATIONAL THERAPY PROCESS

Assessment and Intervention

Wherever possible, an evidence-based assessment process is applied to the determination of what should be included in the OT intervention with elders, as shown in Figure 6.

In the standard practice in which OT personnel work with an individual older adult, a three phase process of assessment is followed and considered to be "best practice" (Dunn, 2000). The first assessment objective is to determine who has this individual been and what does the individual need and want to do, both in a short and long-term period. The second objective focuses on identifying where and how the

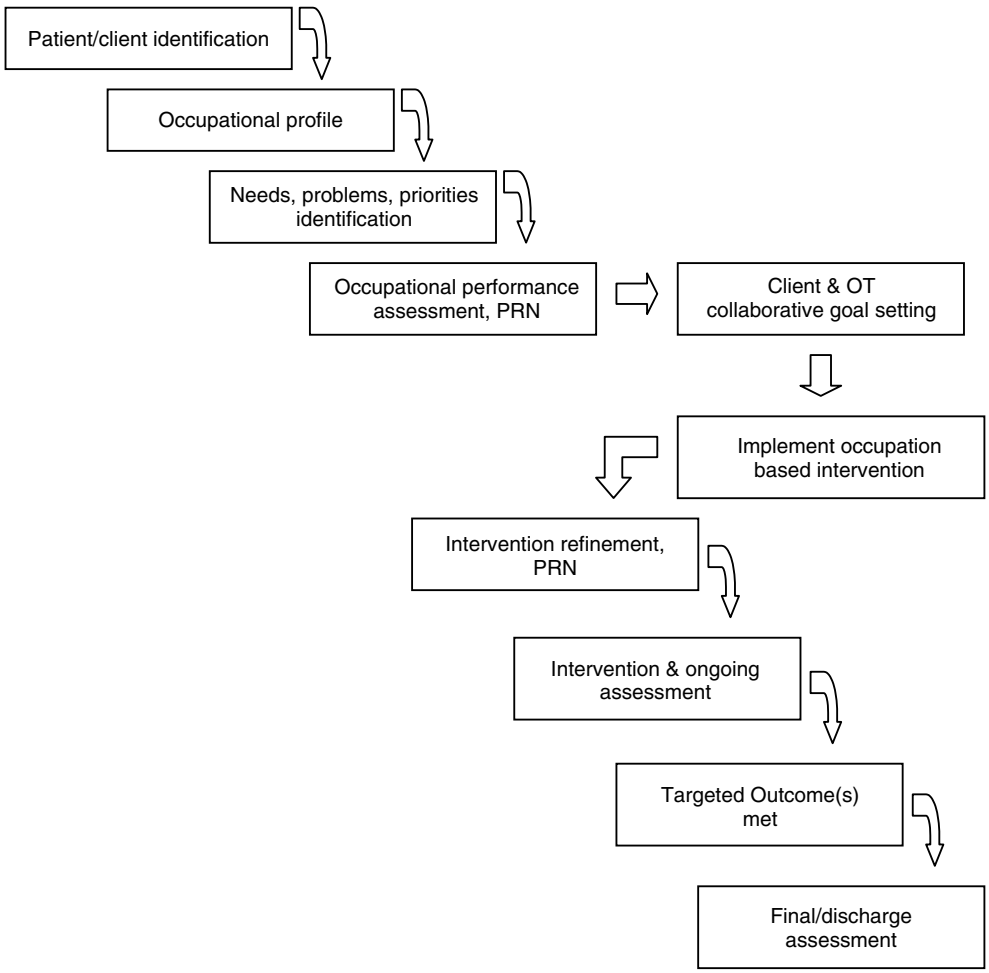

Figure 6 Geriatric occupational therapy assessment & intervention process

activities, tasks, routines, or other occupations can and/or should be done. The third area of concentration in assessment is to determine the biological, psychological, and/or social barriers to the elder's achievement of her/his desired activities. Other individuals or groups may also contribute to the compilation of information on occupational performance issues for the elderly (American Occupational Therapy Association, 2002; Christiansen *et al.*, 2005) (*see* **Chapter 19, Preventive Geriatrics**; **Chapter 57, Cardiac Rehabilitation in Older People**; **Chapter 170, Management of the Dying Patient**; **Chapter 131, Multidimensional Geriatric Assessment**; **Chapter 132, Function Assessment Scales**; **Chapter 153, Nursing Home Care**).

Occupational Profile

The initial step in the OT assessment process determines the client's occupational history and experiences, patterns of daily living, interests, values, and needs. The client's problems and concerns about performing daily and other relevant life activities are identified, the client's priorities are determined, and plans of care and/or management focus on these collaboratively determined priorities (Law *et al.*, 1997). The approach is top-down and client-centered, where enabling participation in personally and culturally relevant and meaningful activities is the focus of planning (Christiansen *et al.*, 2005; Kielhofner, 1995).

Occupational Performance Assessment

This step in the evaluation process specifically determines the client's biopsychosocial assets, needs, problems, or potential problems, based upon results of reliable and valid instruments. Preferably, performance of selected activities is observed in order to identify what supports and what hinders performance. Ideally the assessment process takes place in the elder's usual environment, typically at home, since performance in an unfamiliar environment may be different. Performance skills, performance patterns, context or contexts, activity demands, and client factors are all considered, but only aspects that are specifically relevant to the desired activities may be assessed. Targeted outcomes are identified, based upon the elder's expressed interests and needs.

An OT assessment of the client's occupational performance takes into consideration all pertinent individual and environmental factors. These factors may include the individual's age, gender, socioeconomic background and current status, racial/ethnic and/or religious background, developmental status, health history and current status, and educational and vocational histories. Interviewing the patient/client and/or the family whenever feasible is combined with standardized and agency-based performance assessments to determine the individual's profile from which to plan the individualized intervention plan (Birren *et al.*, 1991; Steiner *et al.*, 1996; Stewart & Ware, 1992). Inquiry covers the following areas:

1. What roles, routines, habits, and/or new activities does the patient/client *want to perform (elder priorities)*?
2. What may be done to facilitate the patient/client in the range of activities that she/he *does perform (current activities)*?
3. What is the patient/client currently *able to perform (intrinsic ability)*?

The environment, scope of activities/occupations, and roles in which elders typically engage in are shown in Figure 7. The knowledge of the context, activities, and those that comprise the roles that the elder assumes assists OT personnel in collaborative assessment and intervention with elderly clients, their carers, families, and other support systems.

Where multiple environmental dimensions serve as barriers to participation and impact the well-being of older adults, OT practitioners collaborate with other disciplines in evaluating the individual's circumstances and planning appropriate interprofessional interventions. On an independent basis, OT personnel frequently evaluate facilities or the elder's home, in order to facilitate the *PEOP* compatibility. These evaluations compare the elder's activity needs and priorities with their functional abilities and the physical environment in which they function, in order to determine and predict the likelihood of their success in being able to perform their necessary and desired activities. These activities are then targeted in the intervention plan.

OT is concerned with how elders perform in their daily lives and how performance affects their engagement in occupations. These occupations typically are components of performance that support their participation in the habits, routines, and roles that provide meaning to their lives. Thus, the evaluation process determines what the patient/client needs and wants to do, what are their functional capabilities, and what are the barriers or supports to performing those priority occupations American Occupational Therapy Association (2002).

When interventions are indicated, due to a poor *PEOP* fit, OT personnel work with the elder and family or other support systems to improve these factors. Recommendations may include specific changes to the physical environment, compensatory changes in their routines and activities, and/or assistive equipment to enable successful occupational performance. These needs are often overlooked completely or underestimated when the individual is being discharged from

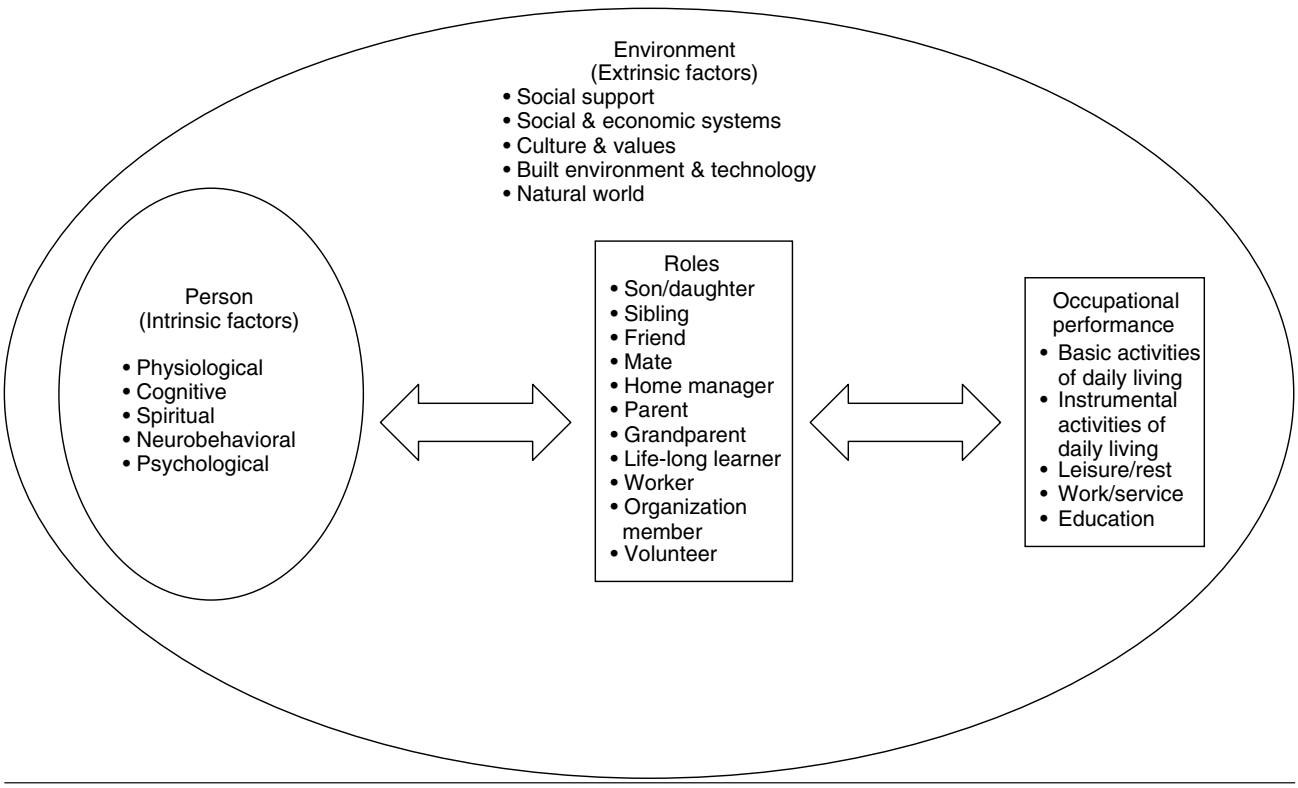

Figure 7 Geriatric occupational therapy assessment & intervention components

one level of medical care to another or to their home. When this insight is lacking, the gaps in environmental support may put the older adult at increased risk for dependency, as well as falls and other injuries (*see* **Chapter 18, Smart Homes**; **Chapter 100, Depression in Late Life: Etiology, Diagnosis and Treatment**; **Chapter 112, Gait, Balance, and Falls**).

Case 1: An 86-year-old Caucasian woman, Grace, was admitted to a local acute-care hospital following a right hip fracture sustained when she fell from a chair while trying to change a light bulb. She was scheduled for a hip replacement.

OT Intervention: During her hospitalization, OT personnel met Grace and completed an occupational profile that informed the therapist about this elderly woman – in particular, her lifestyle, and the activities that she needed and wanted to do. She was provided with a long-handled reaching device to enable her to more easily reach items in her hospital room and at home, once she was discharged. The OT learned that Grace enjoyed knitting and recommended that her daughter bring her mother's current knitting project to the hospital during her stay. Knowing that her right hip mobility would likely be limited for the weeks during her recovery from the hip replacement surgery, the OT worked with Grace on donning her socks, using a sock-aid, and continually reinforcing postsurgical hip precautions. During her hospital stay and immediately prior to discharge, the OT reviewed all activities of daily living (ADL) and instrumental activities of daily living (IADL) implications, as well as other high priority activities that Grace identified during her initial occupational profile. Grace agreed to have the OT arrange for her to have an elevated toilet seat, a tall shower stool, a handheld shower, and grab bars for her home toilet and shower areas for her use following discharge from the hospital. Additional recommendations were made regarding the height of the furniture that Grace would use at home for sitting, eating, and knitting. Grace's daughter agreed to obtain extensions for the legs of Grace's favorite easy chair, so that she would be able to sit and rise from the chair easily. At the time of discharge, Grace's daughter stated that she felt that her mother was well prepared to manage at home during the remainder of her recovery, and most important. . .. Grace agreed.

Case 2: A 65-year-old African man, Kwesi, who completed initial acute-care and rehabilitation treatment for a cerebral vascular accident (CVA) with left side hemiparesis and mild expressive aphasia was referred for continued OT upon discharge to his home. His wife and the OT collaborated with Kwesi in determining the priorities of his current activities and target goals. At this point, he was dependent upon his wife for assistance with toileting, bathing, and dressing, and was not performing IADL tasks that he had assumed prior to his CVA. These activities, plus rejoining his men's group were very important to him. Therefore, over the next several weeks his OT worked with him to upgrade his independence. Since organizing and sequencing the steps within those activities was still difficult, the OT provided him and his wife with strategies to enable him to relearn the steps that were problematic. The OT also worked with his wife to help her realize more success and improved coping with her husband's condition, as well as having more time for the activities that were important to her. Throughout this process the OT coordinated the intervention plan with Kwesi's physician and other health-care providers.

Intervention

Development of the Intervention Plan

OT personnel individually tailor the interventions to the patient/client's needs in order to promote optimal outcomes. The intervention plan is thus developed collaboratively with the patient, so that appropriate strategies, specific interventions, and targeted outcomes are included and mutually agreed upon. Therefore, the approach utilized to increase functional level in ADL, IADL, as well as self-esteem, socialization, and a sense of personal competence in whatever is pursued is unique to each patient/client.

Intervention Implementation Via Client-centered Care

Utilizing goal-directed activities that are meaningful to the patient/client, OT assists the individual to adapt to the physical and social environment. This approach promotes mastery of essential living skills, as well as those skills that represent the patient/client's other priority interests. As a group, elders exemplify highly diverse lifestyles and interests. Therefore, OT personnel identify modalities and activities that are motivating to the patient because they are relevant to her/his particular lifestyle. Collaboration with the patient/client, known as *client-centered care*, facilitates and enables the mobilization of the individual's internal psychological resources. This process then promotes greater participation in the intervention, which in turn, optimally assists in restoring or enhancing function where functional change or decline has occurred or is threatened. All interventions are continually documented, monitored, reevaluated, and adapted or discontinued, based upon the client's overall status.

OT interventions may include any or all of the following:

Use of Occupation to Enhance Quality of Life

1. *Health promotion*: Most individual's lives are comprised of a variety of self-maintenance, productive, leisure, and/or service activities. Thus OT personnel utilize occupations (activities), tasks, roles, routines, and/or habits, as therapeutic agents in achieving long- and short-term goals toward adaptation and habilitation, restoration of function, and/or enhancing the individual's quality of life. Many health promotion programs are provided in the community, however, OT personnel integrate health promotion perspectives in services throughout the continuum of care (Hay *et al.*, 2002; Rothman & Levine, 1992) (refer to Figures 1 and 3).

End of Life: The latter applies also to OT's promotion of quality of life and independence in daily occupations with terminally ill patients, to the extent possible for as long as possible. OT also facilitates maintenance of ADL, pain management, joy, life review, and other meaningful closure activities at the end of life by assisting the elder and their family members to participate in meaningful activities with terminally ill individuals (*see* **Chapter 170, Management of the Dying Patient**).

2. *Community level instruction and patient/client education*: In community settings, OT personnel provide health promotion and other training programs for the elders, family members, carers, and agency employees (Hay *et al.*, 2002; Rothman & Levine, 1992). The content is tailored to the needs of the target group, just as when interventions are implemented for individuals. Subjects covered include those identified or related to those given in Figures 2 and 7.

In acute or subacute care, rehabilitation, and home health care, collaborating with the older patient/client in basic skills training or retraining in functional occupations (e.g. ADL and/or IADL) are standard components of OT practice. Interventions may also focus on making positive transitions in overall lifestyle based on physical, emotional, and/or retirement and service needs of elders (Clark *et al.*, 1997, 2001). Furthermore, the OT personnel collaborate, wherever indicated, with other health-care providers in the rehabilitation team, as well as community agencies to promote optimal patient/client outcomes (Mullins *et al.*, 1997; Reilly, 2001).

Since older adults and their support systems may not be aware of age-related physiological and psychological changes, OT may also employ education or training in these areas to facilitate adaptation to deterioration of function and adjustments in relationships. Topics may include the use of compensatory strategies, recommendations for equipment, and other methods to compensate for loss in function and ensure the ability to participate in meaningful occupations. Health promotion teaching strategies may include the following (Hay *et al.*, 2002):

- prevention of physical deterioration through the use of age-appropriate approaches for participation in activities:
  - body mechanics
  - joint protection
  - energy conservation
  - activity and exercise guidelines
- prevention of psychosocial deterioration through the use of occupation:
  - adjustment of lifestyles to accommodate age-related, role, and other changes in life
  - the role of purposeful, balanced activities in maintaining health
  - overall time management
  - self-esteem, empowerment, mastery strategies
  - interpersonal skills and socialization activities
  - an emphasis on positive aspects of living in promoting a healthy lifestyle.

3. *Remediation strategies for functional decline*: OT interventions to compensate for sensorimotor occupational performance deficits focuses on enabling the elder to participate in the activities identified for maintenance of function and/or improvement. These activities include sitting and standing balance, strengthening, endurance, range of motion, and coordination. Therapeutic approaches employed in all of these occupational performance skills areas are related in the intervention process to ADL and IADL participation, including related tasks and roles performed by and meaningful to the individual.

Furthermore, comorbidities that the older adult experiences are simultaneously factored into the intervention approaches. Interventions are individualized to accommodate cognitive, behavioral, and affective changes that occur following a stroke and/or other neurological conditions, as in dementias or Parkinson's disease. When oral-motor dysfunction, muscular rigidity, joint pain, bradykinesia, or other symptoms impede direct intervention, OT practitioners utilize facilitatory techniques and positioning approaches. These interventions focus on enabling the elder to participate in functional, meaningful activities that accomplish the desired mobilization and overall rehabilitation goals. OT personnel also develop therapeutic programs in a wide variety of settings, which are shown in Figure 3.

4. *Physical environment adaptations*: Because of normal age-related changes, OT consultation and implementation of specific environmental adaptations and modifications may be indicated for most elders, in order to facilitate their continued participation in the activities that are important to them. Where individual or comorbid conditions limit participation, personally relevant physical environmental modifications may be recommended. Additional railings, ramps, grab bars, and assistive devices may be indicated, in order to promote accessibility and independence in mobility and the ability to pursue the elder's necessary and desired occupations. OT interventions also include methods to compensate for cognitive, memory, and psychological changes. These compensatory accommodations that can be implemented in existing or new facilities may make the difference between the elders' dependence and their meaningful participation. OT personnel also provide suggestions for environmental adaptations relative to therapeutic programming and activities for persons with dementia, including cognitive integration, orientation, memory, safety, and pursuit of meaningful activities.

5. *Technological aids and devices*: Low- as well as high-technological assistive devices may be recommended to enhance the elder's occupational performance and participation in solitary, group, or community activities. Low vision aids as well as assistive devices for hearing loss are examples of equipment that may be recommended for use if sensory deficits result in occupational performance deficits. OT personnel often recommend assistive devices for individuals who demonstrate limitations in sensorimotor function, range of motion, strength, coordination, and endurance. Different

types of assistive devices may be suggested for persons who demonstrate occupational performance deficits in their cognitive abilities. Overall, devices are recommended only if they support improved participation in the activities that are important to the elder and/or her/his family or other support system.

Intervention Review

As noted earlier and depicted in Figure 6, OT interventions are continually reviewed and refined, as indicated. Periodic reassessment of the client's status, including ongoing inputs from the elder and/or her/his carers, family members, and other support systems are integrated into any alterations in the intervention plan. When the targeted outcomes are met or it is determined that the elder may not be able to achieve the outcomes despite refinement of the intervention plan, the elder undergoes a final assessment process and is discharged or discontinued from OT services.

Outcomes (Engagement in Activity to Support Participation)

Outcomes – Outcome assessment information determines the extent to which the targeted goals and objectives of the intervention were met. This information is used to plan future actions with the client, discontinuation of services, and to evaluate the service program.

CONCLUSION

OT focuses on the elder's participation in the activities that comprise their lives and that are important to them. The aims of interventions are to (1) collaborate with the older adult to plan client-centered care, (2) tailor the approaches to meet the elderly patient's/ client's activity needs, and (3) address the elder's continued participation in society in a manner that is appropriate and meaningful to that individual, thus affecting her/his overall well-being and quality of life. Fundamental concerns of OT practitioners include supporting the elder's autonomy in setting priorities and making decisions regarding her/his participation and maintaining a level of mastery and control over her/his environment and lifestyle. OT personnel foster an enabling therapeutic relationship with older adults of all ability levels throughout the continuum of care. The emphasis of OT on the elder's ability to participate in meaningful occupations promotes cost-effective care, individual competence, and optimal quality of life (Clark *et al.*, 1997, 2001).

KEY POINTS

- Humans throughout their lives are *occupational beings*. Thus, *who we are* is typically framed by *what we do.* OT is patient/client centered, collaborative, and focuses on what the individual *needs* and *wants to do*.
- OT services aim to sustain or improve the elders' ability to perform necessary and meaningful activities (*occupations)*, whether they are long term and historically a part of the elder's life or newly acquired interests and roles.
- OT identifies the strengths and priorities of the patient/client and partners with the individual and their family members or other support systems to ensure their participation in the occupations that sustain their overall health and quality of life.
- OT interventions focus on supporting age-related changes and/or comorbidities that affect the elder's ability to participate in desired activities/occupations. Interventions thus target the individual's biopsychosocial occupational performance abilities and often include adaptive approaches and assistive devices that compensate for any existing occupational performance deficits.
- OT services are provided throughout the continuum of care, from primary care health promotion and wellness approaches to interventions in tertiary, long-term care, and hospice settings.

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Systems of Health Care: the United Kingdom, the United States, and Australia

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INTRODUCTION

The extraordinary growth in life expectancy at birth in nearly all countries of the world reflects an ongoing revolution in longevity. This revolution encompasses both survival of individuals to older ages and changing age profiles of the entire population. The impact of the longevity revolution has been pervasive and profound. The demographic trend of an increased life expectancy has already changed the age profile of many countries and is continuing to be felt throughout the world. This trend has resulted in significant health-care changes, both on an individual and at societal level.

Developed nations across the world have approached the aging population and need for expanded health services in a variety of ways. Home health, hospital-based, and nursing home care have experienced a profound increase in complexity over the last quarter century. This complexity of care is reflected in the expansion of funding arrangements, number of service providers, and geographic service areas. Governments have expanded health care spending and broadened the scope of medical care. The development of health insurance programs has allowed a greater number of individuals to access medical services.

Institutes of higher learning have evolved to support the growing fields of gerontology and geriatric medicine. Educating the medical providers, workforce, and community on the needs of older adults has become an area of profound interest within and outside of the academic environment. It is important to draw older people into the processes of developing the services and new technologies that they themselves and others of their generation will use. By developing these new health-care opportunities, the greatest gains may be made in health, independence, and quality of life in old age.

OVERVIEW OF HEALTH-CARE DEMOGRAPHICS

United Kingdom

In the last 30 years, the population of the United Kingdom (UK) has grown 6.5% from 55.9 million in 1971 to 59.6 million in 2003. This population growth has occurred substantially more in the older age-groups. The percentage of people over age 65 has increased from 13% in 1971 to 16% in 2003, whereas the proportion younger than age 16 has dropped over the past 30 years. Projections for 2031 predict an increasingly rapid aging of the population with those over age 85 doubling from 1.9 to 3.8% of the UK population (Office for National Statistics, 2004).

Health-care spending in the United Kingdom has grown more quickly than other economic expenditures, reaching 7.7% of the gross domestic product (GDP) in 2002. Government, household, and charitable health-care costs reached £80.6 billion in 2002, compared with £74.8 billion the previous year (Office for National Statistics, 2003). Public health expenditures increased by £5.1 billion (8%) in 2002 compared with £700 million (5%) in private health expenditures. Despite a more rapid rate of growth, the proportion of publicly funded health expenditures has remained unchanged at 83%.

All individuals residing in United Kingdom are entitled to receive treatment from the National Health Service (NHS), which is free at the point of delivery. The NHS, established in 1948, is the third largest employer in the world after Chinese Army and Indian Railways respectively. Dr Tom Wilson was appointed the first consultant geriatrician in 1948 at Cornwall, which marked the introduction of this new medical speciality.

Principles and Practice of Geriatric Medicine, 4th Edition. Edited by M.S. John Pathy, Alan J. Sinclair and John E. Morley.
 ISBN: 0-470-09055-3

By late 2002, there were 1037 consultant geriatricians in United Kingdom, representing one consultant per 55 000 UK residents (Working Party Report, 2005). The British Geriatric Society (BGS) has recommended a ratio of one geriatrician per 50 000 of the population (one geriatrician for each 4000 people over age 75). This ratio does not include the increasing involvement of geriatricians in unselected acute medicine activities. In 2002, 88.6% of consultant geriatricians engaged in acute medicine compared with 30% in 1995. Geriatrics is currently the largest speciality under the Royal College of Physicians.

United States

The United States (US) spends 13% of the GDP, 1.8 trillion dollars, on health-care expenditures. This is more than any other industrialized nation (American Hospital Association and the National Chronic Care Consortium, 2002). Health-care expenditures have doubled in the past 10 years; however, 15% of population does not have health insurance. The provision of health care is equally split between private insurance, governmental programs (medicare/medicaid), and private or out-of-pocket payers.

The number of hospitals and length of hospital admission have dropped consistently since peaking in the early 1970s. Outpatient encounters have tripled since that time (American Hospital Association, 2004). Despite this trend, hospital expenditures have risen 60% in the last 10 years. About one-third of health-care resources are spent on hospitalization and one-quarter on physician services. Individuals, aged 65 or older, utilize one-quarter of outpatient encounters, half of hospitalization days, and one-third of the total health-care expenditures.

Currently 13% of the US population is age 65 or older. This population is projected to reach 20% by 2040 (U.S. Census Bureau, 2005). These trends have caused great concerns both economically and socially. The health-care budget cannot sustain the current growth rate of medical expenditures. Methods to provide cost-effective, quality health care for an aging population are being addressed on a system-wide level. Research funding, educational efforts, and clinical care models are being developed to better serve the health-care needs of the geriatric population.

Australia

Australia has an aging population comparable to most developed countries. In 2001, 13% of the 20 million residents were age 65 and over. With a life expectancy of 76.7 for males and 82.0 for females, it is estimated that one-quarter of the Australian population will be over age 65 by the year 2051. At that time, the projected life expectancy will be 83.3 for males and 86.5 for females. In this population, dementia is the leading cause of disease burden by a factor of two. Dementia accounts for 16.7% of years of life lost to disability. Currently, over 160 000 Australians have dementia and this rate is predicted to increase over 250% by 2041. While vascular disease and cancer remain the two leading causes of death, mortality rates from these diseases in older people have decreased markedly over the last decade.

While the health of the Australian population has generally been improving, the health of indigenous people, the Aborigines and Torres Strait Islanders (ATSI) has not improved at the same rate. These groups suffer death rates of two to three times that of the general population. The leading causes of death in these individuals remain vascular disease, respiratory illness, injury, and cancer. While aged care services for most Australians are targeted toward the population over age 70, for ATSI people these same services are provided for those over age 50.

Australia spent 9.5% of the GDP on health care in 2002 (AUD $72.2 billion). Although health spending has grown as the population has aged, this is mainly attributed to spending on new technology and pharmaceuticals, rather than on the increasing number of older individuals. The percentage of GDP spent on health care is lower than the US, comparable to Canada and European countries, but higher than the UK. The Australian health system is tortuous in its complexity, particularly for the consumer. The services and care for older adults have been particularly complicated.

DEVELOPMENT OF GERIATRIC MEDICINE

United Kingdom

For various historical reasons, specialist geriatric services developed as an integral part of the NHS in the United Kingdom earlier than in any other area of Europe. Margery Warren established geriatric medicine in Britain in the late 1930s. Her message was the need for assessment and rehabilitation of elderly disabled people, education of medical students, and research into the problems of aging and old age (Warren, 1943, 1946). This derived from her work in the workhouse infirmary associated with the West Middlesex Hospital in London. Her methods (careful medical and social assessment, medical treatment, and rehabilitation) were described in a series of publications (Warren, 1943, 1946, 1949). The general conclusion was that elderly patients should be treated in a special block in general hospitals because

- geriatrics is an important subject for the teaching of medical students;
- geriatrics should be an essential part of the training of student nurses;
- general hospital facilities are necessary for correct diagnosis and treatment;
- research on diseases of aging can only be undertaken with the full facilities of a general hospital.

These were visionary proposals in 1943.

The emerging recognition of the needs of older people in an aging society led to a number of major surveys and resulted in the collection of planning data for the introduction of new health-care services. Curran and colleagues (1946) published data on about 1000 males over age 65 and females over age 60 and who lived in poorer areas of Glasgow, all of whom received home visits. A social and medical survey of people in England over age 65 was also performed by the Nuffield Foundation in 1943. The results were published in two reports – "Old People" (1947) and the "Social Medicine of Old Age" (1948) (Nuffield Foundation, 1947; Sheldon, 1948). The British Medical Association (BMA) set up a working group in 1947 to review care of the elderly and infirm and to make general health-care recommendations (British Medical Association, 1947). Of the 21 BMA members, four were active in the new speciality of geriatrics (Amulree, Brooke, Cousin, Warren).

Dr Trevor Howell, originally a general practitioner (GP), became interested in elderly medicine after becoming responsible for Chelsea pensioners. He was appointed consultant physician at Battersea and subsequently opened one of the first geriatric units there (Adams, 1975; Irvine, 1986–1987; Howell, 1974). In 1947, he called a meeting to bring together physicians who had a special interest in older people and skills in rehabilitation, incontinence management, and domiciliary assessment.

This meeting launched the Medical Society for the Care of the Elderly. These pioneering physicians persuaded the Minister of Health to appoint more geriatricians as part of the hospital consultant expansion of the new NHS. The society was renamed the British Geriatrics Society in 1959 to emphasize the scientific basis of elderly medicine. The efforts of this society resulted in a revolution in the delivery of health care and services for the elderly.

During the 1960s and 1970s, remarkable improvements occurred in the medical care of patients who were managed on geriatric units. There was a rapid increase in the number of consultant geriatrician appointments in the 1960s from a total of four geriatricians in 1947, to over 300 by 1973. The NHS has recognized the value of geriatrics as an emerging speciality, and has invested significant time and resources to improve services and standards of care for older people.

During the 1980s and much of 1990s, the trend in United Kingdom was for geriatric practice to become more closely identified with acute general internal medicine and to be less involved with rehabilitation and long-term care. The improved access to acute diagnostic facilities for older people was welcomed. The rise in consumerism and desire for choice, have resulted in the public having a higher expectation of all services. Inadequacies and inequalities in the health care of older people have had a major influence on current heath policy.

A campaign started by a national newspaper and an older people's charity (Help the Aged) led the government to commission an independent inquiry into the care of older people. As a result of the finding, a National Service Framework (NSF) containing standards of care for older people was published on 27 March 2001 in order to apply to the NHS for implementation.

Through the NHS, the NSF for older people has been developed with guidance from an External Reference Group (ERG), cochaired by Dr Ian Philp (now the National Director of Older People's Services) and Ms. Denise Platt, Chief Inspector of the Social Services Inspectorate. The ERG brought together older people and their caregivers, health and social services professional staff, NHS and social services managers, and partner agencies.

The frameworks are designed to improve the quality of health care by setting standards for the structure, process, and intended outcomes of key medical conditions. These frameworks establish minimum practice standards and eliminate unacceptable care patterns. The NSF is a 10-year health-care improvement program implemented through local health and social care partners, and national underpinning programs. Progress is monitored through a series of milestones and performance measures, and is overseen by the NHS Modernization Board and the Older People's Services.

Using the NSF targets, the NHS and social care services treat older people as individuals and enable them to make choices about their own care. The NSF for older people is different from its predecessors (NSFs for cancer care, mental health, and coronary heart disease) in that it focuses on a population rather than on a set of conditions. The focus is larger and more complex, as older people consume about 50% of health and social care expenditures. This is the first framework to establish standards for social as well as health care (Philp, 2002). The NSF has established new national standards, service models, and social services for all older people, whether they live at home, in residential care or in hospital. This is achieved through the single assessment process, integrated commissioning arrangements, and integrated provision of services.

United States

In the United States, geriatrics came into the medical consciousness through the writings of Dr Ignatz Nascher. Although born in Austria, he was raised in the United States and received his medical degree from New York University. In 1909 at the age of 46, Dr Nascher published his first article on geriatrics titled *Longevity and Rejuvenescence*. In this work, he proposes that "geriatrics" be added to the medical vocabulary and that it be considered a distinct aspect in medicine. Over the next 5 years, he authored more than 30 articles on aging and the first American geriatrics textbook titled *Geriatrics: The Diseases of Old Age and Their Treatment*. This text focused dually on the physiology and pathophysiology of aging. Nascher touched on a multitude of topics including organ system physiology, pharmacology, diseases of aging, and psychosocial aspects of medicine. With an optimistic view, he wrote in 1926 that, "Geriatrics is now firmly established as a special branch of medicine. . ."

Unfortunately, geriatrics was not yet widely accepted and the growth of this speciality was quite slow through the 1930s

and 1940s. The mid-1900s were notable for the establishment of two medical societies. Malford W. Thewlis founded the American Geriatrics Society in 1942, and the Gerontological Society (now called The Gerontological Society of America) was established in 1945.

Research in aging was championed by Dr E. Vincent Cowdry who received his Ph.D. in anatomy from the University of Chicago in 1913. During his 65-year career spent predominantly at Washington University School of Medicine, Dr Cowdry focused his research efforts on cancer and the cytologic changes of aging. During the later half of his career he authored several books including *The Problems of Ageing: Biological and Medical Aspects* (1939), *The Care of the Geriatric Patient* (1958), and *Aging Better* (1972).

Geriatrics in the United States developed as much through the establishment of governmental socioeconomic programs as it did from the work of prominent physicians. In 1861, a military pension plan was established to support the civil war era veterans. After the civil war, many states established veterans homes to provide disability and medical care services. These services were consolidated through the development of the veterans administration in 1930. By 1935, a rapidly increasing population of impoverished older adults led to the formation the Social Security Board which reorganized in 1946 to become the Social Security Administration. This program provides a retirement benefit to individuals upon leaving the workforce. Although state and federal subsidies for health-care services were sporadically available in the 1920s, the first private hospital insurance plan (Blue Cross) was not provided until 1933. Further discussion and development of government sponsored health insurance for the elderly spanned five presidential administrations and over three decades.

In 1950, through efforts by President Truman, the Federal Security Administration held a national conference on aging to assess the challenges posed by the changing population. No immediate programs were initiated, but this conference spurred the development of an advisory committee on aging and eventually led to the first White House Conference on Aging in 1961. The conference resulted in the expansion of social security benefits and support for the later development of medicare and medicaid. In 1965, insurance was finally guaranteed to older adults, the disabled, and the impoverished through the passage of medicare and medicaid programs.

During the mid-1900s, the US government was the primary financial sponsor of health-care research and scientific programs. The National Institute of Health (NIH) was formed in 1930 and later became a consortium of institutes and centers dedicated to health-care research. The National Institute on Aging (NIA) was formally established out of the NIH in 1974, but the roots of the NIA can be traced back to the 1940s and 1950s with the unit on aging, gerontology branch, and a section on aging as subsections of NIH programs.

The NIA receives substantial funding for the advancement of aging research. Through NIA support, the 32 Alzheimer's Disease Centers, 9 Claude D. Pepper Older American Independence Centers, and numerous Edward R. Roybal Centers for Research on Applied Gerontology sponsor investigations into the biological, behavioral, and clinical aspects of aging. During the last quarter century, there has been a growth in the private support of geriatric medicine research and education. Hundreds of millions of dollars have been provided by The John A. Hartford, Donald W. Reynolds, and other agencies dedicated to the care of the aging population.

Australia

The speciality of geriatric medicine in Australia is generally considered to have started in 1950 when the Hospital Commission of New South Wales (NSW) requested the Royal Newcastle Hospital to survey the known people with multiple sclerosis in the Hunter Valley, with a view to setting up a hospital clinic for those patients. Dr Richard Gibson and Miss Grace Parbery, a social worker, were appointed to conduct the survey and identified the need for medical, nursing, and domestic care at home for the chronic sick in general. It took another 5 years to institute these outreach services and subsequently hospital rehabilitation services as well. Rudimentary services started soon after in other states but the independent origins led to different patterns of development.

Australia was founded in 1901 as a federation of six states each of which had slightly different history and health system. Each state government retained control of existing health services, mainly hospitals. Over the years, the growth of national government taxation revenue has resulted in the introduction of new health-care programs, mainly nonhospital services. Many of these services were developed in response to genuine health-care deficiencies but as a result, Australia has a dually administered health system through a partnership of the national and state governments. The Australian national government generally retains primary control over the newly established health-care services or programs. The national government pays for community health, nursing home, and visits to doctors offices, but the level of control over these programs varies.

The Australian government pays for visits to doctors under the medicare scheme of universal health insurance. Medicare is partially funded by a 1.5% levy on income tax and a 1% surcharge from those earning at least AUD $50 000. Additional revenue for the physician may be generated from the patients, who are responsible for paying when the physician decides to charge an extra fee. Medicare reimburses physicians 85% of the established *Schedule Fee*, an amount derived from a survey of fees in the early 1970s. The schedule fee has been underadjusted for inflation over time, with a resulting 30% drop in reimbursement rates. This has prompted some physicians to pass on increasing copayment fees to their patients. At this time, the percentage of GP consultations entirely paid for by medicare has declined to about 70%.

Most medical care for older people is administered by GPs. Medicare disproportionately rewards GPs for shorter office-based consultations, which favors younger, single problem patients. General practice has also seen a shift toward

corporatization, where companies employ GPs in multidoctor practices and generally discourage nonoffice work. These trends have resulted in a decrease in the number of GPs who perform home or nursing home visits. In 1999 a range of longer, better-remunerated consultations were introduced to encourage adequate consultations with frail, older people, including annual health assessments, multidisciplinary care planning, and case conferencing. These have recently been augmented to also cover residential aged care; however, these measures have not been adequately assessed to determine whether they provide any benefit.

The Australian government under the Pharmaceutical Benefits Scheme (PBS) pays for medications with some copayments charged to patients. Rapid increases in the cost of the PBS of around 15% per year have led to a variety of measures to decrease costs. One method is to limit the number of new drugs coming onto the PBS. Patients have also been required to pay the full cost of many new drugs. In other situations, drug companies will negotiate to cap payments for a new pharmaceutical agent on the basis of the projected medication expenditures for that agent.

Geriatric medicine is a relatively new, but growing speciality. A survey of all specialist consultant physicians found that there were 185 practicing geriatricians in 2003. One-third also practice general medicine. This provides Australia with approximately one geriatrician per 5900 people aged 75 and over (Dent, 2004; Australian Medical Workforce Advisory Committee, 1997). Because geriatric medicine attracts a higher proportion of female specialists in Australia, and over a lifetime, females work approximately 75% of the hours of male graduates, access to geriatricians is more limited than what is actually calculated. The demand for geriatricians is increasing, but not currently met by the supply of trainees. The profession, health-care industry and the government continue to grapple with this problem.

HOME HEALTH CARE

United Kingdom

The practice of seeing patients in their own homes has been an essential component of geriatric practice since its early stages when consultants inherited large panels of patients with long waiting lists. Home visits are usually ordered by a GP via a referral to the geriatric consultant who carries out the visit. Within the NHS, house calls are part of the consultant's contracts and are called *domiciliary assessment visits*. Nurses, therapists, and other health providers are also important members of the home care team.

The NSF has established numerous standards of care for older adults that relate to home health care (HHC): fall prevention, mental health evaluation, and health promotion. These standards can be incorporated into a multidisciplinary care plan or addressed by an individual medical provider in the home. Through the Health Act 1999, the National HealthCare Corp (NHC) has been establishing new partnerships to allow health authorities to improve HHC and social services. Local strategic partnerships have been formed between the public, private, and community sectors to provide a single and uniform framework through which the NSF mission can be achieved. Through these partnerships, community equipment services will be modernized, integrated home care services will be expanded, and higher standards of quality will be set for the residential care of older adults. Research on the impact of the continuity of care process on patient outcomes is being conducted through the NSF.

Health-care Standard: Falls

The aim of this standard is to reduce the number of falls that result in serious injury and to ensure effective treatment and rehabilitation for those who have fallen. The NHS, working in partnership with health-care councils, takes action to prevent falls and reduce resultant fractures or other injuries in the older population. Older individuals who have fallen receive effective treatment and rehabilitation and, with their caregivers, receive advice on prevention through a specialized falls service.

Some health care trusts and councils are already making significant progress toward the 2005 milestone of an integrated falls service. Although overall progress with integrated falls services has been heterogeneous, there has been considerable growth in certain individual components. For example, a recent Help the Aged survey of 94 primary care trusts found that, although only a few were on their way to an integrated service, most were in the process of developing falls prevention programs.

There are a number of important collaborations in place to promote the falls prevention program. The Healthy Living collaborative focuses on falls services, while other organizations are involved in falls program partnerships. In these areas, organizations and older people have come together to make small but effective changes in health-care delivery to prevent falls and improve services for those who have fallen.

The National Institute for Clinical Excellence has produced guidelines on falls prevention in 2004 and has been asked to produce osteoporosis prevention guidelines by 2005. The institute is also undertaking an appraisal on osteoporosis drug treatments. These guidelines and the appraisal will be very significant in the development of falls services.

Health-care Standard – Mental Health in Older People

The aim of this standard is to promote good mental health in older people and to treat and support those older people with dementia and depression. Older people who have mental health problems have access to integrated mental health services. The NHS and health-care councils ensure effective diagnosis, treatment, and support for patients and their caregivers. About 5% of the population over age 65 has dementia and about 10–15% of the population over age 65 has depression. This represents a large numbers of

individuals who need high quality treatment and support to maximize their quality of life. Improving mental health services is a significant target area for the NSF. It is hoped that the widespread introduction of the single assessment process will result in earlier detection of dementia and depression.

Underdetection of mental illness in older adults is widespread, in part due to the nature of depressive symptoms and the fact that many older people live alone. Older people from minority and ethnic populations are at high risk of being underdiagnosed and undertreated for mental illnesses. Mental health services should be community-oriented, comprehensive, accessible, and individualized. Primary care groups and trusts should take responsibility for planning and delivery of mental health services in the local community.

Health-care Standard – The Promotion of Health and Active Life in Older Age

The aim of this standard is to extend the healthy life expectancy of older people. The health and well-being of older people is promoted through a coordinated program of action led by the NHS with support from local councils. There is significant progress toward the targets of increasing influenza immunization rates, reducing smoking, and improving management of blood pressure.

In an update from Department of Health (2004), older people expressed a willingness to stop smoking and take advantage of health screening and immunizations to stay healthy. Recently published "Better health in old age" report by Professor Ian Philp, National Director for Older People's Health, is an update on the 2001 NSF. According to the report, the services for older people are improving but must continue to expand to meet the needs of an increasingly aged population. The report also reveals that life expectancy has increased. Men reaching age 65 in 2002 can expect to live for another 16 years compared to 14.6 years in 1993. Women reaching age 65 in 2002 can expect to live for another 19 years compared to just over 18 years in 1993. Overall mortality rates for people over age 65 have fallen and death from suicide has dropped from 11.8 per 100 000 population in 1993 to 8.8 per 100 000 population in 2003.

United States

For most of history, medical care has been provided in the home by a physician. In the mid-1900s, 40% of all patient–physician encounters took place at home. With the growth of hospital and office-based care, by 1980, fewer than 1% of health-care visits took place at home (Leff and Burton, 2001). HHC began growing again in the 1980s as new models of home assessment developed and the delivery of home care evolved into an organized, multidisciplinary business. The current HHC model primarily utilizes nursing, therapy, and personal care providers to deliver health-care services. Physician house calls still remain underutilized as a means of caring for frail older adults.

Home visits are an effective method for delivering medical assistance for the aged and chronically ill and homebound individuals. House calls have most often demonstrated benefit in chronic and relapsing diseases such as congestive heart failure and emphysema. Regular visits by a medical professional can improve disease control and reduce hospitalizations (Rich *et al.*, 1995; Stewart *et al.*, 1999). This translates to a societal cost savings, which has prompted medicare, medicaid, and private insurance agencies to continue the funding of home care services.

Medicare and medicaid provided 50% of HHC coverage in the United States between 1990 and 1997. HHC expenditures grew almost sixfold to $18 billion. The growth of HHC utilization prompted a change in reimbursement from a fee for service to a prospective payment system reimbursement model. For each 60-day certification period, agencies are reimbursed around $2000 per enrollee, adjusted for geographic region and intensity of care provided. This has reduced the enrollment length and frequency of HHC visits, but has not significantly impacted the ability of physicians to access HHC services. Currently, 2.5 million visits are performed by 7000 agencies.

To qualify for HHC, an agency must receive a physician order, document that a recipient is homebound (a definition that has remained vague) and provide a skilled intervention by a nurse or a therapist. Common uses of HHC include medication management, disease assessment, wound care, home safety evaluation, physical and occupational therapy, and patient/family education. The average number of visits per enrollee is 36 (Centers for Medicare and Medicaid Services, 2005).

When personal care is needed at home, aides can be hired for in-home assistance with laundry, housekeeping, meal preparation, and personal care needs. Medicare does not pay for personal care aides, nor do most private insurance plans. Individual case management and social services are available to seniors based on resources and needs. Services such as meals-on-wheels, transportation, and legal aid are often provided on a sliding fee–scale basis. The availability of these services varies by community.

Hospice care is another service traditionally provided in the home, although there is a growing use of hospice in the nursing home setting. In 2003, 900 hospice agencies provided care to 290 000 individuals. 55% of these patients were served at home; 23% resided in nursing homes. The average length of service was 55 days but 30% of hospice recipients died within 7 days of enrollment. This suggests that hospice services are largely underutilized for those deemed to have "less than 6 months to live." (National Hospice and Palliative Care Organization, 2003). In addition to nursing, hospice provides therapy, social service, and family support in the home. Hospice agencies are not capable of providing continuous 24-hour personal care.

British physician Dame Cicely Saunders first coined the term *hospice* in 1967. The Dean of Yale School of Nursing, Florence Wald, subsequently adopted this care model in the United States. It was not until 1979 that the Health Care Financing Administration (HCFA) funded 26 hospices as a

demonstration program. In 1982, hospice care was added as a benefit under the medicare and medicaid programs and has since become a standard benefit provided by all health insurance plans. To qualify for hospice a physician must certify an estimated life expectancy of 6 months or less. Eighty percent of hospice recipients are age 65 or older and just over half are female. Half of the hospice enrollees have a terminal diagnosis of cancer. Cancer diagnoses have dropped 10% in the last 3 years due to a rise in use of hospice care for nonmalignant terminal illnesses such as dementia and emphysema.

Australia

Home care services have become increasingly complex in the types of care provided, the funding arrangements, and number of service providers. The health-care needs of patients are also more complex due to greater functional and physical dependency. Medical care at home has traditionally been provided by GPs for patients who were too acutely or chronically unwell to attend office visits. However, the relatively poor reimbursement by medicare and the increasing demand for home visits has led many GPs to abandon them altogether. Because many aged care assessment teams (ACATs) now include a geriatrician or other medical officer, they may provide medical home visits as part of an initial assessment, but not as part of routine care.

Government sponsored community services existed as early as the 1940s, including emergency housekeeper service and meals-on-wheels, delivered by women volunteers on bicycles. The Australian government began funding home nursing services in 1956. Although the management and structure varies considerably between states, there is general availability of visiting registered nurses to provide nursing services in the home. Most commonly these services are time limited and based on the individual needs of the client and family. There are separate but generally parallel services for war veterans and individuals in the private sector.

Home and Community Care (HACC) services expanded in 1969 to support housekeeping or other domestic assistance, senior citizens centers, and welfare officers. Home care was further enhanced with the passage of the Home and Community Care Act in 1985 to include personal care such as bathing and dressing. Demand almost perpetually outstrips supply, because of underfunding, lack of gate keeping at entry, and inadequate exit strategies for maintenance services. A common assumption by service providers is that clients will not significantly improve and thus need prolonged enrollment in the program. Home care recipients assume that services are difficult to access and thus attempt to retain services long term rather than reaccess assistance at a later date.

HACC also funds meals-on-wheels, transportation, home maintenance and modification, counseling, social support, center-based day care, allied health services, provision of aids, respite care, and laundry. HACC services are not exclusively for older people, with 21% of their clients being under age 65, but usage rates do increase with age. For people aged 65–74, 47 per 1000 use HACC services, whereas 144 and 255 people per 1000 aged 75–84 and 85+ were using these services. The most commonly used service is domestic assistance (usually housekeeping). In 2002, 6.6 million hours of domestic assistance, 2.9 million hours of social support, 1.5 million hours of respite care, and 11 million meals were provided under the HACC program. The program was jointly funded by the state (40%) and national government at $1.2 billion in 2003.

ACATs are a network of 128 regionally based multidisciplinary teams that provide comprehensive geriatric assessment at home or in hospital, facilitate access to the best possible combination of services at home, and determine eligibility for residential and complex community care. ACATs often provide health advice and support for the common conditions, which afflict older people, such as dementia and incontinence. ACATs may assume the additional therapeutic role of rehabilitative therapy. ACATs assess approximately 1 in every 10 people over age 70 every year. ACATs have a key role in assessing older people at home in complex situations, such as when elder abuse is suspected or if guardianship is being considered. If residential placement is recommended, the ACAT works with the client and their caregiver to negotiate entry. Staffing varies but generally includes nursing and allied health, social workers, physiotherapists, occupational therapists, and psychologists. Increasingly ACATs have access to a geriatrician, particularly when they are colocated with a hospital aged care service, and sometimes even a psychogeriatrician. In nonmetropolitan areas, the medical officer is usually a GP (family medicine practitioner) with an interest in aged care (Lincoln Gerontology Centre, 2000–2001).

Referral to ACAT is from any source, including self-referral. ACATs perform a standardized initial assessment using a minimum data set, with subsequent assessments according to identified problems. Occasionally, ACATs must assess younger people with disabilities for eligibility to enter residential aged care if no suitable alternatives exist.

The shift away from institutional care has led to ever more complex packages of care being introduced into the community. The Community Options Program was established in the late 1980s to provide case management and brokerage funds in the community to a small group of clients that is up to 10 times the average level of funding for other HACC clients, and also as recognition of the wide range of services available in the community.

Community aged care packages (CACPs) were introduced in 1992 and support people at home with up to 14 hours of care per week as a substitute for admission to a hostel. Assistance with personal care such as bathing, domestic assistance with laundry, shopping, meal preparation, gardening, and transportation outside the home are provided. The median length of time on the program is just under a year. Two-thirds of people who leave the program are admitted to residential care or die. By December 2003, about 28 000 people were receiving this type of care and the government plans to increase availability to 18 CACP per 1000 persons

over age 70. More than half (56%) of all recipients live alone and only 8% live with their children. Recipients pay up to $5.59 per day, with the Australian government providing $32.04 per day per recipient.

Extended Aged Care at Home (EACH) packages were introduced in 1998 to support people at home who are eligible for nursing home placement. Each client receives an average of 16.1 hours of care per week. These recipients tend to be younger (32% under age 75) and more cognitively intact (31% diagnosed with dementia, compared to 80% in nursing homes) than most nursing home residents. Most services are available upon request, although often for a small fee. The more complex packages of care require ACAT assessment of need (Aging and Aged Care Division, 2002).

Although the spectrum of home care appears broad and comprehensive, it is also cumbersome and complex. In practice, 17 separate programs are funded by the Australian government and delivered by a myriad of 4000 different service providers. The result is a complex health delivery system with patchy coordination and insufficient communication, particularly for consumers and their caregivers. In theory, one assessment by ACAT should be sufficient for any other service but, in practice, each service provider makes its own assessment.

That this plethora of providers does not meet the needs of older disabled people and their caregivers was demonstrated by a study of dementia sufferers in Victoria. Data revealed that over 40% of demented individuals do not make use of any community or respite services despite high levels of caregiver strain and little support from family and friends (Thomson *et al.*, 1997). When asked why they did not make use of various community services, 77–88% of individuals stated that the services were not needed. In reality, some caregivers were not managing well as evidenced by poor self-reported health and high levels of strain. Since 1972, caregivers have been subsidized by a domiciliary nursing care benefit to care for a disabled person at home who would otherwise require institutional care. The patient must be over the age of 16 and certified by a medical practitioner to require continuing care.

NURSING HOME CARE

United Kingdom

The NHS has allocated an additional £900 million annually, beginning in 2003, for the expansion of intermediate and nursing home care services. This provides for an additional 5000 beds and 1700 facilities. The NHS is working toward providing nursing care without cost to residents of nursing homes and to protect individuals from losing their home or other resources in order to pay for the costs of nursing home care. The average cost of residential and nursing care homes is between £300–400 per week.

Around 63% of older people permanently entering nursing homes come directly from the hospital. Integrated care services provided via a team of medical professionals are a most effective means of providing a comprehensive plan of care. The comprehensive team approach requires a collaborative effort between the hospital-based consultant geriatrician and the GP providing day-to-day care in the nursing home setting. Consultant geriatricians have been criticized for a relative lack of attention to the long-term care and community-based care needs of the frail elderly population.

In a survey of 810 (38% response rate) consultant geriatricians, one-third of clinical time was spent in emergency care services, one-third in general geriatric/rehabilitation services, and only one-eighth was spent on community-based/intermediate care services (British Geriatrics Society, 2004). Only 14% would change their job description, if allowed, to perform more community-based work, and 60% reported that this was the least important of their four core clinical activities. Given the nursing home needs of the UK population, the BGS recommends that senior consultant geriatricians be allowed to choose career progression pathways into community-based and nursing home care positions.

The NSF has established a specific standard for intermediate care of older adults. The goal is to provide integrated services, to promote faster recovery from illness, to prevent unnecessary acute hospital admissions, to support timely discharge and to maximize independent living. Older people will have access to a new range of intermediate care services at home or in designated care settings. The NHS Plan set out a major new program to promote independence for older people by developing a range of services that are delivered in partnership between primary and secondary health care, local authority services, and the independent sector. One of the critical elements in this program is the development of new intermediate care services.

Nursing homes would develop close association with the geriatric department. Admission to geriatric department was to be directly from the patients' own homes, or in some cases, transfer from other hospital wards for rehabilitation and resettlement. It was hoped that this department would be able to absorb older patients from acute medical wards and also relieve the surgical wards of their elderly patients after the postoperative phase and there must be sufficient beds in the nursing homes to absorb the patients who would be transferred to them from hospital or home.

United States

The number of nursing homes in the United States has dropped slowly since the early 1980s, although the total number of residents in nursing homes has increased almost 10% during that time. In 2002, 16 000 facilities were licensed, with an average capacity of 100 residents. 70% of nursing home residents are female and 90% are Caucasian. The average length of stay is 2–3 years. Despite common misconceptions of the elderly population, less than 5% of citizens over the age of 65 reside in nursing homes. Less than 20% of adults over age 85 live in nursing homes.

Most nursing homes certify a portion of their beds (25–35%) for postacute care, skilled nursing services. These

residents receive intensive nursing, therapy, and medical services after an acute medical illness with the hope of regaining lost function. Medicare funds most of the skilled nursing care in the United States but private insurance also covers postacute rehabilitation services. Medicare beneficiaries receive up to 100 days of skilled nursing care before other insurance or private pay must shoulder costs. The average length of skilled nursing care is 27 days.

Medicare and most private insurers do not pay for nonskilled (custodial) care in nursing homes. The bulk of custodial care is paid for by medicaid once individuals have "spent down" their personal resources to the point of qualifying for this jointly state-federal sponsored health-care coverage. The medicaid qualification level varies by state. An individual generally must have a monthly income less than or equal to the federally designated poverty level ($776/month) and net personal resources of only a few thousand dollars. The average yearly cost of nursing home care is roughly $55 000. Nursing home insurance is becoming available but in general it is costly and not widely purchased by the general population (The National Nursing Home Survey, 2002).

Nursing home care has improved dramatically in the past 20 years. The Omnibus Budget Reconciliation Act (ORBA), passed in 1987, was instrumental in changing the management and oversight of nursing home care in the United States. Unfortunately, previous abuses have resulted in a highly regulated and punitive system of ensuring the quality of institutional patient care. Nursing homes are surveyed annually by the state regulatory agency. Deficiencies and fines are applied liberally and are a matter of public record. The state has the authority to immediately close down any facility that is found to have practices that place residents in "immediate jeopardy" of harm. Areas that are frequently cited include unnecessary use of physical restraints and psychotropic medication, weight loss, development of pressure ulcers, and fall related injuries.

As length of stay in hospitals shortens and the severity of illness of newly admitted residents increases, nursing homes have become more comprehensive in providing medical and therapy services. Most facilities offer intravenous antibiotics and fluids. Gastric tube feeding, suctioning, and oxygen treatment are routine. Facilities contract with mobile laboratory and radiology agencies. Physical, occupational, and speech therapists, nutritionists, and consulting pharmacists are on-staff or consult on a frequent basis.

Nurses are being challenged to perform more sophisticated care and more rigorous assessments while faced with limited staffing ratios and a high rate of nursing turnover.

Assisted living facilities are assuming some of the role that nursing homes played 20 years ago. "Well" elderly who require only some assistance with daily activities live semiindependently in studio-type apartments with or without a kitchenette. Facilities vary in size from several dozens to over one hundred residents in a single building. A licensed nurse is usually available during most of the day and may pass meds, perform assessments, inject insulin, check glucoses, and perform other skilled tasks based on resident needs. The provision of meals, light housekeeping, and social activities are usually included in the cost of room and board.

The cost of care is partly based on the level of services designated by the patient/family. Assisted living costs are highly variable but range from $24 000 to $36 000 or more per year. Almost universally, the cost of assisted living is incurred out-of-pocket by the resident and/or family. Despite being less costly, most long-term care insurance providers will not reimburse assisted living as an alternate to nursing home care. Assistance with activities of daily living (ADLs), instrumental activities of daily living (IADLs), safety checks, and other personal care are provided by 24-hour/day nursing assistants at the facility. At this time 800 000 residents reside in 30 000 assisted living facilities. Most assisted living residents receive medical care in the office of medical providers as opposed to on-site as in nursing homes. There are currently very few governmental regulations or requirements in assisted living facilities.

Australia

The development of residential aged care dates back to the poor houses of the nineteenth century. In NSW, the first state, government asylums for the aged and destitute were built to house the aged poor. By 1890, these homes had become "practically hospitals for chronic and incurable diseases as well as homes for the infirm and indigent". However the introduction of pension plan in 1909 allowed more aged poor to continue living in the community and institutional care was used only for marked disability or poverty (Dickey, 1983). Essentially all residential care was provided by the charitable and public sectors until the mid-1950s, but not-for-profit organizations still provide 63% of all residential care places.

In 1954, there was a swing back to residential aged care when the Australian government passed the Aged Persons Homes Act that provided subsidies to charities (and later to private operators) that built or purchased homes for needy older people. This prompted a surge in construction of nursing homes that continued for three decades. In the early 1970s, a quota of 50 nursing home beds per 1000 population of age 65 and over was introduced. An intermediate level of care, called *hostel*, was announced in an attempt to reduce the number of nursing homes being built, particularly by the private sector. Hostels were aimed at people who needed assistance with IADLs while nursing homes were designed for people who needed assistance with basic ADLs.

A 1978 survey found that 30% of nursing home residents could easily be treated at home with minimal services (Bennett and Wallace, 1983). In 1986, a government review pointed out that the cost of institutional care had risen tenfold in 10 years, from $100 million to $1 billion per annum, and the percentage of the Department of Health's budget paid to nursing homes had increased from 9 to 25% over 20 years. By the mid-1980s nearly 90% of all aged care funding was going to residential care. The rate has now been reduced to about 75% with a commensurate increase in community care.

In 2004, there were 175 000 allocated residential care sites and 30 000 community care sites.

On the basis of the truism that most people prefer to remain in their own homes, the government changed the quota for nursing home beds to 72.6 per 1000 people over age 70. In 1985, the multidisciplinary ACATs were charged with developing more stringent entry criteria, which resulted in a 35% decrease in admissions to nursing homes. HACC services were also strengthened in order to maintain people at home (Warne, 1987). Over the years, the government has changed the ratio of nursing homes and hostel places to increase the availability of home support, but this has been complicated by the growth of the population over age 70. Individuals over age 85 are most likely to require nursing home placement and are the fastest growing segment of the population. A decrease in funding for residential care has caused many facilities to close down. Ninety of licensed residential care centers are now allocated per 1000 population over age 70. These transformations have meant significant increases in disability in hostel care, as well as increased average disability in nursing homes.

A further series of reforms took place in 1997 with the introduction of the Aged Care Act. The two levels of care were unified under one legislative framework with an integrated Resident Classification Scale (RCS) and quality assurance framework. The levels were renamed high (nursing home) and low (hostel) care. The 1997 reforms also introduced a small amount of deregulation and emphasized greater contributions to the cost of health and welfare services by those with the capacity to pay.

In general, the provision of residential aged care remains a controversial issue in Australia. Approximately one in three people who reach 65 years of age will spend some time in residential aged care, but whether the cost should be met more by the community or by the individual and their family is a matter of equity, ethics, and finances.

HOSPITAL CARE

United Kingdom

The BMA set up a working group in 1947 to review care of the elderly and infirm. As per their recommendations, specialist geriatric departments were gradually established over the years in general hospitals, including teaching hospitals in the NHS. A geriatric department is comprised of wards reserved exclusively for elderly patients undergoing evaluation, active treatment, and rehabilitation. A common goal is to discharge patients from such wards either to their own homes or to other appropriate accommodations. Patients requiring ongoing nursing care for irremediable conditions are referred for nursing home admission.

For those aged 65 and over, various hospital admission policies are set up with some departments admitting according to need (i.e. those patients presenting with the "geriatric syndromes" or with mixed medical and social problems) for which the geriatric department was specially adapted. Others are admitted on an age-related basis, varying from 65 to 85 and over (Kafetz *et al.*, 1995; Brocklehurst and Davidson, 1989). These policies apply to emergency admissions while "cold" admissions referred by GPs through outpatient or domiciliary consultation usually include anyone aged 65 or over (British Geriatrics Society, 1995; Grimley, 1983).

Over time, acute-care admission policies have shifted toward an integration of geriatric medicine with general medicine for emergency admissions via a common Medical Admission Unit (MAU). This Newcastle Model (British Geriatrics Society, 1995) has been partially driven by the need to reduce junior doctors' hours of work and the problem of outliers – patients of one consultant being admitted to many different wards of the hospital when their wards are full. Accommodation of these difficulties has produced more rational and economic use of beds and staff.

Two-thirds of acute hospital beds are occupied by people over age 65. Hospitals therefore need to ensure that they are meeting the particular needs of older people, many of whom have a variety of health and social problems. The NSF places great emphasis on quality hospital care for older adults and has established a number of milestones, such as multidisciplinary team care, to measure progress. Nearly three-quarters of hospitals now have specialist multidisciplinary teams for the care of older people. Over 80% of these teams have a nurse leader, often a modern matron, with special responsibility for the care of older adults.

Health-care Standard – General Hospital Care

The aim of this standard is to ensure that older people receive the specialist help they need in the hospital and that they receive the maximum benefit from the hospital services. Hospital care for older adults is delivered through appropriate specialist consultation and by hospital staff who have the right set of skills to meet the needs of the patient. The hospital environment and support services should be targeted to anticipate the care requirements of the older adult.

Health-care Standard – Stroke Management

The aim of this standard is to reduce the incidence of stroke in the population and ensure that those who have had a stroke have prompt access to integrated stroke care services. The NHS will take action to prevent strokes by working in partnership with other agencies where appropriate. People who are thought to have had a stroke must be provided access to diagnostic services, be treated appropriately by a specialist stroke service, and be allowed to participate in a multidisciplinary program of secondary prevention and rehabilitation.

Outcomes for stroke patients are better when they are cared for by specialist stroke teams within designated stroke units. Lengths of stay on these teams are also shorter on average. Since the publication of the NSF for older people, many more speciality stroke services have been established and more

are planned. There have been significant increases in the number of stroke physicians, the proportion of patients being treated in specialist stroke units, and the number of patients returning home after hospital treatment. There have also been important improvements in the care process. For example, 83% of patients are receiving brain scans to improve stroke diagnosis, far more than in the past. Ninety percent of hospitals which treat people with stroke now have stroke units, up from 82% in April 2004. More than one million bed days are being saved a year because of reductions in delayed discharge.

A variety of programs have been developed to improve stroke care. The NHS Modernization Agency has developed a "clinical governance development program", which seeks to engage frontline staff in radical reassessments of care delivery. The Sentinel Stroke Audit is also underway to measure the delivery of stroke care based on Royal College of Physicians' clinical practice guidelines. Despite these initiatives, stroke care across the country remains heterogeneous. Although 90% of hospitals have stroke units, only 36% of patients who have had a stroke are spending time in these units. Clearly, there is still much to do to ensure that the NSF standard for stroke management is met.

United States

Hospitals in the United States are evolving to provide speciality services for the aging patient with the hope of improving patient outcomes and reducing adverse health events. Programs such as adult day care, palliative care, and HHC, offered through the hospital system, address a wide variety of needs for elderly patients both during and after hospitalization. The American Hospital Association (AHA) publishes the prevalence of these services annually. In 2000, geriatric services, home health services, and skilled nursing care units were offered in over 35% of US hospitals (American Hospital Association and the National Chronic Care Consortium, 2002). In the subsequent 3 years, the frequency of all of these services has declined by up to 3% with current data illustrated in Table 1. The only geriatric programs, which have increased significantly, are palliative care and case management with 22.2 and 75.5% of hospitals having these services respectively in 2003 (Health Forum LLC/American Hospital Association, 2005). It is interesting that neither an acute care for the elderly (ACE) unit nor a stroke unit are used as markers in this consumer-evaluation model, but both are accepted by the field of geriatric medicine as beneficial interventions.

ACE Units

The ACE unit is a growing model for comprehensive and multidisciplinary care of the older hospitalized adult. Characteristics of most ACE units include an association with a university hospital, 20-bed unit, initiated in the late 1990s and open to admissions from a variety of medical services (Siegler *et al.*, 2002). The "ACE" concept and term were developed in the early 1990s with key elements of the model being (1) environment alterations, (2) patient-centered care, (3) interdisciplinary planning for discharge, and (4) medical care review, which are outlined in detail in Table 2 (Landefeld *et al.*, 1995). The goal of this model is to reduce the functional impairments which so often develop in acutely ill, hospitalized elders. This "dysfunctional syndrome" is outlined in Figure 1.

Two philosophical differences are employed in the ACE model of care. First, care management is shifted toward a

Table 1 Healthcare facilities and services trends

Special services offered	Number of hospitals	Percentage of hospitals
Skilled nursing care unit	1650	33.4
Intermediate care unit	506	10.2
Adult day care services	400	8.1
Assisted living	263	5.3
Case management	3733	75.5
Geriatric services	1998	40.4
Home health services	1848	37.4
Hospice	1153	23.3
Meals-on-wheels	633	12.8
Psychiatric-geriatric services	1505	30.4
Retirement housing	184	3.7
Palliative care program	1098	22.2

Source: Reproduced by permission of Health Forum.

Table 2 Key elements and illustrative features of the intervention program

Key element	Illustrative features
Prepared environment	Carpeting, handrails, uncluttered hallways Large clocks and calendars Elevated toilet seats and door levers
Patient-centered care	Daily assessment by nurses of physical, cognitive, and psychosocial function Protocols to improve self-care, continence, nutrition, mobility, sleep, skin care, mood, cognition (implemented by the primary nurse and based on the daily assessment) Daily rounds by the multidisciplinary team, led by the medical and nursing directors with the primary nurse, social worker, nutritionist, physical therapist, and visiting-nurse liaison
Planning for discharge	Early, ongoing emphasis on the goal of returning home Assessment of plans and needs for discharge by a nurse at the time of admission Early involvement of a social worker and home health-care nurse, if indicated
Medical care review	Daily review by the medical director of medicines and planned procedures Protocols to minimize the adverse effects of selected procedures (e.g. urinary catheterization) and medications (e.g. sedative-hypnotic agents)

Source: Reproduced by permission of the Massachusetts Medical Society from Landefeld CS, Palmer RM, Kresevic DM *et al.* (1995) A randomized trial of care in a hospital medical unit especially designed to improve the functional outcomes of acutely ill older patients. *NEJM*, **332**, 1338–44.

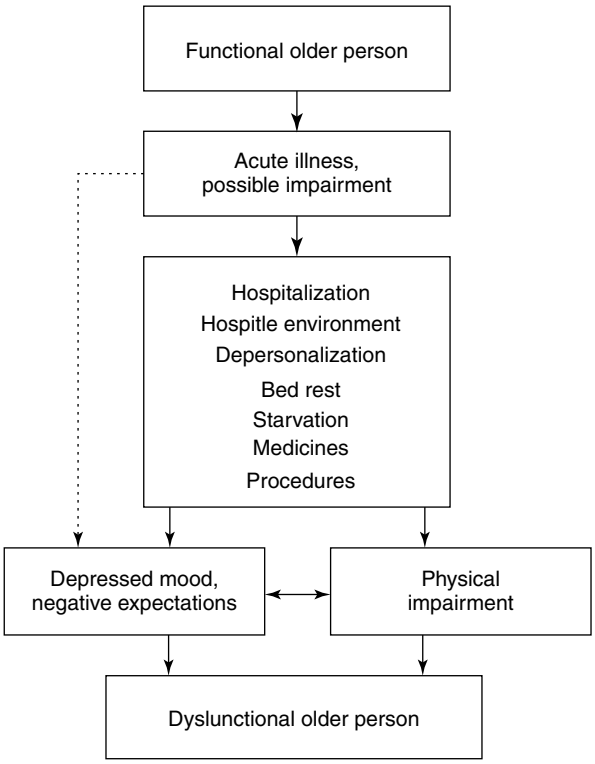

Figure 1 Conceptual model of the dysfunctional syndrome (Reprinted from *Clinics in Geriatric Medicine*, vol 14(4), Palmer RM, Counsell S, Landefeld SC, pp 831–49, Copyright 1998, with permission from Elsevier)

biopsychosocial rather than a biomedical model. Hospitalization and discharge planning focus on the relationship between the patient and the social structures that are needed for effective treatment. Barriers to successful recovery and risks for ongoing functional decline are identified early in the hospitalization. Appropriate interventions such as reduction in polypharmacy, nutritional assessment, social support evaluation, and physical and occupational therapy assessment are initiated for each patient. Discharge plans ensure that the patient transitions to an appropriate environment and with appropriate social services in place.

Second, a functional-based rather than disease-based approach is used in medical decision-making. Many elders suffer from multiple, chronic medical conditions that will not be cured. Goals of care focus on maximizing function in the context of disease management rather than solely marking improvement by measures of disease severity. With this method, functional status and quality of life measures become the markers for successful recovery from illness.

The implementation of an ACE unit has consistently resulted in improved functional status and increased discharge to home compared with usual care wards (Landefeld *et al.*, 1995; Asplund *et al.*, 2000; Counsell *et al.*, 2000). Despite the additional interventions applied by the multidisciplinary team, the total cost of hospital care is not higher on the ACE unit. The benefits of teamwork in caring for the complex and ill elderly adult translates to a more efficient and thorough treatment plan for both the hospital and the patient without incurring excess cost.

Stroke Units

Death from cerebrovascular disease is the third leading cause of death and more than two-thirds of strokes occur in patients over the age of 65. Despite long-standing use of stroke units outside of the United States, and strong evidence demonstrating the morbidity and mortality benefit of this strategy (Stroke Unit Trialists' Collaboration, 1997, 2002), comprehensive stroke management models are just beginning in the US health-care system. Previous literature on the benefit of an organized inpatient stroke care team comes almost universally out of the United Kingdom and northern Europe. For over 20 years, patients with acute stroke have been managed on a dedicated stroke unit: either on a discrete stroke ward or stroke team working exclusively in the care of stroke patients. Focus of the stroke unit can include acute stroke care, subacute rehabilitation, or a combination of strategies.

To improve the consistency and quality of stroke care across the United States, the "Brain Attack Coalition" (BAC) was convened in 2000 to establish recommendation for hospital care of stroke patients. The BAC recommended a two-tier organization for hospital-based stroke care: Primary Stroke Centers (PSCs) and comprehensive stroke centers (CSCs). This group outlined the major criteria of a PSC which are listed in Table 3 (Alberts *et al.*, 2000). PSCs provide the basic emergency evaluation and stabilization, while complex cases requiring speciality imaging and intervention should be referred to CSCs. A recent state-based survey of medical facilities indicates that less than 20% of hospitals have either a stroke unit or have the infrastructure to become a PSC (Camilo and Goldstein, 2003). Furthermore, the prevalence of key stroke services has not significantly changed over the past 5 years.

The stroke units of Europe are more similar in design to the US ACE unit, whereas stroke centers in the United States

Table 3 Major elements of a primary stroke center

Patient care areas
Acute stroke teams
Written care protocols
Emergency medical services
Emergency department
Stroke unit[a]
Neurosurgical services
Support services
Commitment and support of medical organization; a stroke center director
Neuroimaging services
Laboratory services
Outcome and quality improvement activities
Continuing medical education

Source: From 'Recommendation for the Establishment of Primary Stroke Centers' by Alberts, MJ *et al. JAMA*, **283**(23), 3102–3109. Copyright 2000, American Medical Association. All rights reserved.

[a]A stroke unit is only required for those primary stroke centers that will provide ongoing in-hospital care for patients with stroke.

Table 4 Comparison of geriatric complications. Geriatric complications – number (%) of patients and 95% confidence intervals

	Hospital in the home	Hospital	P
Confusion	0	10 (20.4%) 9.1%, 31.7%	0.0005
Falls	1 (2.0%) −1.8%, 5.8%	2 (4.1%) −1.4%, 9.6%	ns
All bowel complications	0	11 (22.5%) 10.7%, 34.1%	0.0003
Constipation	0	7(14.3%) 4.5%, 24.1%	0.013
Fecal incontinence	0	4 (8.2%) 0.5%, 15.9%	ns
All urinary complications	1 (2.0%) −1.8%, 5.8%	8 (16.3%) 6.0%, 26.6%	0.01
Urinary incontinence	1 (2.0%) −1.8%, 5.8%	6 (12.2%) 3.0%, 21.4%	ns
Urinary retention	0	2 (4.1%) −1.4%, 9.6%	ns
Phlebitis	2 (3.9%) −1.4%, 9.2%	3 (6.1%) −0.6%, 12.8%	ns
Pressure area/skin tear	1 (2.0%) −1.8%, 5.8%	3 (6.1%) −0.6%, 12.8%	ns

Source: From Caplan G. *et al.*, Hospital in the home: a randomised controlled trial. *MJA* 1999; 170: 150–160. Copyright 1999. The Medical Journal of Australia – reproduced with permission. ns, not significant.

are modeled after a "trauma center" concept. In contrast to the physical model of stroke and ACE units, the PSC represents a "process model" that focuses on delivery of care and availability of personnel and speciality services. Like trauma centers, stroke centers rely on a network of coordinated resources within a facility. The challenge for the future will be to meet the growing need for acute stroke care in the aging population.

Australia

In 1993, a government survey of 942 Australian hospitals found that 32% operated a geriatric service. These were almost exclusively based in the public sector, and usually consisted of visiting care services (Dorevitch and Gray, 1993). Only 13% of programs included a geriatrician. Replication of the survey in 2001 found that 31% of 778 hospitals had a geriatrician providing inpatient care (Gray *et al.*, 2002).

The distribution of geriatric services varies between states. Those states with more acute geriatric medical beds typically provide care to patients admitted through the emergency department. New South Wales, Western Australia, and South Australia have the highest ratio of acute geriatric beds (0.67–0.85 beds per 1000 people over age 70 in 2002). In Victoria and Western Australia there are more designated aged care rehabilitation beds (0.62–0.63 per 1000 people) than in the other states. The extent of geriatric services vary by hospital, with 11% reporting a day hospital, 7% having bed-based psychogeriatric services, and only 4% having orthogeriatric services. Orthogeriatric services provide coordinated orthopedic and geriatric management for older traumatic and elective orthopedic patients.

The type of geriatric services available to patients tends to mirror the hospital environment. Where the hospital focuses on acute-care and managing emergency admissions, more attention is devoted to improving assessment and management of older people in the emergency department and on acute hospital wards. Where the hospital has developed a stand-alone rehabilitation center, more emphasis is placed on managing chronic conditions, such as dementia, Parkinson's disease and incontinence. However, with time the scope of available services is increasing and differences between states are receding.

Stroke units are becoming increasingly popular, although geriatrician involvement is not universal. A recent study found that only 40% of all strokes were treated in stroke units (Lee *et al.*, 2003). Hospital in the home for older patients is increasing in popularity, but is essentially in its infancy as a model of health care. This service provides patient-centered care in the patient's home or a residential care facility, while decreasing the risk of hospital associated adverse events. Major geriatric complications were less likely to occur in the hospital in the home model compared with the traditional hospital model and are listed in Table 4 (Caplan *et al.*, 1999). Public hospitals, which are the majority, are under the control of state governments.

Only about 30% of hospitals are private and these concentrate on elective procedures. Almost all large and teaching hospitals are public, so that the vast majority of acute and more complicated medical or surgical work is done in public hospitals. Admission to a public hospital as a public patient is free to Australian residents. However, if a patient wants a choice of doctor, they must enter as a private patient. Owing to recent tax incentives, about 50% of the population has private insurance for hospital care. Public hospitals receive about half their budget from the national government and half through the state governments.

This dichotomy of control of the health system has led to lack of coordination, and incentive to cost-shift between the hospital and nonhospital sectors. There are also limited health services run by local government (the third tier), religious and charitable organizations, individuals, and private commercial interests.

ACADEMIC GERIATRICS

United Kingdom

The first academic chair of geriatric medicine was established in 1965 in Glasgow, Scotland. The first professor of elderly medicine was William Ferguson Anderson (1914–2001).

A pioneer of geriatric outreach clinics, he established a famous partnership with the GP of Rutherglen Health Centre.

Every medical school in United Kingdom now has a Department of Geriatric Medicine with at least one professor of medicine in geriatrics. Recently, the Royal College of Physicians has mandated that the membership examination contain questions from geriatrics medicine and rehabilitation. Knowledge of geriatrics has become a requirement for physicians-in-training.

Like other physicians, geriatricians must complete a period of general professional training (GPT) in acute medical specialities before starting higher training in their chosen speciality. The primary purpose of training is to promote the development of a physician who has the appropriate level of knowledge, skills, and competence to work independently and effectively as a consultant in geriatric medicine.

Applicants for higher medical training (HMT) should have completed a minimum of 2 years' GPT in approved posts at Senior House Officer (SHO) level and obtained the Diploma of Membership of the Royal Colleges of Physicians (United Kingdom or Ireland). A period of experience in geriatric medicine at SHO grade is considered desirable but not essential, before entry to HMT. The duration of HMT in geriatric medicine is 4 years. Those who wish to obtain dual certification with general (internal) medicine will require at least one extra year. HMT will require experience in both teaching hospital(s), or other major centers with academic activity, and district general hospitals.

Application for the certificate of completion of specialist training (CCST) can be made after successful training. CCST is granted by Joint Committee of Higher Medical Training (JCHMT) of Royal College of Physicians. CCST is mandatory requirement for specialist status, registration with the specialist register of General Medical Council (GMC), and to be eligible for substantive or honorary consultant post in United Kingdom. There are currently 466 specialist registrars geriatrics trainees in England, Wales, and Northern Ireland according to Consultant Census 2001–3/JCHMT database, October 2004.

A period of supervised (clinical or laboratory) research of good quality is considered a highly desirable part of specialist registrar training in geriatric medicine. A relevant research period may contribute up to 12 months toward the total duration of the training program. Each trainee is encouraged to have experience of participating in research whether it is laboratory-based (basic science) or clinical (health services) research.

United States

The development of academic geriatric programs and medical training has lagged behind the demand for a larger and more skilled geriatric medicine health-care workforce. This is in part due to the lack of universal acceptance of geriatrics as a unique discipline within the medical profession. With the increasing age, functional impairment, and psychosocial complexity of older adults, the mantra that "I'm a geriatrician because most of my patients are elderly," is fading, but slowly.

In 1982, Mount Sinai School of Medicine established the first Department of Geriatrics. At this time 80% of medical schools have some form of a geriatrics program. The vast majority of programs are organized as divisions or sections within a Department of Internal or Family Medicine. Few institutions have the financial capability of supporting independent departments of geriatric medicine. Two-thirds of programs have been in existence for less than 20 years. Fifty percent of these programs have less than six faculty members. Two-thirds of program directors have been in that position for less than 8 years. The first professorship in geriatric medicine was granted at Cornell University in 1977.

Dr Les Libow at Mount Sinai School of Medicine offered the first geriatric medicine fellowship program in 1966. Since that time the number of trainees and training sites remained fairly limited until the early 1980s. In the 1970s, the Veterans Administration (VA) was charged with the task of increasing the understanding of aging and passing this knowledge to health-care providers. Funding was provided in 1975 for the first VA Geriatric Research Education and Clinical Center (GRECC). Twenty-two GRECCs have since been established. GRECCs began offering geriatric medicine fellowship training opportunities in 1978.

In 1988 the Accreditation Council for Graduate Medical Education began accrediting geriatric medicine fellowship training programs. Sixty-two Internal Medicine and 16 Family Medicine programs offered fellowship training at that time. 1988 was also that year when an examination became mandatory to attain the Certification of Added Qualification (CAQ) in geriatrics after at least 2 years of fellowship training. To be eligible for CAQ, physicians must have completed US residency training and be board certified in either Internal or Family Medicine.

Until the mid-1990s, most fellows in geriatric medicine engaged in 2 or more years of training. Extended training was vital for the development of an academic and research career in geriatrics. In 1995, the training requirement for CAQ in geriatrics was reduced to 1 year. Although this may have partly achieved a desired goal of an increase in the total number of fellowship trained geriatricians, it has not resulted in a greater number of physicians adequately prepared to embark on a successful academic career. Over the last 10 years, the number of accredited programs has grown to 125 with roughly 400 first-year fellowship training positions. Unfortunately, almost one-third of fellowship slots go unfilled each year (Warshaw *et al.*, 2002a,b).

Australia

In NSW, geriatric medicine originated in the Royal Newcastle Hospital, an acute public hospital and later became an acute speciality hospital. Lidcombe Hospital in NSW was another early center of geriatric medicine that evolved away from the mainstream, having originally been an asylum which developed into an acute hospital, but retained a large

group of long stay chronic patients. Many of the doctors involved there went on to be national leaders in geriatric medicine. In Victoria, South Australia, and Queensland the speciality started in chronic hospitals, which developed out of the poor houses, and continues as a rehabilitation hospital model, though it now also interacts with acute hospitals. In Victoria, the Mount Royal Hospital was a custodial institution for elderly people where the state hospital and charities commission decided to open a geriatric center, aimed at rehabilitation. Though the initial director was only part-time, the center flourished and also became a center for aging research.

The Australian Association of Gerontology formed in the early 1960s as a multidisciplinary organization interested in later life, and the doctors involved went on to form The Australian Society for Geriatric Medicine (ASGM) to meet the special needs of medical practitioners. Many geriatricians take a leading role as advocates for older people together with consumers and other service providers.

The first full professor of geriatric medicine was appointed at the University of Melbourne in 1975, though early professorships were often in "community medicine and geriatrics". Now each medical school boasts of at least one Professor and there are research institutes dedicated to age-related research in the larger states.

The Royal Australasian College of Physicians (RACP) recognizes geriatric medicine as a speciality. Trainees must complete 3 years of advanced training in geriatric medicine, though 1 year of this may include working in another speciality or in full-time research. Advanced training can only be undertaken after successfully completing the demanding written and oral basic physicians examination, which is generally attempted 4–5 years postgraduation from medical school. Only about two-thirds of candidates are successful in this exam. Almost all basic physician trainees, who later go on to various internal medicine subspecialities, have some exposure to working in geriatric medicine. This is most beneficial for attracting trainees for advanced training. However, workforce issues are as much a problem in terms of shortages in the supply of doctors for older people, as well as nurses and allied health professionals.

Many other research institutes also have some interest in age-related research. Clinical research is also conducted in many teaching hospitals. Most research funding derives from the National Health and Medical Research Council that does not yet have a section devoted to aging. However, in 2002 the Australian government released a national strategy for aging research and identified national research priorities which included "promoting and maintaining good health" whose goals include "aging well, aging productively". This led to the establishment of two research networks designed to encourage and seed fund collaborative interdisciplinary research into aging.

CONCLUSION

In the next 50 years, the population demographic in developed countries will change substantially. Up to a quarter of the citizens will be over age 65 with the highest growth rate in age seen in the oldest age-groups. Older adults are the highest consumers of health-care resources and are usually supported, at least in part, by local and national governmental medical programs. With health-care costs rising, countries like the United Kingdom, United States, and Australia are exploring alternate means of caring for the aging population.

Home care encompasses a wide variety of programs and services, most of which are not physician-directed. Traditional physician house calls dropped substantially in the early 1900s and despite a recurrence in interest, are still a minority of the home care encounters performed today. The provision of medical and nonmedical services allow individuals to remain independent and in their homes for a longer period of time. Many services are community based and thus help individuals maintain a connection with society.

Nursing home care increased substantially during the mid-1900s. As the aging population expanded, health expenditures increased tremendously. In an effort to control escalating long-term care costs, intermediate care settings have evolved to allow individuals more autonomy in a less costly setting. Resources and supervision are provided to individuals on an as-needed basis in most of these facilities. For individuals in need of comprehensive supervised care, nursing homes still provide the maximal degree of therapy, social work, and nursing support.

Hospital care has evolved to focus more on the delivery of quality health care to the elderly individual. Stroke units are well established as an effective model for managing hospitalized older adults. ACE units are now growing in the same manner. It is apparent that quality care for complex elderly patients requires a team of medical providers working together toward common goals.

Academic geriatrics has grown substantially over the past 50 years with most medical schools and academic centers establishing a department or section of geriatric medicine. The role of geriatricians, relative to GPs, is still evolving in the care of the older adult. As the older population expands there is an ongoing need to training physicians, both generalists and specialists, in the principles of geriatric medicine.

KEY POINTS

- The elderly will account for over 20% of the United Kingdom, United States, and Australian population in the next half century.
- Services for the elderly have grown most extensively in the realm of home health care.
- Geriatric wards, stroke units, and acute care for the elderly (ACE) units are well-developed and are effective models of hospital care for the elderly.
- The growth of nursing home care has slowed and is shifting to "intermediate care" service models.

- Geriatrics as a unique field of medicine has developed over the past half century.

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Geriatric Day Hospitals

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INTRODUCTION

Geriatric Day Hospitals (DHs) are key components of specialized health services for the elderly throughout the world. They usually provide a community-based rehabilitation service for older persons and a bridge between hospital and community care, but have different contributions to make to the health care of older persons in various health-care settings. While the main emphasis of DHs relates to rehabilitation of the older person, the precise function varies depending on the health-care setting. The role of the DHs can vary from a predominantly diagnostic and assessment center to a more supportive and holistic facility used to optimize patient function with a wide variety of techniques and professional disciplines. In recent years, DHs have evolved to include preventative approaches to disease management.

Patients attending a DH present with a wide range of health and social problems. But the multidisciplinary nature of the care enables the best management of multiple pathology while minimizing disability and handicap.

Dr Lionel Cosin developed the concept of the first DH in 1957 in the Cowley Road Day Hospital in Oxford, United Kingdom as an extension of ward-based multidisciplinary assessment. Other Geriatric Medicine pioneers such as Professor John Brocklehurst and Dr John Dall further developed its role and persuaded local authorities to add vital transport services and diagnostic facilities.

The DH evolved at the same time as specialized services for the elderly and has continued to evolve, although its predominant role still revolves around the effective assessment, treatment, and rehabilitation of community living older adults with multiple health-care needs. The concept of Geriatric DHs was exported from Britain to other European countries, Canada, Asia, the United States, and Australia (where they are called *Community Rehabilitation Centres*). New Zealand DHs are usually sited in urban areas and serve geographically defined populations. There have been few attempts to provide such services to persons in rural settings (Rockwood *et al.*, 2000). The first DHs were set up in response to the clinical needs of frailer older people who could be effectively assessed and treated without the need for inpatient hospitalization. As a result, DHs were designed to function in response to many different parameters, but in general, the population of patients served is ambulant. Psychogeriatric DHs also exist, but are not as abundant as those with rehabilitative or medical purposes. They are not considered further in this chapter.

Day Hospital services have the potential to decrease hospital admission and prevent institutionalization, although, this has only been substantiated in communities where there is no comprehensive geriatric care system.

REFERRAL AND FUNCTION

While some patients are referred to DH following inpatient hospital treatment, family doctors form the usual referral source, often at the instigation of home-care health personnel. There are still few referrals from hospital specialists to DHs, although this is increasing.

Referral to DH rather than the outpatient clinic may be appropriate for a number of reasons, not least of which is transportation. This is usually provided without charge in the United Kingdom while other countries have nominal payments.

Most DH services concentrate on predominantly rehabilitative aspects of care, although others now focus on medical management in frail older people of specific diseases such as gastrointestinal disease, cardiovascular disease, and problems related to bone diseases including falls. Family doctor's involvement is also important. All DHs provide only periodic care and any medical management change must be quickly shared with the primary care physician.

One of the most useful aspects of DH assessment is the provision of adequate time and several viewpoints in the assessment of the older patient, not so readily

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available in a short outpatient clinic consultation. A particular strength is the tailored nature of care to the older patient with consideration of transport issues, meal provision, and mobility problems. The contributions of each member of the multidisciplinary team, especially the physiotherapist and occupational therapist are important for many patients.

In those DHs, which provide investigation and medical management, the greater amount of time allocated to patient assessment relative to conventional outpatient clinics means that investigations such as X rays and ultrasound can be performed on the same day enabling rapid therapeutic decisions to be made with minimum inconvenience to the patient. While patients may often derive intangible benefits from the social aspects of attending a DH, this is generally not the primary objective of DH nor has its impact on health been measured in clinical trials.

In most communities, day centers, programs, and clubs provide social and maintenance care specifically tailored to the needs of the older individual. Although the differences between each of these facilities from DH may be clear to those who work within specialized services for the elderly, they are not so readily apparent to the general public and even other health-care professionals. In contradistinction to the day centers, DHs have a defined role in assessing and improving management and health and have a greater number of health professionals available. It is important to note that day centers and day programs are seen as increasingly important in *maintenance of function* in elderly patients.

Patients with "*geriatric giants*" (Table 1) are referred to DH, with the possible exception of patients with a dementia of such severity that they cannot benefit from the services provided or are apt to wander away in nonsecure premises and for whom a medical DH is not appropriate. In recent years with the advent of newer treatments for Alzheimer's disease (and the likelihood of other complicating coexistent conditions), more patients with dementia are being *referred* for medical assessment give the likelihood of other complicating coexistent conditions. Patients frequently have visual and mobility problems and the provision of arranged transport by ambulance or some other means can have a major impact on the older patient's access to treatment facilities. In general, most DHs provide assessment and treatment of the common general internal medicine conditions of old age (Table 2).

The optimum period of attendance for DH is not clear and has never been addressed in a formal clinical trial. But patients generally attend for 6 weeks, as this time framework should enable the assessment and treatment of most of the appropriate conditions. The relative merits of longer attendance are not clear and longer periods of attendance are unlikely to contribute to significant health-care benefits.

Patients may attend DH for 6 to 12 weeks for rehabilitation, usually 10 to 20 visits, but this may vary in individual day hospitals. At each visit they will have specified periods of treatment, although this has never been standardized in practice or by comparison in clinical trials, with therapy predominantly directed toward specific goals. Many DHs strive for shorter admission periods. The ideal length of stay has never been firmly established nor the ideal amount of therapy.

Day Hospitals are best situated in easily accessible situations, avoiding congestion at elevators and allowing easy drop off, of the attendees. There should be generous toilet facilities and adequate space for the physiotherapist and the occupational therapist and the other professionals (nutritionist, speech pathologist, social worker, nurse, nursing aides, and recreational therapist as example) who may form the team. Increasingly, medical students, other learners, and postgraduate trainees spend time in DHs and students appreciate the wide array of pathology and the willing cooperation of patients. Day Hospitals are often sited in contiguity to inpatient rehabilitative services, which has the advantage of sharing the staff and reinforcing the continuity of care. They can also be sited in Centers for Ambulatory Care where there is more of an emphasis on the community aspects of management or in other sites such as shopping malls, but with an association to a larger health facility.

Table 1 Conditions frequently managed and assessed in DH

Geriatric giants
Incontinence
Autonomic instability
Adverse drug reactions
Cognitive impairment
Falling

Poor mobility/falls
1. Stroke/TIA
2. Parkinson's disease
3. Osteoarthritis
4. Osteoporosis
5. Cardiac arrhythmias
6. Postural Hypotension

Breathlessness and fatigue
1. Heart failure
2. Chronic obstructive pulmonary disease
3. Chest infection

Anemia secondary to
1. Gastrointestinal blood loss
2. Chronic disease
3. B_{12} deficiency
4. Malignancy
5. Other causes

Symptoms caused by depression/dementia
1. Hypothyroidism
2. Vasculitis

Table 2 Some indications for referral to DH

- Postdischarge surveillance
- Rehabilitation following recent illness, for example, stroke, hip fracture
- Investigation and management of medical conditions, for example, anemia, heart failure, arthritis, Parkinson's disease, other neurological conditions.
- Falls assessment
- Assessment by speech and language therapist, dietician, physiotherapist, or occupational therapist.
- Nursing procedures, for example, catheter insertion/change
- Respite

FUNCTION

The key function of DH is access to comprehensive multidisciplinary assessment followed by instigation of appropriate treatment for older adults living in the community. Part of the comprehensive assessment process includes a team review with treatment programs tailored to individual patient's requirements. The integrated treatment plan and time for adjustment and socialization are important for older persons as they recover from illness and improve their overall function from the point of referral. In this regard, the simple aspects of rehabilitation such as encouragement, listening, socialization, and education are important, not only for conditions associated with immobility such as stroke or depression but also for other more "organic" conditions of old age such as diabetes or heart disease. It is likely that the socialization and company provided are helpful, although this has never been measured as an outcome. Educating the patient is an important role.

Most DHs with a rehabilitation focus set specific achievable goals for each patient, often in collaboration with the patient and/or family members. Discharge takes place when those goals have been attained or as near to them as the patient is likely to get. Often the person is discharged to a day center or to a community exercise or activity program.

In the current climate of rigorous economic health evaluation, many regions are trying to more clearly define and focus the functions of their DHs, one of the main driving forces being to decrease acute-care admission and prevent institutionalization. This has led to an important trend over recent years in the United Kingdom. The *medicalization* of DH services has resulted in more patients attending for specific medical therapy and interventions than 10 years ago (Table 2). In addition to conventional rehabilitation, patients may be referred for assessment and treatment of heart failure or for multidisciplinary assessment following a fall.

Journey of Care

A typical schedule for patients attending DH may include:

1. transport;
2. initial assessment, medical evaluation/assessment by other team members;
3. establishment of goals to be met by patients during admission;
4. investigations, ideally on the same site, but if not, may be able to facilitate or assist with preparation for diagnostic tests;
5. variable number of sessions per week (usually 2, lasting 4 or 5 hours);
6. therapies including transfers, mobilizing, exercise, improved balance and strengthening, kitchen practice, recreational therapy, health education, and midday meal provided;
7. team review;
8. discharge with connection to community programs, if appropriate.

Within this framework, DH patients receive the synergistic benefits of multidisciplinary assessment and treatment. Although there may be overlaps between the different modalities of treatment, if the patient can attend regularly and has rehabilitative potential, progress is made in a relatively short period of time.

For example, the older patient who has recently fallen and suffered a loss of confidence as a result of several falls may have his/her balance and walking assessed and evaluated by a physiotherapist while during the same attendance he/she be assessed for potential arrhythmias, medication, and other medical triggers for falls. In addition, stroke prevention issues can be addressed if the patient has coexistent hypertension and atrial fibrillation. Input from a pharmacist, physician, or from the nursing staff to check patients' adherence with their pharmaceutical regime and to improve their understanding may help minimize drug interactions and may prevent problems such as postural hypotension or difficulties associated with anticoagulation. Further assessment by the occupational therapist may reveal functional or cognitive aspects not immediately apparent in the conventional medical assessment process. The information is shared at a case conference enabling a consistent and realistic overall management scheme for the patient. Sometimes the specific requirements of each patient may not be immediately apparent, but over the time, will become clearer with the predominant issues influencing overall function becoming more readily apparent.

EVALUATION

Several studies over the years have assessed the effectiveness of the DH services throughout the world with differing degrees of emphasis. Most have been designed to answer specific questions relevant to specific cohorts of patients, including the effect of treatment on morbidity, readmission to hospital and mortality. In the early years of DH services, cost effectiveness was less of an issue, but in modern health-care economics, this is an important consideration in the evaluation of any health-care service.

Evidence for the effectiveness of DHs from clinical trials is weak, although intuitively, many health professionals who work with frail elderly patients and their families believe that DH services contribute significantly to all aspects of care. The details of selected illustrative clinical trials are discussed below.

A meta-analysis (Forster *et al.*, 1999) considered 12 randomized controlled trials selected by predetermined criteria (2867 participants) and prespecified outcome measures which were death, institutionalization, disability, global "poor outcome", and use of resources. The researchers also divided the comparative analysis of the included studies into three preselected groups: DH versus comprehensive care (inpatient and

outpatient comprehensive geriatric assessment), DH versus domiciliary care (delivered in the patient's own home), and thirdly, DH versus no comprehensive care. The main conclusion was that DH patients showed trends in reduction in hospital bed use and placement in institutional care, but that there was no reported difference in mortality and subsequent deterioration. No cost saving was noted in any of the studies, although Long Term Care (LTC) placement and its substantial associated costs were reported for only two of the studies. Finally, it was noted that patients who underwent DH treatment regimes fared better than those patients who did not receive any form of comprehensive medicine for the elderly intervention.

Tucker *et al.* (1984) evaluated the impact of DH referral from both hospital and community care in a cohort of 120 patients in New Zealand at the inception of a DH service. Patients attended for on average 3 weeks for two sessions per week following an initial assessment of activities of daily living. Participants were randomized to DH care or standard care in their local health network. Overall function was improved in patients receiving DH care, although this function was not maintained in the medium term following discharge. Mood was improved over a 5-month period. Although this intervention was effective, there was difficulty in maintaining the benefit for a longer period of time without the need for rereferral.

In another study from Canada, Eagle *et al.* (1991) evaluated DH care compared with the usual care provided by the same group of geriatricians. The patient group was frail older patients referred to geriatricians, who included the patients into the study, if they felt that they would benefit from geriatric assessment. The study group attended DH for 2 days $week^{-1}$ for approximately 3 months. The control group was followed by the same geriatricians in geriatric outpatient clinics or if indicated in a geriatric inpatient unit. A total of 113 patients were studied. Outcome measured using the Barthel Index (Mahoney and Barthel, 1965), a Quality of Life Index (Guyatt *et al.*, 1993), was similar between the two cohorts of patients. In this study, the DH intervention was no better than usual geriatric care and there was no cost saving. Both groups deteriorated during the follow-up period. It should be noted that many of the patients were too cognitively impaired to complete a complex quality of life questionnaire.

Hui *et al.* (1995) in Hong Kong in another randomized clinical trial noted improvements in the Barthel Scores in stroke patients who received DH input as part of their intervention package after being discharged from hospital. More recent work has evaluated the 3-month follow-up of patients discharged from Geriatric DH. Although the number of patients included in the evaluation is small, there was no evidence of sustained improvements in mobility or functional status at 3 months following discharge from Geriatric DH. This is perhaps not surprising, as previous studies have not shown large benefits to such a group of patients. In one DH evaluation, those patients with the greatest disability as measured on the SF12 scale (Rand Corporation and Ware, 1979) and who were able to attend a DH derived the greatest benefit (Lewis *et al.*, 2000), a finding which needs further study. Other work has attempted to evaluate the economics of geriatric DH care and found, following a cost-benefit analysis, that benefit relating to a geriatric DH exceeds the cost of the program.

DEVELOPMENTS

Despite the lack of definitive evidence relating to clinical effectiveness, DH services continue to flourish throughout the world. In terms of factors shaping the development of DH services, and other medical services for older people, the Community Care Act in the United Kingdom has had a significant influence as the redesign and modernization of many services has focused on the need to deliver health care in more of a community setting. As a result, the number of hospital-based long-term care beds are decreasing with more older people being managed in both residential and nursing homes. In principle, reduction of long-term beds makes initial sense, but has resulted in a trend for an increase in the numbers of frailer older people referred to secondary health-care facilities.

One of the increasing roles for DH is the management of conditions which require some of the services usually associated with hospitalization in the short term, but which do not require all the high-tech facilities in an acute-care center.

In principle, therefore, prevention of decompensation is an important function of community-specialized programs for the elderly. Maintenance therapy has in the past been provided in day centers and in some DHs. There is little to be gained by patients attending DH for prolonged periods of time following initial assessment and treatment. With advances in investigative and radiological technology, there are opportunities for DHs to provide additional integrated services for older patients. For example, neurovascular clinics for the management of those patients who have had a transient ischemic attack (TIA) are becoming more widespread and integrated services for patients with Parkinson's disease and incontinence are already established on a fairly widespread basis. Newer initiatives include falls clinics, which have ready access to bone densitometry and facilities for the management of heart failure including echocardiography. More established roles for DH in some countries include provision of blood transfusions, preparation for gastrointestinal investigations and medication reviews by a clinical pharmacist.

Additional newer services provided by DHs make use of the increasing role of extended nursing duties. These include visits to the patients' homes to monitor International Normalized Ratio (INR)s or attach a 24-hour ECG tape if required. Further roles could relate to optimizing medication adherence, although it is important to act in conjunction with services already provided by district nursing teams.

In reality, the roles for DH are considerable, but it is important to achieve the balance between medical and

nursing care as well as the social aspects of care. When patients require predominantly nursing and medical care as well as the input of therapists, they should attend DH usually for a period of 4 to 6 weeks. Rehabilitative services may require a longer period. However, when patients are benefiting mainly in terms of social interaction that is the point at which they are best encouraged attending day centers and luncheon clubs.

Exercise plays an important role in the prevention of illness and the optimization of function. Many studies highlight the benefit of exercise in old age and patients attending DHs should be encouraged to attend exercise programs whether they are based in the DH itself or in another location. In addition to preventing cardiovascular disease and promoting well being, there is evidence that balance can be improved and falls decreased as a result of increased muscle strength and improvements in coordination (Gillespie *et al.*, 2001).

Most DHs have a considerable emphasis on holistic approaches to care. While this is important, it is still important that a diagnosis be established so that appropriate and effective treatments can be offered. While the use of specific therapies and drug treatments is likely to continue to increase, the multidisciplinary nature of care must be protected. Day Hospital provides a means by which effective, sometimes complex models of care can be delivered to an older population in a way acceptable to the patient.

Important changes are occurring in United Kingdom DHs and are being watched with interest elsewhere in the world. The concept of expanded comprehensive interdisciplinary assessment at the same time as management of significant medical problems is attractive and may avoid the hospitalization that is so often hazardous to the frail elderly.

Heart failure clinics improve management of chronic heart failure (Rich *et al.*, 1995). In older patients with heart failure, managed in a multidisciplinary setting, similar if not identical to many DH facilities, hospital admissions for heart failure are reduced with overall cost savings. This type of effective disease-specific intervention may be justifiable on a widespread basis in caring for the elderly in complex illness. Multiple pathology is the norm in the very old and multifaceted assessment and management are required. Epidemiological studies have confirmed the high prevalence of congestive heart failure (CHF) in specific cohorts of older people, but such patients with CHF often have cognitive impairment and mobility problems. Contributions from geriatricians, nursing team members, pharmacists, and other therapists combine synergistically to improve the overall quality of care. In addition to providing effective multidisciplinary management for older patients with established heart failure, DH patients can be prescreened for suspected cardiac disease.

A recent report highlighted the ability of brain natriuretic peptide (BNP) to incrementally detect cardiac disease in a cohort of older patients attending DH.[1] Screening older patients at DH with BNP may result in detection of cardiac disease and be useful in the assessment of older patients with vague symptoms who may have underlying cardiac disease (Hutcheon *et al.*, 2002).

DISCUSSION

When evaluating various forms of treatment, the randomized controlled trial is the benchmark for assessing efficacy. This is not the only valid means of evaluating DH care as qualitative evaluations and descriptive studies have some uses in these types of patients.

Traditionally, Barthel Index and Clifton Assessment Procedures for the Elderly (CAPE) (Pattie and Gilleard, 1979) scores have been used to evaluate geriatric medicine interventions. However, these instruments may be too insensitive to measure health-care benefits provided by DH care. Newer rating scales which concentrate on a population of less-frail, more ambulant older patients may be more useful in demonstrating some of the benefits on quality of life for DH patients. Disease-specific health-questionnaires may have a role as well as other general health-care questionnaires. A number of newer quality-of-life and health-care evaluation questionnaires for older people are currently being developed and may have a role in future studies. Goal attainment scaling allows the specific goals to be set by the patient and therapist and works well in showing response to change, although it does not function as well for comparison between patient groups (Rockwood *et al.*, 2003). The more recent health promotion aspects of DH care may reduce institutionalization and disability, but this has not been demonstrated as yet. Evaluation of these new uses should be a priority area for DH research.

Although the benefits of attending a DH may seem small, it is likely that small differences in management can result in significant benefits in function for the older patient. Maintenance of any benefits is important, but the reality is that many of the patients have multiple medical problems, which will wax and wane over a period of time with the chronic nature of their illness often the major limiting functional issue. Continued attendance at a day program may maintain function, but the ability to continue to attend may depend on health status.

In the nontrial world of routine clinical practice, the reality is that patients may benefit from different aspects of a comprehensive Geriatric Medicine Service at different times, as often they have multiple problems varying in severity over a given time course with differing and fluctuating health-care needs. Day Hospitals are heterogeneous and it is impossible to quantify the physiotherapy and other services patients receive either in the DH or in their own homes. There is no strong evidence for the amount and duration of therapy that is needed. In all of the published studies, outcomes important to patients are rarely considered. Minimization of handicap may be more important to a patient than disability or hospitalization. For example, if one can walk independently and without apprehension using a walking aid, this is a better outcome than the same disability without the ability to walk confidently. Focusing on the minimization of handicap rather than disability may also provide more positive outcomes. Such measures have not been used in the controlled DH trials.

Mortality as an outcome may not be as important to many older adults as it is to younger individuals and avoiding

institutionalization is of great importance to most elders. Quality of life issues, mood improvements, and the social impact on health of lonely older adults attending DH and subsequently connected to other programs should be included as outcomes.

One key question is whether DH services provide any additional benefit to conventional geriatric medicine assessment. The outpatient nature of DH care is likely to be more appealing to those patients who are more mobile and who could derive benefit from therapy while remaining in their own homes. In the comparisons of heterogeneous groups of patients, it is difficult to demonstrate the particular benefits of various service types. It is easier to demonstrate the benefits of a particular type of therapy provided to specific patients with defined disease states.

Staff who work in DHs like working there. They enjoy the ongoing patient contact and the hours of work. However, they must also be able to adapt to change, as DH attendance is an intervention in itself and, thus, may change when different evidence becomes available.

Patient preference is another relevant patient issue. Many patients who have considerable mobility problems prefer treatment to be delivered in their own homes. But this should be weighed up with the issues associated with the social benefit of encouraging older patients to mix where possible and the negative health effects of loneliness. Outreach services from tertiary centers may be effective in the management of the older patients discharged from hospital. In some cases, patients are managed by teams who contributed to their care while the patients were still in hospital.

Other ways of potentially evaluating and justifying the continuation and development of DH services include assessment of specific intervention programs as well as additional activities in the DH facility including exercise programs and fitness regimes.

The latter have proven to be effective in promoting a more active lifestyle for older patients and thus facilitating the postponement of disability. Exercise in older patients is increasingly being recognized as useful for patients with heart failure, falls and balance problems, as well as a means of maintaining mood and DHs provide an ideal site to start this process.

CONCLUSIONS

Day Hospital services have been in existence for over 50 years and have developed to include many newer features. As with most aspects of specialized health services for the elderly, the multidisciplinary nature of the care is of crucial importance. While the benefits of this type of care are clear to those involved in the management of patients, the evidence base is less compelling for a number of reasons including the difficulties of obtaining suitable controls for evaluation in randomized trials, the broad diversity of the patients, the actual professional services provided and the patients' expectations.

Not surprisingly, DH care does best when compared with no care at all. It is difficult to compare DH care with other forms of care, as the unique nature of this multidisciplinary care is its strength. Day Hospitals are in a time of development as health care changes its focus to provide more community care and the numbers of frail elderly continue to increase. Some of the more disease-specific components of a DH service including management of chronic diseases such as Parkinson's disease, heart failure, diabetes, and gastrointestinal blood loss are easier to evaluate. However, the benefits in situations such as poor mobility, falls, and incontinence are less easy to measure, but nonetheless just as important to patients. If responses to treatment are slow, referral to other appropriate services may be necessary to ensure optimum function and a DH should be part of a continuum of specialized geriatric services and a key component of medicine for the elderly services. Day Hospital bridges the gap between comprehensive inpatient geriatric assessment and community-based care of the older patient.

Although most DHs have a considerable emphasis on holistic approaches to care, it is important to establish a clear diagnosis in individual patients so that appropriate and effective treatments are offered. While the use of specific therapies and drug treatments is likely to increase, the multidisciplinary nature of care must be protected. Day Hospital provides a means by which effective and sometimes complex models of care can be delivered to an older population in a way acceptable to the patient of the twenty-first century.

NOTE

[1] BNP a cardiac neurohormone is elevated in heart failure and other cardiovascular conditions and can be easily detected by a simple blood test.

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KEY POINTS

- Geriatric DHs are key components of specialized health services for the elderly throughout the world.
- They usually provide a community-based rehabilitation service for older persons and a bridge between hospital and community care.
- The DH role can vary from a predominantly diagnostic and assessment center to a more supportive and

holistic facility using a wide variety of techniques and professional disciplines.
- Randomized trials have suggested that DH attendance reduces hospital bed use and placement in institutional care.
- Day hospital services are likely to expand and diversify in the future.

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Health and Care for Older People in the United Kingdom

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INTRODUCTION

The provision of health and care for older people in the United Kingdom is difficult to understand without a sense of its history, in particular the funding and management arrangements. This chapter seeks to provide an overview of these to enable an understanding of contemporary services (2004). The need for a continuity of service provision means this is an account of evolutionary development not revolution. Two key factors shape health and care needs (however determined) and resources (money, facilities, and most importantly people).

A lack of substantive information regarding population needs and evidence to underpin policy development is a recurring weakness in the United Kingdom. Two drivers, namely, the will to improve services (often prompted by the scandal of inadequacy) and cost containment have been consistent features. Continued changes to operational structures and practices have been introduced in an attempt to improve performance and control the threshold of access to services. There has been a tendency to add layers of services to cover cracks and plug holes rather accepting a coherent strategy of development, which has complicated matters. Lengthy periods of underinvestment have been followed by crises of provision and hurriedly conceived initiatives and investment.

The evolving nature of the older population in the United Kingdom are addressed elsewhere (*see* **Chapter 9, The Demography of Aging**), and the evolution of the health and care needs and the socioeconomic context in which they occur are clearly fundamental. Before the arrival of effective medical treatments, the patterns of disease and disability were quite different. Epidemic infections such as tuberculosis have been controlled and the burden of morbidity and mortality from diseases variously associated with lifestyle and environmental factors are now being impacted upon by improvements in prevention, screening, and various interventions. Concurrent improvements in general health and living standards have meant that within the overall improvement in the health of older people, the "geriatric" population is now significantly older and impaired through diseases (such as the Alzheimer's disease) that currently are characterized by limited treatment opportunities and progressive dependency. These new patterns of dependency have other implications; partners, peers, and friends are of limited ability to care. Similarly, the family support from children is changing; offspring are typically fewer in number, older, and often living geographically distant. These changes need to be considered in the context of the relatively low esteem and attractiveness of a career in care for younger people. It follows that care will become increasingly costly and whilst an increasing proportion of older people have considerable wealth, typically related to the value of their homes, there are present real and further future problems regarding the adequacy of income in later life. Simply, people retiring in mid to late fifth decade with increasing longevity have put pension funds under stress. The difficulties of funding retirements that are sometimes exceeding the contributory working life beneficiaries has been compounded by the poor performance of many of the pension fund investments.

AN OVERVIEW OF HEALTH AND CARE IN THE UNITED KINGDOM

The origins of current approaches to the provision of health and care can be traced to the Poor Law policies from 1597 and 1601. A key objective of these was to exert a control on societal order and reduce the numbers of vagrants and "masterless men". Before effective medical treatment, care was "the" option for the incapacitated.

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Much of the early provision was privately funded, often by wealthy philanthropists (e.g. industrialists). During the latter years of the nineteenth century, public involvement increased; for example, local parishes were enabled to form unions with workhouses becoming designated specifically for children, the aged, and infirm. Seeking admission to a Poor Law institution was not a soft option, and amongst many onerous commitments and selection procedures was a common requirement that applicants adopted the status of "pauperism", effectively being without personal means. Pauperism was commonly associated with a loss of the democratic right to vote. A Royal Commission (a British non-party political tool for gathering information and providing guidance for policy makers) was convened between 1832 and 1834 to consider the Poor Law system. It drew on extensive factual and subjective evidence (how many and what sort of people were in care) and in 1834 a new Poor Law was passed. As the nineteenth century progressed, the need for individuals to seek refuge under the Poor Law increasingly was as a result of illness and disability for which "infirmaries" were established by Poor Law authorities. The rules of Poor Law institutions were often well intentioned but in retrospect misguided; a typical example was observed in rules of a work house in north Somerset from the late 1800s that forbade inmates to be fed salmon more than thrice weekly (at that time, salmon was abundant and cheap, but considered to be of poor nutritional value).

The law requiring people to be classified as paupers before gaining entry to the infirmaries was abolished in 1885. The Poor Law was ultimately superseded by the local government act in 1929 and resulted in the transference of the functions of the old boards of guardians of the infirmaries to the county and borough councils. From 1930 to 1948, three forms of health-care provision could be recognized:

- Municipal hospitals: maternity hospitals, hospitals for infectious diseases like smallpox and tuberculosis, as well as hospitals for the elderly, mentally ill, and mentally handicapped, which were formed from the Poor Law infirmaries.
- Private health care: hospitals were fee-paying or voluntary; primary care was mainly fee-paying or insurance-based.
- Charity and the voluntary sector.

Older people were generally treated in municipal hospitals with the lingering vestiges of the Poor Law while most general hospitals evolved from the voluntary hospitals. Municipal hospitals had a lowly status that was unhelpful for older people, and commonly, clinical equipment consisted of discarded items from the general hospitals. There is a delightful irony in that some of the most distinguished teaching hospitals in the United Kingdom that evolved from large old infirmaries retain the name of Infirmary, with modern generations having little awareness of the historical stigma associated with the name.

In 1942, Sir William Beveridge pronounced "five evils" that overshadowed Britain – want, disease, ignorance, squalor, and idleness. Beveridge recommended a series of actions of which the welfare state was and is the most enduring and important for the United Kingdom, whether it is from a perspective of the vision, controversy, cost, or value. Beveridge was originally only asked to sort out the web of insurance services that were hindering development. In this, the rationalization of many small organizations unified to become the British United Provident Association (BUPA), which has continued to grow from insurer to extend into the provision of a wide range of health provisions including a large portfolio of facilities for the care for older people. The National Health Service (NHS) became reality on 5 July 1948. The key principles of the NHS were as follows:

- health care provided free at the point of use, although prescription changes and dental charges were subsequently introduced;
- universal eligibility, even for people temporarily resident or visiting the country. Anybody could be *referred* to any hospital, local or more distant;
- funding almost 100% from central taxation. The rich therefore contribute more than the poor for similar benefits.

The inception of the NHS coincided with a period of rapid medical development. Previously untreatable infections could be treated and often cured with newly developed antibiotics, while other drugs broadened the scope of medical effectiveness (for example, new diuretics for heart failure, anesthetic agents, and medication for the management of mental illness). While welcome, these early new developments ensured that balancing costs and expectations became embedded early and have remained an enduring feature of the NHS.

At the outset the NHS was, for administrative purposes, divided into three streams of activity, hospital services, family practitioner services (doctors, dentists, opticians, and pharmacists who remained self-employed contractors), and local authority health services (community nursing, midwifery, health visiting, maternal, and infant welfare clinics, immunization, and the control of infectious diseases). A "unified" structure was introduced in 1974 with three main levels of management, at district, area, and regional level. The 1974 organization proved wanting, being excessively managerially driven. In 1982, area health authorities were abolished to improve matters, but this also had a negative consequence on the integration and coordination of health and social services authorities.

Providing services for older people in the community (non-hospital settings) has remained contentious often because of an uncertainty in distinguishing health care from care (Timmins, 2001). Care services may be exemplified by home help support (cleaning, shopping, washing, and the like). Some health-care support is well defined, for example, visiting services for leg ulcer care, but there are substantial areas of overlap that remain disputed, illustrated by whether assistance with personal care such as bathing is a health intervention or an act of care. The significance of this becomes clear when it is recalled that health care remains free at the point of delivery, but that care is means-tested. Where services have not been well integrated and local

arrangements remain unclear, these issues have often proved quite intractable!

In the early 1980s, the realization that long-term care provision was quite inadequate led to a freeing up of benefits for older people who needed or "chose" to enter care. Care homes mushroomed outside the usual restraint of planning and while many homes were laudable in their aims and the standards of care provided, a large proportion of facilities were provided from largely redundant boarding houses in seaside resorts and the like. Needs and means assessments were perfunctory, and care homes proliferated on the largesse of an inadequately managed benefits system. Concurrently, a lack of commitment was evident for NHS long-term care competing with new treatment technologies.

During the late 1980s and 1990s, an attempt to make the health service less monolithic and more responsive to needs resulted in a policy that created an internal market splitting purchasers and providers. General practitioners were encouraged to become "fund holders", a driving force was to reduce waiting lists for elective treatment. The internal market of the NHS and Community Care Act 1990 produced some of the biggest changes in the welfare state since the Second World War, with local authorities having overall responsibility for community care. From April 1993, local authorities became responsible for the assessment of people's needs and care management. This included the allocation of funds for places in nursing and residential homes as well as other services such as domiciliary care. Furthermore, local authorities were mandated to encourage and promote the development of private and voluntary agencies by purchasing care or services from them. The intention was that a "mixed economy of care" would bring better services as a result of increased competition from a variety of providers. An objective was to remove the financial incentive for people to be placed in care homes and promote the development of domiciliary support and other services that enable people to stay in their own homes. The budgets of local authorities were limited, and commonly older people were provided with levels of care that were "just" adequate with little capacity to address increasing dependence.

Community care enabled the frailest old to largely escape the outdated facilities that lingered from the Poor Law and promoted more home care and more domestic institutional care in new care homes. The infrastructure of geriatric medicine remained largely centered in hospitals, and the clinical responsibility for the most frail and vulnerable defaulted to over-stretched primary care (general practitioners). The internal market brought some change to traditional waiting lists, but it did not extend into acute and emergency systems or chronic disease management. Many older people whose needs could have been more proactively managed avoiding acute episodes were managed reactively by acute services with increasing numbers of older people being uncharitably termed *bedblockers*.

Following the election of "New Labour" in 1997, a new "third way" of running the NHS – driven by performance and benefiting from partnership – was sought. This was largely based on a more collaborative approach than the overt competition of the internal market. It is premature to determine whether the substantial investment to support this will produce lasting benefit to the health service. A series of National Service Frameworks (NSFs) have accompanied the modernization program including one for older people, that signaled objectives with varying levels of expectation regarding achievement. Published in 2001, the NSF for older people provided an extensive program that sought to (NSF, 2005)

- tackle age discrimination, to make it a thing of the past, and ensure older people are treated with respect and dignity;
- ensure older people are supported by newly integrated services with a well coordinated, coherent, and cohesive approach to assessing individual's needs and circumstances and for commissioning and providing services for them;
- specifically address those conditions which are particularly significant for older people – stroke, falls, and mental health problems associated with older age; and
- promote the health and well-being of older people through coordinated actions of the NHS and councils.

The NSF sought to make progress through a series of eight standards that were linked to targets (milestones); these were:

1. Age discrimination: People should be treated equitably on the basis of needs rather than by age.
2. Person-centered care: Interventions should have the best interests of the individual as the central objective.
3. Intermediate care: In recognition that older people may require longer to recover or rehabilitate following illness, a range of services are to be provided to enable them to achieve the best possible outcome and minimize the risk of inappropriately being admitted to long-term care. The expectation was of a host of new services, but much of what has been reported has been a renaming of existing services.
4. General hospital care: Older people's care in hospital is to be delivered through appropriate specialist care and by hospital staff who have the right set of skills to meet their needs.
5. Stroke: The NSF was perhaps most explicit in making clear expectations for community and hospital approaches to stroke by April 2004, but audit by the Royal College of Physicians indicates a significant failure to achieve the milestone.
6. Falls: The aim of this standard is to reduce the number of falls which result in serious injury and ensure effective treatment and rehabilitation for those who have fallen. The NSF sought that services should be operational by April 2005.
7. Mental Health in older people: Older people who have mental health problems should have access to integrated mental health services provided by the NHS and councils to ensure effective diagnosis, treatment, and support, for themselves and their carers. The lack of specification and significant means of audit has rendered this

little more than a well-reasoned recommendation in many areas.

8. Promotion of health and active life in older age: Health and well-being of older people is to be promoted through a co-coordinated program of action led by the NHS with support from councils. While there have been sporadic initiatives, Thai Chi and other commendable exercise initiatives remain rare.

The principles of the NSF were to apply to the care of older people wherever they were receiving care across the spectrum of health and social services, in their own home, a care setting, or in a hospital. Unlike other framework programs such as those for heart disease and cancer, new investment was notably absent and targets somewhat fuzzy. For many older people awaiting planned interventions such as cataract surgery or joint replacement modernisation initiatives have significantly improved, though it is unlikely that the NSF can claim any significant part in this. The vulnerable old, particularly those needing ongoing care, have simply not benefited. Indeed, while the hearts and minds of enthusiastic practitioners found a rallying point in the NSF, the lack of managerial targets have undermined its success. Much work has been focused on avoiding "inappropriate" admission to hospital and facilitating discharge from hospital to reduce "bedblockers" rather than questioning and addressing the causes and underlying trends in needs.

The concerns and uncertainty that surrounded long-term care led to the establishment of a Royal Commission by the new Labour government to provide guidance with regard to long-term care policy, as reported in 1999. The principal recommendation concerned funding and establishing processes to provide understanding of needs and assurance in care provision:

- The costs of long-term care should be split between living costs, housing costs, and personal care. Personal care should be available after assessment, according to need and paid for from general taxation: the rest should be subject to a co-payment according to means.
- The Government should establish a National Care Commission to monitor trends including demography and spending, ensure transparency and accountability in the system, represent the interests of consumers, and set national benchmarks, now and in the future.

(Royal Commission on Long Term Care, 1999)

Though there was a broad welcome for the Commission's report, the policy response was partial, in no small part due to the fact that not all the Commission supported the majority findings and a minority report was appended. The lack of unanimity regarding funding liability undermined political commitment. In spite of the Commission's concerns regarding the complexity of processes and administration, the route to care and responsibilities have increased. In England, the present policy is broadly outlined by an illustrative example of an older person sustaining a stroke with severe disability, for which hospital assessment and circumstances determine that long-term care in a care home would be the most appropriate care option. Firstly, it should be determined whether the individual warrants fully funded NHS care. It remains a matter of concern that the criteria for this are less than transparent, and fully funded care remains exceptional. More generally, living, housing, and personal care costs will be provided to a locally agreed level on the basis of means-testing.

The local authority has a statutory duty under the National Assistance Act 1948 to pay for the costs of care, provided that the individual is assessed as needing it and is unable to pay. The local authority also has an obligation to offer the individual a choice of a care home. If the care home of choice costs more than the local authority would usually pay, if no other home is available or the needs of the individual are such that the home is suitable to provide the care, then the local authority must meet the full cost of the care (subject to any contribution paid by the resident as a result of a means test). If the care home costs more than the local authority would usually pay for the care, under limited circumstances the resident may pay the difference between the cost of the care and the amount the local authority is prepared to pay. More usually a third party, a relative or a charity, may pay the difference. The payment is generally referred to as a *top-up* or *third party contribution*.

Under the Health and Social Care Act 2001, the responsibility for purchasing nursing care was transferred from local authorities to the NHS. Primary Care Trusts undertake an assessment of the individual's nursing care needs. If the individual is assessed as needing nursing care he/she will be allocated a band of low, medium, or high, subject to need. Payment is made directly to the nursing home subject to the band the individual falls into. The lack of consistency and clarity regarding eligibility for fully funded nursing care has led to a large number of complaints which the Health Service Ombudsman has investigated and have been the subject of several critical reports.

At the time of writing this chapter, further change in English health and care provision is likely. Health services are undergoing a radical change led by changing control of financial flows, with health commissioning increasingly vested with primary care and assessment and provision of means-tested personal care with social services. Increasingly, both sides can see the futility of parallel tracks and the confusion it creates for everyone and generally are keen for change. The Royal Commission report of 1999 recommended the establishment of a Care Commission; in practical terms this has been largely interpreted as a need for increasing regulation (see later in this chapter). What evidence exists indicates that the mental and physical disability of people in care is very high and is increasingly a consequence of neurodegenerative diseases and other forms of brain failure that require high levels of care.

An emerging trend is for new forms of housing that provide assisted living to become viable alternatives to care homes with externally sourced care being increased to meet even the highest levels of dependency. While choice is welcome, many professionals are becoming concerned that

this trend reflects more about encouraging a greater personal responsibility for resourcing care through self-funding.

GERIATRIC MEDICINE IN THE UNITED KINGDOM

The specialty of geriatric medicine has its roots in the Poor Law infirmaries that had been run by municipal authorities, with the early physicians emerging from the posts of the medical superintendents. Some of the pioneers in the specialty were remarkable individuals, physicians with vision, conviction, commitment and ability. Marjory Warren is rightly acclaimed for her work and influence from the West Middlesex hospital proselytizing key lessons such as diagnosing and treating remedial conditions and promoting rehabilitation. Warren wrote a number of influential papers that are exemplified by an enduring pragmatism; for example, in 1946, she wrote of the inadequacy of existing geriatric services (Warren, 1946)

> "In the past, with no comprehensive geriatric service, most hospitals in a desire to have a quick turnover, have tried to reduce to a minimum the number of admissions of chronic sick cases, and of these chronic sick less interest and attention have been given to the aged than to others, with the result that they have been lamentably neglected from a medical point of view".

The early physicians were astonishingly effective in making improvements to the quality of life experienced by institutionalized older people and undertaking research regarding the big issues that afflicted their patients. The limitations imposed by the basic facilities that these clinicians worked within cannot be overstated. The relative lack of support along with the lack of recognition of their contribution is even more outstanding. A number of names are venerated and listing them invariably leads to important omissions, so readers are recommended to the paper by (Barton and Mulley, 2003).

The specialist medical society, now the British Geriatrics Society was founded in 1947 the stated purpose of this being "the relief of suffering and distress amongst the aged and infirm by the improvement of standards of medical care for such person, the holding of meetings and the publication and distribution of the results of such research" and it defined geriatric medicine (geriatrics) "is that branch of general medicine concerned with the clinical, preventive, remedial and social aspects of illness in older people. Their high morbidity rates, different patterns of disease presentation, slower response to treatment and requirements for social support call for special medical skills".

The Society appointed Lord Amulree as its first President in 1948 and it gradually developed, holding its first Autumn Scientific Meeting at the Royal College of Physicians (London) in 1966. In 1972, the journal *Age & Ageing* was launched. The society now boasts a membership of over 2000, hosts two major scientific meetings for members each year, it has a number of special interest groups, and its journal has an enviable international status.

Many of the early geriatricians found themselves responsible for literally hundreds of beds with long waiting lists for admission. A principal role was triage and an attempt to avoid institutionalization by recognizing and treating or rehabilitating remedial cases. A feature from the early days of geriatric medicine was the collegiate working and interdependence with a wide range of health professionals. Nursing was fundamental to the specialty, but other disciplines developed with the specialty particularly, physiotherapy and occupational therapy. As time progressed, the range of professionals and as their professionalism has increased, the maintenance of a led team has become increasingly difficult.

A recurring theme of the specialty has been the classification of patients, initially by ability (ambulant, bedridden, incontinent, simply confused and demented – requiring special care); then the specialty became increasingly defined by age. The retirement age of 65 initially marked the arbitrary transition from status as a medical patient to geriatric responsibility, itself having echoes to the old Poor Law. Subsequently, as the aging population evolved and the ability of general medicine extended, the defining age increased. Age-related services have in many places given way to integrated or needs-based approaches, and where they persist, the age qualification may be as high as 85. Integrated services typically include acute care for older people with general medicine and often provide "slower stream" resources for older people with complex or rehabilitation needs.

In 1984, Professor James Williamson from Edinburgh reviewed, in a lecture to the British Geriatrics Society, three phases of development of geriatric care, The Warren phase, The Community Care phase and a Preventative phase. Williamson voiced uncertainty regarding the specialties' future.

- *The Warren phase* is hallmarked by the understanding that there was potential for recovery and rehabilitation in many people who were typically consigned to institutional long-term care, that for those who did need long-term care had specialist needs in terms of facilities and equipment, and that surplus or discarded equipment from general hospitals were insufficient.
- *The Community care phase* is characterized by the recognition that intervention in the community was likely to avoid dependence, and that ongoing support often of a simple nature such as domestic support (cleaning, shopping) and ensuring heating could avert a need for more costly care. At this time, the institution widely known as the *day hospital* came into being. The driving force for this was primarily a crisis in staffing long-term care wards and realization that nurses and carers with family commitments may be available for day time employment, and that similarly some families would be able to provide care and support for their elders during the evening and night but not during the day when they were employed. The "day hospital" at its inception was fundamentally a provision of care and refuge. It was a product that typified the pragmatic, essentially practical, approach of the specialty, and soon day hospitals extended from providing refuge

to assessing, treating, and rehabilitating community-based older people.

- *Preventative phase* is built on the recognition that many older people underreported illness, and that screening could improve well-being and independence. This period during the mid-1960s coincided with a surge of development both in primary care and geriatric medicine, with academic recognition in universities and associated momentum in practice development.

Geriatric medicine in the United Kingdom enjoyed an international reputation and many countries developing services for older people visited to learn from the UK experience. British geriatricians have consistently taken the view that only by timely detection and intervention can admission to long-term care be minimized. Unsurprisingly, the notion that resources allocated for screening, diagnosis and early treatment would reduce the need for care found ready political support from successive governments responsible for financing.

The explosion of care homes and the shift of long-term care from the NHS to facilities deemed to be in "the community" led to geriatric services losing responsibilities for long-term care becoming fire fighters of acute disease in addition to general rehabilitation. Progressive geriatricians developed "disease"- and "presentation"-based practices targeting conditions that occur more commonly in later life (for example, Parkinson's disease, falls and continence). With some notable exceptions the admission to long-term care and continued oversight slipped from the grasp of geriatric medicine and the frailest old became increasingly disenfranchised from the specialty that had evolved primarily in response to their needs, and the clinical leadership and advocacy dissipated.

Many geriatric services had limited access to district hospital facilities until the mid- to late 1990s. This often meant that frail older people often acutely ill frequently had to travel to undergo simple X-ray examination. The widespread integration or establishment of geriatric services within acute hospitals has largely brought to an end these anomalies. Improvements in living standards cannot be overlooked, because as recently as the mid-to-late 1980s, many geriatricians could rely on admitting older people with hypothermia throughout winter as a consequence of inadequate heating. This has become a real rarity with hypothermia and its management almost disappearing from the skill set of geriatric departments.

The changing landscape of provision with entry to long-term care determined largely by social services departments and the level of nursing care to be commissioned determined by primary care arguably led to a loss of focus of geriatric medicine. Previous responsibilities to long-term care were replaced by a new commitment to acute care, and patterns of provision varied widely from hospital to hospital diminishing the clarity of purpose for the specialty.

In 1972 Bernard Isaacs, then a consultant at the Glasgow Royal Infirmary (later Professor of geriatric medicine at the University of Birmingham), published a book with colleagues entitled, "Survival of the unfittest: a study of geriatric patients in Glasgow" outlining serious deprivation for many older people and in particular describing a "Geriatric Hard Core" (Isaacs *et al.*, 1972):

> "The hard core is a black circle in the heart of the aging population. It is growing rapidly as the number of people who survive into advanced old age grows; as they outlive their spouses and friends; as their economic and social resources dwindle; and as the strength of their bodies and the clarity of their minds become eroded by undiagnosed and untreated disease".

Isaacs and colleagues described geriatric medicine as not being the medicine of the hard core, but that it might define the approaches of doctors that practice in this domain. The transfer of commissioning to primary care and the national service framework for older people (as described earlier) has effectively set a new framework within which geriatric medicine will need to reinvent itself. Some Primary Care Trusts have recognized the loss of specialist geriatric support and made appointments of "Community Geriatricians", often experienced consultants keen to be reengaged with their patients.

THE REGULATORY MAZE

Regulation of health and care has a tradition of developing in response to crises and scandal, which lead to new standards to be met by health and care providers.

The Health Advisory Service (HAS) was created in the early 1960s in response to a scandal regarding the care of people with learning difficulties in the Ely Hospital in Cardiff, a body that oversaw the "Cinderella" services, namely, psychiatric and geriatric health services. The HAS undertook programmes of service reviews that reported to health authorities, not only did the HAS point out deficiencies but it also commented positively on examples of good and innovative service provision. Perhaps the greatest strength of the HAS was that its director presented an annual report to government. Its directors and assessors were appointed on secondment from consultancies or academe either related to geriatric or psychiatric care. Many of the critical HAS reports were in respect of health service provided long-term care.

The HAS lost touch with a significant part of its constituency of older people with the shift of long-term care provision from the NHS to local authority social-services-commissioned care. Whether the HAS failed to respond to the changes in provision or was unable to do so, its role as a statutory entity for developing standards of care waned. It persists, though it now has the characteristics of a consultancy rather than a statutory centrally funded body that inspected and reported on services.

Central bodies and regulatory authorities have been established, for Health Services, the Commission for Health Audit and Inspection (CHAI) was founded in 2000 to be succeeded in 2004 by the Healthcare Commission which in addition incorporated aspects of the Audit Commission. Concurrently, social care was regulated initially by the National

Care Standards Commission (NCSC) that has been superseded by the Commission for Social Care Inspection (CSCI) that has incorporated the social services inspectorate. Both the Healthcare Commission and the CSCI are, at the time of writing, still relatively immature bodies. Serious gaps in regulation persist, for example, regulators of care hold providers to account, but there is a discontinuity with commissioners of care not being regulated by CSCI. This means that if inadequate care is purchased for an individual, it is the provider that presently remains accountable. It remains to be seen whether collaborative working between the two regulatory commissions will be forthcoming. The disjointed monitoring and regulation of health and care has proved problematic. An example that has attracted much public concern is the use, misuse, and abuses of medication, particularly neuroleptic agents. CSCI have increasingly inspected the storage, administration, and documentation of medication in care homes. However, the Healthcare Commission has (at the time of writing, late 2004) not actively been involved in the acts of prescribing or dispensing.

Concern regarding the abuse and mistreatment of older people receiving care has led to complex procedures for vetting potential employees and the establishment of a register of miscreants who have been determined unfit to work with vulnerable adults. Paradoxically, these arrangements were introduced into care provided by independent and charitable providers but not as yet to NHS workers, yet perhaps the most shameful case has been that of Dr Harold Shipman, the NHS GP who systematically murdered hundreds of his predominantly older patients.

The regulation of services for older people has become a major industry not only with CSCI and the Healthcare Commission but also the health and safety executive, not to mention advisory organizations such as NICE (National Institute of Clinical Effectiveness) SCIE (Social Care Institute for Excellence) and various Royal Colleges relating to professional groups. It is seemingly inevitable that the next step in developing regulation will be a degree of convergence of CSCI and the Healthcare Commission.

RESEARCH AND DEVELOPMENT

The early pioneers of geriatric medicine undertook much research in often extraordinarily testing circumstances. Dr Thomas Wilson, the first appointed NHS geriatrician (to Redruth in Cornwall) was typically innovative. Wilson reported various forms of bladder dysfunction in the Lancet, which have largely stood the test of time, having access to little more than red rubber tubing and manometers in surroundings that were extremely basic.

Development of the care for older people relies upon sustained programs of longitudinal research that can inform changing needs and provide authoritative reference regarding the effectiveness of various innovative approaches. In general medical specialties of interventional and therapeutic medicine there is a great pressure for evidence – for example, pharmaceutical innovations have a limited patent life, so companies need to ensure that products have an active evidence-base and they also have to have a "pipeline" of further new products to maintain their momentum; standing still is not an option. The scenario is very different when considering the provision of caring services. The most obvious pipeline is of older people!

Tension whether research should be clinically led or more socially orientated often leads to suboptimal parallel streams of work that is variously duplicated (clearly the correct approach is "integrated").

The care of older people has not been an area of major investment in relation to the size of the resources consumed by older people. Additionally, this chapter has described how geriatric medicine has become remote from the frailest and more concerned with acute care. The processes through which universities in the United Kingdom appraise the value of academic departments are largely centered on financial performance (grants won). Collectively, these factors have undermined academic geriatric departments in the United Kingdom generally and substantive research into frailty and care has become very limited.

CONCLUDING OBSERVATIONS

Geriatric care emerged from the Poor Laws and in many ways has contributed to the successful care of the aging in the British population. The needs and opportunities for health and care continue to change. The dual drivers of improving standards and managing resources remain key determinants of change and value. The population of older people in the United Kingdom generally is likely to continue to improve in health and life quality. An important and growing section will require high levels of care, and the difficulty of finding people willing to undertake caring roles is likely to be a continuing challenge. In 1962, Peter Townsend concluded his famous survey of residential institutions and homes for the aged in England and Wales with a statement that seems as pertinent today as then (Townsend, 1962):

"It may be worth reflecting, if indeed a little sadly, that possibly the ultimate test of the quality of a free democratic and prosperous society is to be found in the standards of freedom, democracy and prosperity enjoyed by its weakest members".

KEY POINTS

- Care of older people in the United Kingdom has a tradition rooted in philanthropy that has evolved through the welfare state to an increasing personal responsibility.
- The needs of the aging population are changing with the social deprivation of poverty being replaced

by disability related to the chronic diseases of aging.
- A key focus of geriatric medicine in the United Kingdom has been a proactive approach to minimize the numbers of people entering care. Processes and practice in care have received relatively little attention.
- A tension between increasing standards of care and resource management has been a consistent feature in the United Kingdom.
- Regulatory zeal has been disproportionate to research, commissioning, and, in particular, investment in training.

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Geriatrics in the United States

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INTRODUCTION

Modern geriatrics was developed in England starting with the innovative work of Majorie Warren and her colleagues. However, it took workers in the United States into the 1980s and beyond to provide a scientific basis for the theories of geriatric care. The United States can also claim the honor of naming the discipline "geriatrics". Ignatz Leo Nascher, who was born in Vienna, obtained his medical degree from New York University in 1885. He coined the term geriatrics from *geronte*, a group of men over 60 years who ran the legislative council (*gerousia*) of Athens. The birth of geriatric psychiatry can be traced back to Benjamin Rush who, in 1805, wrote an article entitled, "On the Condition of the Body and Mind in Old Age" (Morley, 2004). Geriatrics in the United States at the start of the twenty-first century is extremely fragmented, but still provides some of the most innovative high-quality care. In many cases, however, geriatric medicine still functions on principles of care that were in vogue 50 years ago.

DEMOGRAPHY

At the start of the twentieth century there were 3.1 million persons over the age of 65, representing 4.1% of the total population of the United States. By 2000, there were 34.9 million older persons, representing 12.6% of the total population. It is estimated that by the middle of the twenty-first century 20% of the population will be 65 years and older (Figure 1). There has been a particularly dramatic growth in the old-old with over 4.5 million persons being over the age of 85.

Table 1 lists the major causes of death in persons 65 and over (National Vital Statistics Report, 2005). While heart disease remains the leading cause of death, the age-specific death rate for both heart disease and cerebrovascular accidents has declined by over 50% in the last 50 years. In contrast, the rate of malignancy-associated deaths has risen by 30% in older males and nearly 10% in older females. The leading causes of hospitalization include heart disease, pneumonia, cancer, strokes, and fractures in older persons. These lists of deaths and hospitalizations are in contrast to the common chronic conditions seen with great frequency in older persons (Table 2). The United States (US), like most developed nations, is seeing a "squaring off" of the life expectancy curve, meaning individuals are living longer and dying at a greater frequency in the older years. This then means that older individuals are living longer with a greater number of chronic medical conditions.

The United States spends 13% of the gross domestic product (GDP), 1.8 trillion dollars, on health-care expenditures. There are 271 000 hospital discharges per year for persons 65 to 74 years of age and 482 000 for those over the age of 65. The number of US hospitals and length of hospital admission have dropped consistently since peaking in the early 1970s, but the number of outpatient encounters has tripled since that time (American Hospital Association, 2004). The average number of visits made to a physician each year increases from 1.6 at 15 to 24 years of age to 5.2 at 65 to 74 years of age and 6.8 at 75 years and older. The majority of these visits in persons 65 and older are for the management of chronic problems as opposed to persons under 45 years where most visits are for acute problems. Individuals aged 65 or older utilize one-quarter of outpatient encounters, half of hospitalization days, and one-third of the total health-care expenditures.

Approximately half of all physician contacts for older persons occur in the physician's office (Xakellis, 2004). The most common providers are internists and family physicians. Hospitalized older persons are most likely to be cared for by internists, while geriatricians (internal or family medicine trained) most commonly provide nursing home and home care. In contrast, over half of the outpatient visits of older persons are to specialists (Bragg and Warshaw, 2005). Nearly half of the practice of ophthalmologists, cardiologists, and

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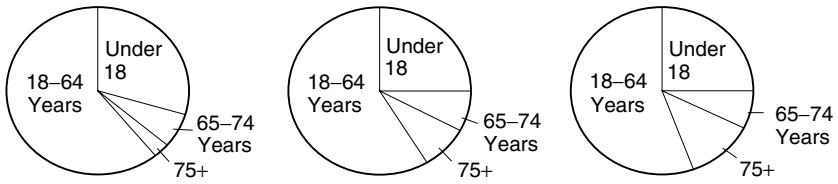

Figure 1 Percent of population in four age-groups: United States, 1950, 2000, and 2050. (*Sources*: US census bureau, 1950 and 2000 decennial censuses and 2050 middle series population projections)

Table 1 Causes of death in persons 65 years and older compared to the whole population in 2000

	Percent of all Deaths	
Cause of Death	Persons 65 and older	All ages
Heart disease	32.4	29.0
Malignant neoplasms	21.7	22.9
Cerebrovascular disease	8.0	6.8
Chronic lower respiratory tract disease	5.9	5.1
Influenza and pneumonia	3.1	2.6
Diabetes mellitus	3.0	3.0
Alzheimer's disease	3.0	2.2
Nephritis, nephritic syndrome, and nephrosis	1.8	1.6
Accidents	1.8	4.2
Septicemia	1.4	1.3

Table 2 Common chronic conditions per 1000 persons 65 years or older

Condition	Male	Female
Arthritis	411.2	534.5
Hypertension	298.0	410.8
Heart disease	311.3	238.0
Hearing impairment	386.8	243.2
Cataracts	140.1	194.3
Deformity or orthopedic impairment	156.5	158.4
Chronic sinusitis	109.6	122.5
Diabetes	121.8	84.3
Tinnitus	117.4	66.1
Visual impairment	103.8	70.0

urologists consists of patients 65 years of age and older. For this reason, 27 of the allopathic residency programs in the United States include special requirements for geriatrics in their training program.

Despite these health-care trends, older Americans in many ways are much better off than in the past. Seventy-two percent of the older population has graduated from high school compared to 17% in 1950. Overall, the net worth of older person households increased by 82% in the last 20 years. In 1959, 35% of older persons lived in poverty and by 2002 it was 10%. At age 65, the average life expectancy is 19.4 years for females and 16.4 years for males. Health screening and preventive medicine is accessible and funded by the vast majority of insurance plans. Figure 2 demonstrates the percentage of the different segments of the population who received influenza and pneumococcal vaccinations. The prevalence of chronic disabilities has decreased from 25% in 1984 to 20% in 1999.

HISTORICAL BACKGROUND

The development of social systems for geriatric care can be traced to 1861 with the military pension system for veterans of the Civil War. This was the precursor of the Veteran's Administration, formalized in 1930, which has had a major role in the development of scientific geriatrics as well as in providing outstanding care for older veterans. Other early care for old persons was provided in nursing homes run mainly by religious organizations, for example, Lafon Asylum of the Holy Family in New Orleans opened in 1842, or by poorhouses or rural poor farms.

By 1935, a rapidly increasing population of impoverished older adults led to the formation the Social Security Board which was reorganized in 1946 to become the Social Security Administration. This program provides a retirement benefit to individuals upon leaving the workforce. Although state and federal subsidies for health-care services were sporadically available in the 1920s, the first private hospital insurance plan (Blue Cross) was not provided until 1933. Further, discussion and development of government sponsored health insurance for the elderly spanned five Presidential administrations and over three decades.

Several important organizations developed in the 1940s and helped in establishing the discipline of geriatric medicine. The Club for Research in Aging was founded in 1939 with support of the Josiah Macy Jr Foundation. This group set the foundation for the Gerontological Society of America in 1945 with first President William MacNidder establishing the publication *The Journal of Gerontology* in the following year. The American Geriatrics Society (AGS) was organized in Atlantic City in 1942 by Malford W. Thewlis, with first President Lucien Stark presiding in 1943. The affiliated Journal of AGS was established in 1953. Both organizations have continued to sponsor these peer-reviewed publications.

Several decades later, in 1978, The American Association of Geriatric Psychiatry was established which spurred the development of fellowship training and certification in geriatric psychiatry in 1990. The American Medical Directors Association (AMDA) was also formed in 1978 and has become a leader in quality improvement initiatives in long-term care. AMDA has developed numerous clinical practice guidelines, training programs, and quality standards for nursing home care. This organization also administers and maintains the only recognized medical director certification program in the United States.

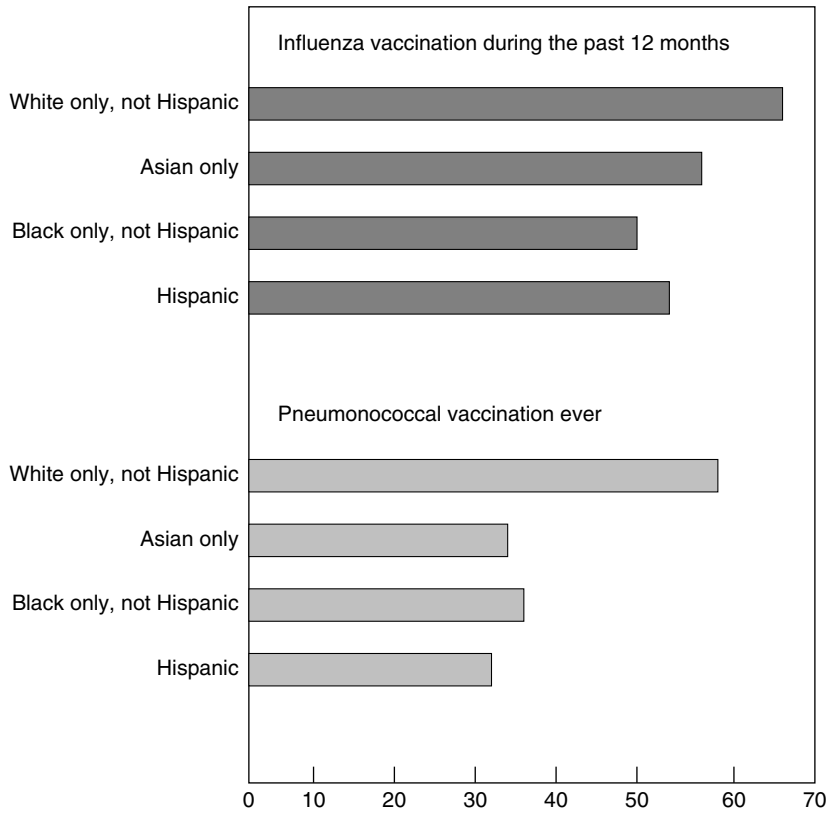

Figure 2 Influenza and Pneumonococcal vaccination among adults 65 years of age and over by race and hispanic origin: United States, 2000–2002

In 1950, through the efforts of President Harry S. Truman, the Federal Security Administration held a national conference on aging to assess the challenges posed by the changing population. No immediate programs were initiated, but this conference spurred the development of an advisory committee on aging. In 1958, Congressman John Fogarty, a Democrat from Rhode Island, called for the first White House Conference on Aging which took place in 1961. The major focus of the 1961 Conference was health care and significant outcomes included expansion of Social Security benefits and support for the later development of government funded health-care financing. In 1965, insurance was finally guaranteed to older adults, the disabled, and the impoverished through the passage of Medicare and Medicaid programs.

Subsequent White House Conferences have been held nearly every decade since 1960. Of importance, the 1971 White House Conference on Aging recommended the creation of a separate National Institute on Aging. Recent Conferences have emphasized health-care coordination and maximizing the effectiveness of existing programs for the elderly.

Geriatric Research, Education and Clinical Centers (GRECCs) were authorized by the federal government with the first sites established in 1975. The GRECC mission is to focus attention on the aging veteran population, to increase the basic knowledge of aging, and to transmit knowledge to health-care providers and improve quality of care to rapidly aging communities. GRECCs are based at Veterans Affairs Medical Centers (VAMC) and have played a major role in the development of scientific research and, in particular, in translational research and education in geriatrics. There are currently 21 GRECC sites across the United States.

The Veterans Administration (VA) also funded geriatric medicine fellowship programs beginning in 1978. 275 fellows were funded between 1980 and 1991. The purpose of the fellowship training program was to develop a cadre of physicians committed to excellence in geriatric research, education, and clinical care with the skills to become leaders of local and national geriatric medicine programs. In 2000, the VA established a Special Fellowship Program in Advanced Geriatrics at seven sites to develop academic and health systems leaders who are committed to leading this discipline in the twenty-first century.

As the discipline of geriatric medicine has evolved over the latter half of the twentieth century, US scientists and clinicians have been extraordinarily successful in developing assessment tools for older persons, which have gained worldwide acceptance (Table 3). Two new tools that have been recently developed are the Saint Louis University Mental Status Exam (SLUMS); (Banks and Morley, 2003) and the Simplified Nutritional Assessment Questionnaire (SNAQ; Wilson *et al.*, in press). These tools, provided in Table 4 and 5, are more refined than previously developed screening instruments.

Table 3 Screening tools for geriatric assessment developed in the United States

Date	Scale	Reference
1955	Barthel Index	Goldberg *et al.* (1980); Mahoney and Barthel (1965)
1963	Activities of daily living	Katz *et al.* (1963) Katz *et al.* (1970)
1969	Instrumental activities of daily living	Lawton and Brody (1969)
1975	Mini-mental status examination	Folstein *et al.* (1975)
1983	Geriatric Depression Scale	Yesavage *et al.* (1982–1983)
1986	Performance-orientated assessment of mobility	Tinetti (1986)
2000	ADAM	Morley *et al.* (2000)
2003	St Louis University Mental Status test	Banks and Morley (2003)
2005	Simplified Nutrition Assessment Questionnaire	Wilson *et al.* (2005)

ADAM, Androgen deficiency in aging males.

RESEARCH IN GERIATRICS

Research in aging was championed by Dr E. Vincent Cowdry who received his Ph.D. in anatomy from the University of Chicago in 1913. During his 65-year research career, spent predominantly at Washington University School of Medicine, Dr Cowdry focused on the cytologic changes of aging and cancer. He led both the Departments of Cytology and Anatomy at Washington University and was a strong proponent of interdisciplinary investigations in gerontology. During the later half of his career he authored several books including The Problems of Ageing: Biological and Medical Aspects (1939), The Care of the Geriatric Patient (1958), and Aging Better (1972).

During the mid-1900s, the US government was the primary financial sponsor of health-care research and scientific programs. The National Institute of Health (NIH) was formed in 1930 and later became a consortium of Institutes and Centers dedicated to health-care research. The National Institute on Aging (NIA) was formally established out of the NIH in 1974 and allocates significant funding to the advancement of aging research.

The roots of the NIA can be traced back to the 1940s and 1950s with the Unit on Aging, headed by Dr Edward J. Stiegliz, the Gerontology Branch, and the Section on Aging subsections of NIH programs. The first NIA director, Dr Robert N. Butler, was appointed in 1976 with Dr Nathan W. Shock directing scientific programs for the Institute.

Dr Shock was already well known to the geriatrics research community for his involvement in the Baltimore Longitudinal Study of Aging (BLSA) which he established in 1958. The BLSA originated through a 1-year grant to the NIH from the Josiah Macy Jr Foundation to develop a gerontology unit in the Baltimore City Hospital in 1940. Dr Shock was named chief of this unit, which later became the Gerontology Branch of the newly developed National Heart Institute. The BLSA evolved into a highly funded Gerontology Research Center which became the core program of the NIA at its inception.

In 1984, the NIA initiated Alzheimer's Disease Centers. The 32 existing centers focus on translation research, community education, and support of programs designed for patients and families. In 2001, the NIA funded nine Claude D. Pepper Older American Independence Centers, in honor of the former Florida Senator who devoted his career to improving the lives of older Americans. The Pepper Centers conduct interdisciplinary basic science and clinical and applied research that directly improves the lives of older people. The NIA also supports the Edward R. Roybal Centers for Research on Applied Gerontology through the Behavioral and Social Research Program. These centers are designed to move promising social and behavioral basic research findings out of the laboratory and into programs, practices, and policies that will improve the lives of older people. Supported for 5 years, the centers receive a total of $1.8 million in funding during their initial year.

During the last quarter century, there has been significant growth in the private funding of geriatric medicine research and education. Strong fiscal support has come from a number of organizations, starting with the Macy Foundation sponsorship of Dr Cowdry's 1939 textbook. Hundreds of millions of dollars have since been provided by charitable agencies dedicated to the care of the aging population.

Founded in 1929, The John A. Hartford Foundation is committed to health care, training, research, and service system innovations that will ensure the well-being and vitality of older adults. The mission of the Foundation is to increase the nation's capacity to provide effective, affordable care to its rapidly increasing older population. The Foundation is the leading philanthropic organization in the United States dedicated to the interests of aging and health. Since the early 1980s the Foundation has granted hundreds of millions of dollars to physicians, scientists, nurses, social workers, and other health-care providers for education, training, and research activities.

The Donald W. Reynolds Foundation, established in 1954 by media entrepreneur Donald Worthington Reynolds, is committed to improving the quality of life of America's growing elderly population through better training of physicians in geriatrics. The Foundation launched its Aging and Quality of Life Program in 1996. Its goal remains improving the quality of life for America's elderly by preparing physicians to provide better care for them when they become ill. The first Reynolds Center at the University of Arkansas was established with a grant of nearly $20 million. Since that time, 21 other centers have been funded with over $70 million in awards. In 1990, The Reynolds Foundation also began supporting the Association of Directors of Geriatric Academic Programs (ADGAP) to encourage the growth of training programs in geriatric medicine.

The Brookdale Foundation, originally endowed by the Schwartz Family, shares a common outlook and focus on the needs and challenges of America's elderly population.

Table 4 (SLUMS) Examination goes here

Saint Louis University

Mental Status (SLUMS) Examination

Name_____ Age _____

Is patient alert?_____ Level of education _____

/1	1	**What day of the week is it?**
/1	1	**What is the year?**
/1	1	**What state are we in?**
		Please remember these five objects. I will ask you what they are later. Apple Pen Tie House Car
		You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20.
	1	**How much did you spend?**
/3	2	**How much do you have left?**
		Please name as many animals as you can in one minute.
/3		0 0-4 animals 1 5-9 animals 2 10-14 animals 3 15+ animals
/5		**what were the five objects I asked you to remember? 1 point for each one correct.**
		I am going to give you a series of numbers and I would like you to give them to me backwards. For example, if I say 42, you would say 24.
/2		0 87 1 649 1 8537
		This is a clock face. Please put in the hour markers and the time at ten minutes to eleven o'clock.
	2	**Hour markers okay**
/4	2	**Time correct**
/2	1	**Please place an X in the triangle.**
	1	**Which of the above figures is largest?**
		I am going to tell you a story. Please listen carefully because afterwards, I'm going to ask you some questions about it. Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.
/8	2	**What was the female's name?**
	2	**When did she go back to work?**
	2	**What work did she do?**
	2	**What state did she live in?**
____		**TOTAL SCORE**

Department of Veterans Affairs

SAINT LOUIS UNIVERSITY

SCORING		
HIGH SCHOOL EDUCATION		LESS THAN HIGH SCHOOL EDUCATION
27-30	Normal	20-30
20-26	MCI	15-19
1-19	Dementia	1-14

The Foundation is committed to enhancing the training of a new generation of leaders in geriatrics and gerontology. The Brookdale National Fellowship Program, which began in 1985, sought those who had the professional expertise, capacity, and potential to become leaders in the fields of geriatrics and gerontology. Brookdale National Fellows conduct research which, it is hoped, leads to a society that is more knowledgeable and more responsive to issues related to aging.

SPECIAL PROGRAMS FOR OLDER PERSONS

Acute Care for the Elderly (ACE) Units

Since the original demonstration of the efficacy of these hospital-based units (Landefeld *et al.*, 1995; Palmer *et al.*, 1994; Miller, 2002), a number of university and community hospitals have established ACE units. The key features of the ACE Unit include (1) geriatric-sensitive environmental alterations, (2) patient-centered care, (3) interdisciplinary planning for discharge, and (4) medical care review. The goal of this model is to reduce the functional impairments that so often develop in acutely ill, hospitalized elders. Barriers to successful recovery and risks for ongoing functional decline are identified early in the hospitalization. Social and environmental factors that may impact independence and health are addressed by the hospital team. The quality of ACE units is variable across the country. For success, hospitals must commit to both the philosophy and care process of the ACE unit. Appropriate resources must be allocated, including recruitment and training of staff, time, and space for daily team meetings, and willingness to change the hospital environment for acutely ill elders.

Table 5 Appetite questionnaire to predict weight loss in older persons – SNAQ (simplified nutritional appetite questionnaire)

1. My appetite is
   (a) very poor
   (b) poor
   (c) average
   (d) good
   (e) very good
2. When I eat
   (a) I feel full after eating only a few mouthfuls
   (b) I feel full after eating about a third of a meal
   (c) I feel full after eating over half a meal
   (d) I feel full after eating most of the meal
   (e) I hardly ever feel full
3. Food tastes
   (a) very bad
   (b) bad
   (c) average
   (d) good
   (e) very good
4. Normally I eat
   (a) less than one meal a day
   (b) one meal a day
   (c) two meals a day
   (d) three meals a day
   (e) more than three meals a day

Instructions: Complete the questionnaire by circling the correct answers and then tally the results on the basis of the following numerical scale: A = 1, B = 2, C = 3, D = 4, E = 5.
Scoring: If the mini-CNAQ is less than 14, there is a significant risk of weight loss.

Acute Delirium Management: Delirium Intensive Care Units (Delirium Rooms)

A new model of care for patients with delirium in the hospital, called the *Delirium Room* (DR), was developed by Flaherty *et al.* (2003) The DR, established at St.Louis University Hospital, is a specialized four-bed unit that provides 24-hour intensive nursing care and is completely free of physical restraints. The DR is an integral part of a 22-bed ACE unit at the hospital. As such, patients in the DR benefit from features of the ACE unit while being closely managed by nurses and physicians who are acutely aware of the dangers to delirious older adults. This setting has shown to be effective in managing patients with delirium.

Another approach to delirium, through the use of a delirium consultation team, was pioneered by the geriatricians at Yale University (Inouye *et al.*, 1999). A standardized hospital protocol was implemented for the management of six risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. Addressing these six factors led to a reduction in the incidence of delirium in hospitalized elders.

Geriatric Care for Speciality Conditions

A number of special care units have been developed to allow physician comanagement or multidisciplinary management of hospitalized older adults. Despite longstanding use, and proven benefits of Orthogeriatric "Hip Fracture" Units and Stroke Units in the United Kingdom, these models are relatively new and infrequently applied in the US health-care system. On Orthogeriatric Units, geriatricians work together with orthopedists to manage hip fractures from acute injury through the rehabilitation process. In the United States, this partnership has been limited by the potentially competing roles of geriatricians and general/primary physicians in the care of hospitalized elders. On Stroke Units, patients are managed by a "Stroke Team" with the use of reflexive care management protocols and consultations to physician and therapy providers. Historically, geriatricians have not been providers on Stroke Units, and continue to have a limited role in the acute care of stroke patients. For these reasons and others, there has been growing interest in the training of subspecialty physicians in the care of the elderly. The John A. Hartford Foundation, specifically, has emphasized and funded programs to increase the training of geriatric medicine within subspecialty medical programs.

Geriatric Evaluation and Management Units (GEMUs)

The Geriatric Evaluation and Management Unit (GEMU) model was pioneered by Dr Larry Rubenstein at the Sepulveda VAMC (Rubenstein *et al.*, 1984). This model of subacute, multidisciplinary care has demonstrated effectiveness in a multicenter study (Cohen *et al.*, 2002) and in a meta-analysis (Stuck *et al.*, 1993). Although no difference was seen in short or long-term mortality, the GEMU process has demonstrated higher physical performance and better outcomes on general health survey scales for patients at time of discharge. Some of these benefits were still apparent at 1-year follow-up. GEMUs are commonly found in the VA, but are extremely rare in the general medical setting. The development of subacute care centers represents an attempt to translate GEMUs to the private sector (Makowski *et al.*, 2000). However, with the advent of the Prospective Payment System, the majority of these units are too costly to provide this level of specialized nursing care.

Program of All-Inclusive Care for the Elderly (PACE)

This model was developed out of the On-Lok program in San Francisco, which supplied social and medical support for predominantly the older Chinese community living in the downtown area. The 26 existing programs now provide care for older persons who are frail enough to meet the requirements to enter a nursing home (Gross *et al.*, 2004). The mission of PACE (Program of All-Inclusive Care for the Elderly) is to allow the older person to continue living at home rather than being institutionalized. Each PACE site provides comprehensive medical and social services to around 200 participants. Care is provided through participation in an adult day health center, but inpatient and home

care is provided as needed. Services are available 24 hours a day through the interdisciplinary care team. The PACE program provides near daily contact with enrollees by providing medications, meals, social services, recreational services, and transport, as well as routine health-care services. Each PACE site is federally funded via capitated payments from the Centers for Medicare and Medicaid Services and is expected to achieve a revenue-neutral status within several years of operation. In the United States, PACE represents one of the few comprehensive, all-inclusive systems of geriatric care.

Assisted Living Facilities (ALF)

Assisted care centers developed out of the "retirement community" model which traditionally accommodates only fully independent older adults. Assisted living facilities (ALFs) provide a bridge for older persons who are not yet impaired enough to require nursing home care, but cannot live alone. Also called Residential Care Facilities, these sites tend to provide minimal supervision in the medical area and instead focus on social and personal care needs. ALFs tend to be expensive, and because services are purchased in an *a la carte* fashion, potentially do not fully address the care needs of an older individual. To this point, ALFs are relatively unregulated by state or federal agencies. The quality of care and supervision is thus extremely variable, yet ALFs are a rapidly growing model of quasi-health care for seniors. Reimbursement for physician care provided on-site at ALFs is significantly lower than home care or office visits, despite the increasing level of chronic care delivered in these settings. Physicians are thus reluctant to focus care efforts at these sites and instead encourage patients to make the often difficult trip to a medical office. Given these issues, the American Geriatrics Society (AGS) in a 2005 position paper (AGS Health-care Systems Committee, 2005) has suggested the need to improve the quality of geriatric care at ALFs.

Nursing Homes

Four percent of persons over 65 years of age are in nursing homes. There are approximately 18 000 nursing homes with an average of just over 100 beds per nursing home. Fifty percent of nursing home residents are 85 years and over and 75% are female. At any time, approximately half of nursing home residents are receiving posthospital skilled care with a focus on rehabilitation. Federal sources (Medicaid and Medicare) account for 68% of the payment sources. Approximately 66% of nursing homes are owned by the propriety (for profit) sector, 30% by charitable nonprofits and the rest by the Federal and State governments (i.e. Veteran's Administration and Old Soldiers' Homes).

In 1986, the Institute of Medicine issued a report entitled, "Improving Quality of Care in Nursing Homes" and pointed out the shortcomings in nursing home care. In 1987, the Office of Budget Reconciliation Act (OBRA) created a number of regulations for nursing homes including the mandating of physician administrative services, nursing aide training, restraint and psychotropic drug reduction, and guidelines for reducing polypharmacy. Dr Mark Beers developed a list of drugs that should not be used in older persons – the so-called "Beers list" (Beers *et al.*, 1992). This list was revised in 2003 (Fick *et al.*, 2003) and despite its relative controversy, is applied to nursing home care by state survey agencies.

OBRA '87 also resulted in the development of the Minimum Data Set for Nursing Home Residents. This is now utilized to determine reimbursement for nursing homes and to provide a report card on nursing home quality that is available to the public on the Internet. Nursing homes are surveyed at least twice a year by teams of inspectors from the state. Poor performance can lead to fines or even closure of the nursing home. Many nursing homes in the United States have developed well-organized Continuous Quality Improvement (CQI) programs. CQI has led to extraordinary changes in quality of care in nursing homes in the United States. The focus on nursing home CQI was led by Schnelle and Ouslander (Schnelle *et al.*, 1993) and the Division of Geriatric Medicine at St Louis University (Morley and Miller, 1992; Miller *et al.*, 1995).

A specialized innovation in nursing homes has been the Eden Alternative. This model attempts to de-emphasize the medicalization and place emphasis on the home aspect of nursing homes. These nursing homes encourage pets in the facility and provide gardens for the residents. Empowerment of the residents to take initiative is an important component of this model.

Home Care

Physician-delivered home care was first implemented by the Homeopathic Medical Center in 1875. Originally, home care services were mainly obstetrical, then pediatric, but by 1975, 62% of visits were to the elderly. Under the guidance of Knight Steel, the center became a model for geriatric home care at what had become the Boston University Medical Center (Steel, 1987).

Over the past half-decade, the frequency of physician home visits has dropped significantly. In the mid-1900s, 40% of all patient–physician encounters took place at home. By 1980, less than 1% of health-care visits took place at home (Leff and Burton, 2001). Medicare and Medicaid provide 50% of home care coverage in the United States. The growth of home care services in the 1990s prompted a change in reimbursement from a fee for service to a prospective payment system reimbursement model. For each 60-day certification period, agencies are reimbursed around $2000 per enrollee. Over the last half century, home care in the United States has been predominantly delivered by nurses, social workers and physical therapists. Home visits in the United States have been shown to delay functional decline and improve health outcomes (Stuck *et al.*, 1995; Stuck *et al.*, 2002; Fabacher *et al.*, 1994). Recently, demonstration projects utilizing telemedicine in the home appear to be showing a new approach to home care.

Prescription Drug Financing: Medicare Part D

Medicare has not historically provided reimbursement for prescription medication. Medicaid does cover the costs of most medications for those elders who meet financial eligibility, generally those with an income at or below the federally established poverty level. Some seniors have supplemental insurance for prescription medication; however most pay substantial out-of-pocket medication costs. Medicare Part D, established under the presidency of George W. Bush, is a prescription medication benefit developed for Medicare eligible seniors. This program will begin on January 1, 2006, as the result of the Medicare Prescription Drug Improvement and Modernization Act of 2003. In an article titled "Understanding the Incomprehensible", Marshall (2004) attempts to explain Medicare Part D: "This act requires a basic premium of $420 a year and does not pay for the first $750. It then pays 75% of the next $2000 but nothing of the next $2850 (the truly incomprehensible part) and then pays 95% thereafter under most circumstances. This certainly is not a free drug benefit for seniors and as can be seen, is an incomprehensible bureaucratic policy!" Clearly, Medicare Part D will provide some prescription drug relief to seniors; however the long-term financing of health care and medication costs is in its infancy.

GERIATRIC EDUCATION

The development of academic geriatric programs and medical training has lagged behind the demand for a larger and more skilled geriatric medicine health-care workforce. This is in part due to the lack of universal acceptance of geriatrics as a unique discipline within the medical profession, and also reflects the declining trends in primary care residency training. Over the past 5 years, the percentage of internal medicine residency training positions filled by US medical graduates has dropped from 58 to 55%. The percentage of family medicine residency positions filled by US medical graduates has dropped from 57 to 41%. (National Residency Matching Program, 2005) The rising indebtedness of medical trainees and insecurity of Medicare/Medicaid reimbursement to physicians has compounded the problem. As a result, geriatric medicine fellowship training positions have become increasingly difficult to fill, with one-third remaining vacant in 2003. Over half of fellowship positions are filled by international medical trainees who have little guarantee of being employed in the United States as a geriatrician upon graduation. The number of fellows-in-training has remained essentially constant at 350 over the past 5 years despite the addition of 15 new fellowship training programs and 140 new positions available to trainees.

Dr Les Libow at Mount Sinai School of Medicine offered the first geriatric medicine fellowship program in 1966. The first professorship in geriatric medicine was granted at Cornell University in 1977. In the 1970s, the VA was charged with the task of increasing the education of health-care providers in geriatrics. Funding was provided in 1975 for the first VA Geriatric Research Education and Clinical Center (GRECC). Twenty-two GRECCs have since been established. GRECCs began offering geriatric medicine fellowship training opportunities in 1978.

In 1982, Mount Sinai established a Department of Geriatrics, the first of three to function as independent departments in the United States. Few of the 80% of medical schools with a geriatrics program have the current financial capability of supporting independent departments of geriatric medicine. Two-thirds of these geriatric programs have been in existence for less than 20 years. Two-thirds of geriatric medicine program directors have been in that position for less than 8 years and 50% have less than six faculty members.

In 1988, the Accreditation Council for Graduate Medical Education (ACGME) began accrediting geriatric medicine fellowship training programs. Sixty-two Internal Medicine and 16 Family Medicine programs offered fellowship training at that time. 1988 was also the year that an examination became mandatory to attain the Certification of Added Qualification (CAQ) in Geriatrics after at least 2 years of fellowship training. To be eligible for CAQ, physicians must have completed US residency training and be board certified in either Internal or Family Medicine.

Until the mid-1990s, most fellows in geriatric medicine engaged in two or more years of training. Extended training was vital for the development of an academic and research career in geriatrics. 1994 was the last year that a CAQ was offered for those who had not completed fellowship training in geriatrics. In 1995, the training requirement for CAQ in geriatrics was reduced to 1 year. Although this may have temporarily achieved a goal of more of fellowship trained geriatricians, it has not resulted in a greater number of physicians adequately prepared to embark on a successful academic career.

Despite the growth in the elderly population and the ACGME mandate for geriatric training in internal and family medicine residency programs, geriatrics continues to be underrepresented in the graduate medical education (GME) curriculum. Two-thirds of internal medicine programs reported 24 hours or less of geriatric medicine didactic training over the 3-year training cycle. Half of family medicine residency programs devote 24 hours or less to geriatric medicine didactic training (Warshaw website). It is thus of little surprise that, when surveyed, graduates of these programs report being unprepared to tackle the challenges of the aging population. Whereas 68% of graduating internal medicine residents feel "very prepared" to manage critically ill patients, only 52% feel very prepared to manage the elderly patient. Thirteen percent feel very prepared to manage nursing home patients (Blumenthal *et al.*, 2001). Forty-eight percent of graduating family medicine residents feel very prepared to care for the elderly and 27% to care for nursing home residents.

Other GME programs such as anesthesiology, obstetrics/gynecology, emergency medicine, urology, and physical medicine/rehabilitation now require geriatric medicine

training. Internal medicine, family medicine, and geriatric medicine programs frequently provide the training for these disciplines. The John A. Hartford Foundation, a significant granter of geriatric medicine programs, has specifically targeted surgical and medical specialties, as well as subspecialties of internal medicine, to improve the education of trainees in these disciplines.

Even though most medical schools have some form of structured geriatric program, the vast majority of undergraduate medical education curriculum integrates geriatrics into other coursework rather than requiring a separate geriatrics experience. Less than 8% of geriatric academic time is spent on teaching medical students. Didactic lectures on geriatrics occupy a mean of 14.4 hours in the medical school curriculum (Eleazer *et al.*, 2005). Students may not recognize these integrated experiences in geriatrics, however. Thirty-five percent of all graduating medical students indicated that geriatrics was inadequately taught across the 4 years of medical school, as reported by the Medical School Graduation Questionnaire in 2004 (Association of American Medical Colleges, 2004).

As the older population expands there is an ongoing need to train physicians, both generalists and specialists, in the principles of geriatric medicine. The emphasis on geriatrics must begin in undergraduate medical education if interest in primary care geriatric fellowship training is to increase.

GERIATRICIANS IN PRACTICE

The role of geriatricians, relative to general practitioners, is still evolving in the care of the older adult. Geriatricians receive a certificate of added qualification in geriatric medicine by the American Boards of Family Practice or Internal Medicine for a period of 10 years (Warshaw and Bragg, 2003; Warshaw *et al.*, 2002). There have been just over 10 000 physicians certified as geriatricians. Recertification rates have been disappointingly low with 43% of internists and 61% of family practitioners recertifying. The Certificate of Added Qualifications (now subspecialty) in Psychiatry became available in 1991. Nearly 2600 psychiatrists have certified and the recertification rate is 65%. On the basis of these figures, there are currently 6615 certified geriatricians in the United States or one geriatrician for every 2510 American citizens. It is estimated that 36 000 geriatricians will be needed by 2030 in the United States, a number far above what is likely to be achieved with current training program enrollment.

As might be expected, geriatricians practice predominantly in the outpatient setting. Two-thirds reported weekly involvement in outpatient primary care and long-term care. One-quarter to one-third were regularly involved in the inpatient management of geriatric patients. (Medina-Walpole *et al.*, 2002).

A survey of past geriatric fellows identified a major deficit in administrative training especially in long-term care medical directorship and Medicare/managed care. Graduates also felt a need for further training in psychiatry, neurology, rehabilitation, and hospice/palliative care. This may explain why less than one-third of practicing geriatricians report regular clinical activity in the areas of rehabilitation services and hospice/palliative care. The perceived training deficits are due, at least in part, to the time constraints of a 1-year fellowship training program. (Medina-Walpole *et al.*, 2004). After just 1 year of training, less than half of graduated fellows report practicing "essentially all" geriatrics. One-third of graduated fellows practice "primarily geriatrics" in addition to another discipline (e.g. general internal medicine) and one-quarter practice "secondarily geriatrics" (Medina-Walpole *et al.*, 2002).

Another explanation for geriatrician practice patterns is salary and compensation. The average assistant professor in geriatrics earns $118 000 and a full professor $174 000. These are similar to the amounts earned by general internists and pediatricians. Chiefs of geriatric divisions earn an average of $212 000. Geriatricians in private practice, however, earned a mean of $155 276 which is less than pediatricians and general internists. In comparison, gastroenterologists, a procedure-orientated speciality, earned $351 614. Thus, with significant school loans to repay and the disparity in earning potential with other specialties, it is not surprising that geriatrics has problems recruiting physicians in the United States. Despite these factors, geriatricians have reported themselves to be among the most satisfied of all specialists (Leigh *et al.*, 2002).

Geriatricians frequently focus on end-of-life care and may elect to become certified in hospice and palliative medicine. This certification requires either fellowship training in palliative medicine or significant clinical experience in the field. A certification examination is required. Physicians who work extensively in the nursing home setting can become certified medical directors through the AMDA. This certification requires completion of coursework and evidence of good standing as a medical director, but at this time requires no examination. Neither of these certification programs requires fellowship training in geriatrics or CAQ in geriatric medicine.

Nonphysician practitioners are increasingly involved in the care of older adults. Gerontological nurse practitioners (GNP) have a Masters degree in nursing, focused on the care of the elderly. These practitioners have become leaders in improving care in nursing homes. GNPs frequently work in partnership with a physician in the outpatient and nursing home setting. In most states, GNPs are provided some degree of independence in prescribing medications. Some states allow GNPs to practice independently or with limited supervision by a physician. Physician assistants (PA) also provide care for older persons but generally have less independence in clinical practice. The scope and duration of medical training for PAs is more limited than GNPs and closer supervision by a physician is generally required.

LEGAL ASPECTS OF GERIATRICS

In the United States, patients expect to be fully informed of their diagnoses. They also have the right to choose their treatment even if it does not appear to be the best choice to the physician. Patient autonomy frequently overrides the principle of societal justice. All patients are encouraged to have a living will and/or a durable power of attorney for health care. The ability of a physician to withhold treatment or withdraw life-sustaining technology requires the patient to have made clear statements regarding medical decisions while in full control of their mental faculties. Unfortunately, patient wishes and legal directives are often vague or unknown. If a patient has no legally stated wishes or guardianship and cannot make decisions for him- or herself, care can be directed by the next of kin. Most states consider the spouse, followed by adult children, and then parents as the hierarchy for next of kin. Surrogate decision making by the next of kin can be a frustrating and inflammatory situation when the opinions on care differ between family members, physicians, and customary ethical standards.

When unexpected or negative medical outcomes develop, there is a tendency to blame a person or a group for purposes of financial reconciliation. It is increasingly recognized, however, that medical errors result from a series of system-wide problems and require system-wide solutions. Nonetheless, legal suits have become a way of life in the United States. Malpractice insurance premiums have driven physicians out of certain states and out of practice, in some cases. Obstetrical, surgical, and nursing home providers are especially vulnerable to malpractice claims and rising insurance costs. Many nursing homes cannot afford malpractice premiums and simply operate without insurance coverage for the facility or the medical director. Many physicians simply chose not to practice in the nursing home or in regions where malpractice premiums and claims are prohibitive. The legal system has become a game where the plaintiff's lawyer takes cases on contingency and a substantial share of the judgment. In many cases, these lawyers pay physicians substantial amounts to be expert, but not necessarily honest, witnesses. Fear of large jury awards has resulted in the majority of cases being settled out of court for between $100 000 and $200 000, regardless of the merits of the case. This ultimately contributes to "defensive medicine" practices and escalation in the cost of medical care.

CONCLUSION

In the next 50 years, the population demographic in the United States will change substantially. Geriatric care now and in the immediate future represents an incredibly expensive, inefficient, and inequitable practice of health care. Older adults are the highest consumers of health-care resources and are increasingly dependent on state and federal governmental medical programs. Unfortunately, the current medical system rarely provides the comprehensive health-care services required to maintain function and independence in the aging and frail population. Inpatient medicine must evolve to ensure a safe and multidisciplinary approach to care of the older adult. Home and intermediate care settings require greater attention from physicians and leadership from geriatricians. Outpatient medicine must utilize comprehensive approaches to support the wellness of aging adults. While the United States has been a leader in geriatric research, there is insufficient emphasis placed on the training of future leaders in geriatric medicine. As the "baby boomers" age, there is a growing need to make all physicians and health-care settings better equipped to care for the elderly population.

KEY POINTS

- Geriatricians in the United States have provided leadership in conducting controlled trials on systems of geriatric care.
- Geriatric care in the United States is extremely fragmented.
- The Veterans Administration has been the leader in geriatrics research and education.
- There is a shortage of trained geriatricians in the United States.

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Geriatrics and Gerontology in Japan

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INTRODUCTION

The purpose of this chapter is to outline the trends of geriatrics and gerontology in Japan. The manuscripts on geriatric medicine and geriatric nursing were written by the coauthor, Takahashi, on the basis of reviewing the literature as well as conducting interviews with leading researchers in the areas. Following the same procedure, the manuscripts on geriatric psychiatry, epidemiological studies on aging, social gerontology, and psychological studies on aging were written by the author, Suda. These manuscripts were written first in Japanese and sent to the informants for proofreading, and eventually translated into English by the author.

GERIATRIC MEDICINE

Senior Citizens and Medicine

The longevity of Japanese men is 78.4 years. It is longer than that of those in other countries, with the exception of men in Ireland and Hong Kong who also have about the same longevities. The longevity of Japanese women is 85.3 years, which is the longest in the world. When viewed from a different perspective, more than half of Japanese men and three-quarters of Japanese women live for more than 80 years (The Ministry of Health, Labor and Welfare, 2004a).

Japan saw an increase of the older population within a very short time. The rate of increase of the population who were 65 years old and over was 7% in 1970. Within only 24 years, in 1994, the rate reached 14%. By comparison, France took 115 years, Sweden 85 years, England 47 years, and Germany 40 years to witness the same increase. Japan recently surpassed Italy and Sweden in terms of the rate of increase of the old population, and the rate is expected to reach 20% soon. The present high percentage of the old population is attributed to a progressively decreasing infant mortality rate and increasingly better health conditions among seniors (The Ministry of Health, Labor and Welfare, 2004a).

What is unique to Japan is that the longevity is significantly different between men and women. The difference is now about 7 years, and has been increasing over the past 20 years. This increasing difference of longevity between sex stems from the continuing decrease in longevities among men of younger age-groups since 1998. Especially, the increase in suicide deaths among men between the ages of 55 and 59 and above wields a serious impact on the overall longevity.

The primary causes of death among Japanese people are carcinoma, cardiovascular diseases, cerebral vascular diseases, pneumonia, accidents, and suicide. The differences by sex in the causes of death becomes distinct at the age of 80. The primary causes of death among men who are 80 years old and above are carcinoma (22.1%), pneumonia (17.3%), cardiovascular diseases (16.1%), and cerebral vascular diseases (14.2%). The primary causes of death among women who are 80 years old and above are cardiovascular diseases (20.7%), cerebral vascular diseases (17.0%), carcinoma (14.6%), and pneumonia (13.9%) (Cabinet Office, 2004).

Compared to other countries, the in-hospital days in Japan have been relatively long over the past few decades. However, the length of these days is becoming shorter in recent years (Table 1) as a result of the new reimbursement system introduced by the Ministry of Health, Labor and Welfare (MHLW).

The purpose of the new system is to control medical expenditures. Medical services in Japan are provided through the national public health insurance system. Formerly, the cost of care was reimbursed to hospitals or clinics on the basis of the treatment actually provided to patients. On the other hand, under the new system called the *Diagnosis Procedure Combination* (DPC) System, the payment from the national health insurance system is predetermined for each diagnosis and expected treatment for it. In addition, the reimbursement rate for acute care considerably drops when the in-hospital days of the patient exceed a certain period. In intermediate care, where patients do not need acute

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Table 1 In-hospital days in recent years

Year	2003	2002	2001	2000	1999
In-hospital days	20.3	22.2	23.5	24.8	27.2

Source: Ministry of Health, Labor and Welfare (2004b).

care but are in need of certain medical interventions, the reimbursement rate for medical activities is set low, whereas better rates are given to rehabilitation and personal care.

The new system first had an impact on the 82 hospitals that were designated as hospitals to provide advanced acute care, such as university hospitals. In order for the hospitals to maintain the high-tech equipment and human resources necessary to provide advanced acute care, they had to control the in-hospital days in a cost-effective manner. Because providing intermediate care in these 82 hospitals reduced their cost-effectiveness, the task was delegated to other hospitals. The hospitals specialized for intermediate care then attempted to maintain the provision of medical services at a minimum, because medical activities did not bring in enough reimbursement. As a result, fewer and fewer hospitals are accepting senior patients who need both medical interventions and personal care, such as those suffering from chronic heart failure or chronic obstructive pulmonary diseases.

Despite these problems, MHLW seems to be determined to control the medical expenditures further. One of the new approaches under consideration is to establish a separate insurance system for seniors. But such a system is expected to increase the financial burden on seniors, and fierce controversies are aroused.

Origins and Primary Institutions of Geriatric Medicine

The origin of geriatric medicine in Japan dates back to the history of Yoikuin. In 1872, the heir prince of Russia was scheduled to visit Tokyo. It was an imminent task to sweep away the mentally or physically challenged and the homeless who were living on the streets. As a solution, Yoikuin, a private nonprofit organization, was established to institutionalize these people. As years went by, the function of Yoikuin gradually changed to a permanent shelter for the poor. Because poverty was primarily the problem of seniors in those days, the majority of the residents were seniors, and Yoikuin naturally built skills to care for them. Physicians were invited from the University of Tokyo, who provided medical care to the residents in exchange for using the facility of Yoikuin as a field for teaching students. The building of Yoikuin was burned down in the Tokyo Great Air Aid by the Allied Forces during the Second World War, and the new Yoikuin Nursing Homes were built in 1958.

In 1972, the Tokyo Metropolitan Geriatric Hospital, the first geriatric hospital in Asia, was built on the same campus as Yoikuin. The academic activities of the geriatric hospital were focused on clinicopathological studies. The number of autopsies conducted were over 8000. The efforts were especially focused on clarifying the mechanisms of the diseases which were common to the Japanese such as cerebral vascular diseases and cardiovascular diseases (Kameyama, 1979; Ohkawa *et al.*, 1986; Sugiura *et al.*, 1982).

Another important institution, Yokufukai, was established in 1925. The Kanto Great Earthquake had occurred 2 years before. The purpose of Yokufukai was to accommodate the victims from the disaster who were old and had no relatives or those who were mentally or physically challenged.

Fujiro Amako came to Yokufukai as the chief doctor in 1926. Amako established a system to organize and store detailed records on episodes and laboratory reports on the 500 residents in Yokufukai. The data were compared with autopsy data that were collected after the resident's demise. The outcomes from the comparisons were shared in the Clinicopathological Conference that was sponsored by Yokufukai. Years later, leading researchers in neuro-internal medicine, circulatory medicine, and other areas appeared in great numbers through these activities led by Yokufukai.

The project led by Toshio Ozawa deserves attention as well. In the mid-1980s, Ozawa evaluated the physical functional capacity of seniors living in a small town where the rate of increase of the old population was extremely high. The functional capacity examined included activities of daily living (ADL), cognitive functions, social interactions, and so forth. In those days, focusing on functional capacity rather than on diseases was innovative. The awareness of the importance of a comprehensive geriatric assessment was dramatically raised after this project. In 1993, Ozawa was appointed as the president of the Tokyo Metropolitan Geriatric Hospital (1983) where he established the Geriatric Evaluation and Management Unit, the first institution in Japan solely focusing on geriatric assessment (Ozawa, 1998).

In recent years, as a result of the combination of a staggering economy and policy changes of the Tokyo Metropolitan Government, Yoikuin Nursing Homes and the Tokyo Metropolitan Geriatric Hospital were dissolved. The function of the The Tokyo Metropolitan Institute of Gerontology (TMIG) was extremely constricted as well. In the meantime, the National Institute for Longevity Science was established in 1995. The institute was merged with a hospital in 2004 and its name was changed to the National Center for Geriatrics and Gerontology.

Academic Activities and Education

The first academic journal on geriatric medicine was the "Yokufukai Geriatric Journal" or "Acta Gerontologica Japonica" under another name, which was first issued in 1928. The "Nippon Ronen Igakkai Zasshi", the journal of the Japan Geriatric Society, was first issued in 1964, and 30–70 original papers have been published every year since then.

The first annual meeting of the Japan Gerontological Society was held in Tokyo in 1956. In 1959, the Society changed its function to an umbrella organization to unite two suborganizations: the Japan Geriatrics Society and the

Japan Socio-Gerontological Society. Recently, new academic associations joined the Japan Gerontological Society: the Japan Society for Biomedical Gerontology established in 1981, the Japanese Psychogeriatric Society organized in 1986, the Japan Society of Gerodontology joined in 1991, and the Japan Society of Care Management in 2003.

Examples of the distinguished outcomes obtained in this area are as follows:

- Tauchi and Sato (1968) clarified the changes by age in size and number of mitochondria of human hepatic cells.
- Uchida and Tomonaga (1989) found that the brain extract from Alzheimer's disease (AD) brains did not efficiently inhibit the abnormal sprouting responses. Uchida and colleagues also isolated a unique metallothionein-like protein that controlled the process. The metallothionein-like protein was named as *Growth Inhibitory Factor* (GIF). The study suggested that deficient GIF may induce abnormal sprouting responses in AD brains, which entailed the neuronal death accompanied by the accumulation of senile plaques, neurofibrillary tangles, and curly fibers.
- Yokode *et al.* (1995) clarified that cigarette smoke extract directly influenced cholesterol metabolism, which promoted the development of atherosclerosis.
- Seniors whose swallowing reflex and coughing reflex are weakened tend to suffer from deglutition pneumonia because they swallow viruses in the mouth with saliva while they are sleeping. Yoneyama and colleagues (2002) indicated that mouth hygiene was effective in preventing such infection.
- The Ethic Committee on Geriatric Medicine in Japan (2001) suggested possible roles geriatricians could undertake in terminal care.
- Yamauchi *et al.* (2003) discovered that calcitonin is effective in the treatment of osteoporosis.
- Hirai *et al.* (1980) and Kobayashi *et al.* (1981) identified that eicosapentenoic acid (EPA) influenced blood viscosity and platelets. EPA is contained in fish and the Japanese eat fish more frequently than people in many other countries. The study suggested the possible relation between food intake and the low prevalence rate of cardiovascular diseases in Japan.

The system to train geriatric practitioners was not established for many years. In 1912, Tatsukichi Irisawa, then professor of internal medicine of the University of Tokyo, wrote in his textbook that "geriatric medicine would be the indispensable part of medicine in near future" (The Japan Geriatrics Society, 2003). However, it was not until the beginning of the 1950s that geriatric medicine was finally included in the curriculum for the first time in Japan at the Medical School of the University of Tokyo. In 1962, the first division of geriatric medicine was initiated in the University of Tokyo, and the second was established in the University of Kyoto in 1968. As of 2004, 24 medical schools have a division of geriatric medicine, which is about 30% of the total number of medical schools in Japan.

One of the challenges faced by geriatric medicine is stemming from the conventional system of medical schools and their related institutions. Each medical school comprises divisions that are focused on their own specialities, and there are little interactions among them. Likewise, the Japan Geriatric Society is considered as a branch of the Japanese Society of Internal Medicine and is isolated from other associations such as the Medical Association on Respiratory System and the Medical Association on Digestive System. This condition is in contrast with the way geriatric medicine operates in other countries, where the importance of the holistic understanding of patients and collaborative relationships with experts in different areas seems to be more emphasized. As an attempt to claim for recognition as a unique and independent profession, the Japan Geriatric Society introduced the certified geriatric-physician system in 1988. However, there are no good job opportunities for the certified geriatric specialists even to this date.

In 2000, the Blue-Ribbon Committee on Aging, which was summoned by the Japan Science Council, expressed their concern on the poorly organized condition of geriatric medicine while the number of old patients was rapidly increasing. Even though they strongly recommended the improvement of the system for education, care-providing, and research on geriatric medicine, little progress was made.

Recent changes in the society brought about more difficulties. For example, the legal status of national universities changed from governmental to private-public organizations in 2004. Because the subsidies from the government are decreasing, attracting enough students and funds is an urgent task. As part of the effort, national medical schools are concentrating on distinguishing themselves in cutting-edge studies. Private medical schools are facing a different challenge. The private medical schools have accepted a far larger number of students compared to national medical schools so that they could provide medical training with reasonable tuition. However, the central government has been changing its policy recently to control the number of physicians. In response, the private medical schools are providing highly advanced training to their students so that their graduates of many numbers will still survive in the competitive job market. In the turmoil, both national and private medical schools are turning away from the areas where prominent achievement is hard to make in a short time, such as education for and practice of geriatric medicine.

GERIATRIC PSYCHIATRY

Geriatric psychiatry has been playing a leading role in the studies on dementia. The effort to clarify the prevalence rate of dementia started in the 1970s. Kazuo Hasegawa conducted a survey of a large sample in 1972 and 1973, and identified that the prevalence rate of memory problems among seniors living in a community was 4.5%. In the 1980s, many prefectures conducted similar surveys as Hasegawa did, and the conditions of seniors with memory problems were clarified nationwide in the beginning of the 1990s.

Table 2 Scales commonly used in Japan for screening of memory problems

Name of the scale	Sensitivity/specificity	Subjects used to develop the scale	Author
The Japanese version of MMSE	82.8%/93.3%	90 subjects without memory problems and 61 subjects with memory problems	Mori *et al.* (1985)
HDS-R	90%/82%	62 subjects without memory problems and 95 subjects with memory problems	Kato *et al.* (1991)

Source: Homma (2004).

Scales to screen those suffering from memory problems have been developed as well. In 1973, Hasegawa developed the Hasegawa Dementia Scale (HDS). It was truly innovative, considering that it was developed 1 year before the Mini-Mental Scale Examination (MMSE) was developed. These days, the Hasegawa Dementia Scale-Revised (HDS-R) (Kato *et al.*, 1991) is most commonly used. HDS-R is shorter than HDS and its usability has been improved. The largest advantage of HDS-R is that the questionnaire naturally fits in the context of Japanese culture, as it was developed in Japan. Its sensitivity and specificity in comparison with the Japanese version of MMSE is shown in Table 2.

A recent topic in relation to dementia is that the prevalence rate of Alzheimer's-type dementia is becoming higher than the prevalence rate of vascular dementia, whereas the latter was more commonly observed than the former until the early 1990s in Japan. As an attempt to delay the onset of Alzheimer's-type dementia, behavioral intervention programs are being developed. In order to detect memory problems at the early stage, educational programs for physicians to improve their skills are developed as well (Homma, 1998, 2004). For treatment, Akira Homma, with the TMIG, served as an organizer of clinical trials of donepezil (Aricept) and used it in a clinical setting for the first time in Japan.

Another important topic of geriatric psychiatry is depression. In Japan, seniors have the highest incident rate of suicide (Figure 1), and depression is considered to be one of the reasons. Efforts have been made to develop standardized scales to identify seniors suffering from depression, such as the Japanese version of the Geriatric Depression Scale (GDS) and the Japanese version of the Center for Epidemiological Studies Depression Scale (CED-D). However, depression among seniors still tends to be overlooked to this date.

Primary academic associations related to geriatric psychiatry are the Japanese Psychogeriatric Society and the Japan Dementia Care Society, both of which publish their own journals.

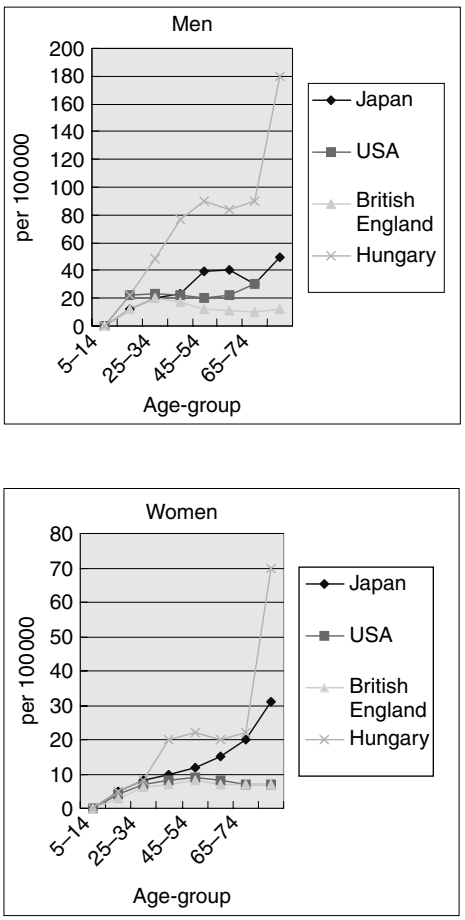

Figure 1 Comparison by country on suicide rate by age-group. *Source*: World Health Organization (1995)

EPIDEMIOLOGICAL STUDIES ON AGING

Background

The TMIG, which was established in 1972, undertook a crucial role in epidemiological studies on aging. TMIG was located on the same campus as Yoikuin Nursing Homes and the Tokyo Metropolitan Geriatric Hospital, and researchers from a wide range of areas, such as biology, medicine, epidemiology, psychology, psychiatry, sociology, nursing, and architecture, were engaged in studies on aging. In addition, the offices of primary academic associations related to aging were seated in TMIG, such as the Japan Geriatric Society, the Japanese Association of Geriatric Psychiatry, and the Japan Socio-Gerontological Society. Such an environment enabled TMIG to function literally as the center of aging studies in Japan.

Hiroshi Shibata, who led the Department of Epidemiology at TMIG from the 1970s to 1990s, recognized the importance of an interdisciplinary approach in aging studies

from the beginning. He organized longitudinal projects of large samples, while involving different departments in TMIG such as the Department of Psychiatry, Sociology, and Psychology. Among the projects, the Koganei Study, which was conducted from 1976 to 1991, is especially well-known. The subjects were 500 seniors living in the Koganei City, located in the west part of Tokyo, and were followed every 5 years to examine their medical, behavioral, social, and psychological changes.

In 1997, the National Institute for Longevity Science initiated a comprehensive longitudinal study on aging. The subjects were 2300 people of ages 40–79 years, and their MRI-and CT-data were collected in addition to the data obtained through questionnaire surveys. The sample size and the comprehensiveness of the data collected were compatible to the Baltimore Longitudinal Study of Aging organized by the National Institute of Aging (NIA) in the United States (Shimokata *et al.*, 2000).

Related academic associations in the epidemiological studies on aging are the Japan Public Health Association and the Japan Socio-Gerontological Society.

Academic Studies

As the longevity is prolonged, functional capacity emerged as an important issue that influences the quality of life in the prolonged old age.

The first survey on functional capacity of the elderly with representative sample was conducted by the Tokyo Metropolitan Government in 1980. The survey reported that less than 5%, with the exception of dressing (5.5%), suffered from disability in each category of ADL such as locomotion, eating, dressing, bathing, and going to the toilet. On assessing hearing, vision, and communication ability, 79.6% of residents over 65 years and over were regarded as competent in daily living. The Tokyo Metropolitan Government is repeating the same study every five years since then. It has been reported that the age-adjusted ratio of disabilities is being improved (Shibata *et al.*, 2001) (Figure 2).

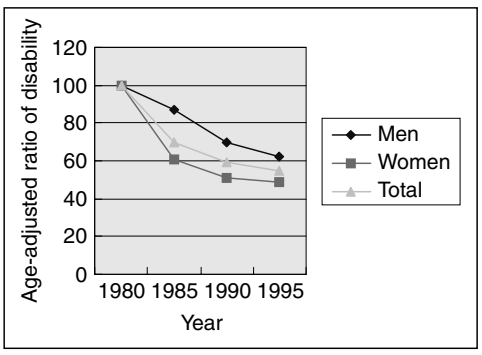

Figure 2 Age-adjusted ratios of disability in people >65 years old in Tokyo (Reproduced from Shibata H *et al.*, Functional capacity in elderly Japanese living in the community, *Geriatrics and Gerontology International*, 2001, **1**:8–13, with permission from Blackwell Publishing Ltd.)

Figure 3 Prevalence rates of impaired functional capacity between the United States and Japan. Note: The data of the US sample were derived from America's Changing Lives Survey. The subjects in the Japanese counterpart were selected nationwide on the basis of a stratified two-stage random sample. In the case of incompetence in any one of three items of functional capacity (bathing, climbing stairs, and walking), they were regarded as disabled (Reproduced from Shibata H *et al.*, Functional capacity in elderly Japanese living in the community, *Geriatrics and Gerontology International*, 2001, **1**:8–13, with permission from Blackwell Publishing Ltd.)

In a cross-cultural study between the United States and Japan on functional capacity of those who were 60 years old and over, the Japanese were more likely to be competent than American seniors (Figure 3). Shibata *et al.* (2001) suggested that "this difference in the prevalence may result from a cross-cultural difference in responding to this type of interview. Otherwise, there may be some contributing factors to prevention of disability in Japan".

Factors related to functional capacity have also been examined. In the Koganei Study, the variables that predicted the functional capacity years later were: "history of hypertension" and "electrocardiogram (ECG) abnormalities" for men, "anxiety about present health status" and "being overweight" for women, and "low social activities at baseline" for both men and women.

In another study which was started by TMIG in 1991 as the Tokyo Metropolitan Institute of Gerontology-Longitudinal Interdisciplinary Study on Aging (TMIG-LISA), both ADL and instrumental activities of daily living (IADL) were related to the following variables examined 3 years before: "age (75 or older)", "less hand-grip strength", and "history of hospitalization in previous 1 year". The predictor for ADL alone was "lack of exercise". The predictors for IADL alone were "poor intellectual activities" and "poor social roles" (Shibata, 2000).

Psychological health is another issue that is closely related to the quality of life in old age. In the 1980s, the Japanese version of the Life Satisfaction Index (LSI) and the Philadelphia Geriatric Center (PGC) Morale Scale were developed. Recent studies report that the factor compositions of these scales are different between the United States and Japan (Ishihara *et al.*, 1999; Wada, 1979).

A number of studies on nutrition have also been conducted, focusing on the pattern of food intake. Developing the Japanese version of the Nutritional Screening Initiative (NSI) was once discussed in the 1980s. The problem was that the

scale included the question on financial difficulty. Seniors suffering from malnutrition as a result of poverty existed only rarely in the Japan of those days because of the overall improvement in economic conditions and the successful management of the social security system. However, recent social changes, such as the increase of stratification and the decrease of pension payment because of the growth of older population, will make the middle class more susceptible to poverty in their old age. It is unfortunate, but screening malnutrition problems using such scales as NSI will be needed soon in Japan.

GERIATRIC NURSING

Background

In 1972, the Department of Geriatric Nursing was initiated in the TMIG. It was the first academic entity specialized for geriatric nursing in Japan. Because there were little professional publications on geriatric nursing in those days, the department started from organizing information in related areas through mass media such as newspapers. In practice, the department served as a pioneer in establishing the method of visiting nurse activities. The department also engaged in the development of assistive devices for frail seniors.

In 1989, the Branch of Geriatric Nursing was formed in the Japan Society of Nursing. Separate from this organization, the Japan Academy of Gerontological Nursing (JAGN) was established in 1996. The Branch of Geriatric Nursing is more attended by nurses engaged in practice in nursing homes and hospitals, and their discussions are focused on daily practice in the field. JAGN is more attended by those who work with universities or other academic institutions, and a wide range of academic interests are covered such as the development of nursing techniques for patients with geriatric diseases including dementia, developing methods for care in group home settings, improvement of community care systems, elder abuse, health promotion, and so forth.

In the 1990s, geriatric nursing was introduced in the educational system of nursing schools, as well as schools for midwives and public health nurses. Responding to these changes, universities for nurses followed the trend by introducing geriatric nursing in their curricula.

Recently, the Japan Society of Nursing introduced the system of the Certified Nurse Specialist (CNS). While the CNS in the United States stands for the Clinical Nurse Specialist, the CNS in Japan are those who have advanced skills in practice, consultation, and academic studies, and are specialized in certain areas such as geriatric nursing, oncological nursing, and psychiatric nursing. The idea of CNS was developed as a by-product of the discussion held in the 1970s, in which the possibility of introducing a similar system as the Nurse Practitioner (NP) in the United States was explored. The reason for abandoning the introduction of the NP system was based on the concern that the NP might be used as a cheap substitute for doctors. Thus, the CNS was created to emphasize the independence of nursing as a profession. The training to be a CNS is provided through 10 graduate schools of nursing. As of April 2004, there are 74 CNSs in Japan, among whom, five are specialized for geriatric nursing. The CNS in geriatric nursing are expected to serve as leaders in establishing care techniques in intermediary institutions for seniors as well as in visiting nurse programs.

Academic Studies

A wide range of topics are discussed in the area of geriatric nursing such as the role of visiting nurses in terminal care, team approach with other professionals in community care, the role of nurses in supporting victims of natural disasters, reminiscence, strategies in coping with senior patients who are not collaborative, and the effect of massage in the care for seniors.

In the past 10 years, the so-called geriatric syndrome, disability or decrease of functional capacity which are commonly observed among senior patients, has been an important issue. In dealing with the problems, care techniques have been developed for decubitus, other skin problems, eating or deglutition problems, and so on. Assessment tools to identify those who have high risk of falling, as well as the strategies to prevent falling, have also been developed.

Eminent progress is seen in the understanding of seniors with dementia. More understanding is being obtained on the meaning and rules for the way in which dementia patients wander and stop. Other behaviors such as touching, fingering, picking up, peering, and banging are also being paid attention to as possible avenues of communication with seniors having dementia. In addition, the effect of environment on memory control is identified through the studies on metamemory.

Effort has been made in developing scales and assessment tools such as the Japanese versions of the General Health Questionnaire (GHQ), the Oral Health Impact Profile (OHIP), and the Health-related Quality of life (SF-36). Other assessment tools include the ones to examine the quality of care in a short-stay setting, health-care needs of seniors with dementia living in community, and the seriousness of dried skin.

SOCIAL GERONTOLOGY

Background

The origin of sociological studies on aging dates back to soon after the Second World War. In those days, many seniors were left without families to depend upon. Especially, poverty among the elderly was a serious problem. Young and healthy men who could have become breadwinners in households had died during the war. Those who survived were occupied with supporting themselves and their children. Sociologists started to become interested in seniors through these problems, which provided leverage to

the establishment of the Japan Gerontological Society in 1956. The public gradually started to pay attention to the predicament experienced by seniors as well, and social gerontology received attention from a wide range of people as an emerging area to respond to the issue.

Sociological studies on seniors in the late 1950s and in the beginning of 1960s were closely related to policies. Before 1963, when the Law of Social Welfare for the Elderly, a law similar to the Old Americans Act (OAA) in the United States, was installed, discussions were focused on what kinds of public services should be provided for the seniors in need. Once the services started to be provided through the law, the focus of studies turned to examining how the services were used, as well as identifying still-unmet needs and advocating for improvement (Maeda, 1975).

In the 1970s, as the Japanese economy expanded, needs among seniors changed from the "needs stemming from poverty" such as the needs for financial aid, food, and housing, to the "needs unrelated to poverty" such as the needs for in-home help services and opportunities for social activities (The Committee for Social Problems Related to Aging, 1974). Fumio Miura, with the National Institute on Social Policy at the time, served as a strong advocate for policy change in order to respond to the "new" needs among seniors. He especially undertook a crucial role in turning the focus of policy makers from institutional care to community care.

Social scientific approach to aging started in the late 1970s. Daisaku Maeda, the then Chief of the Department of Sociology at the TMIG, made an incomparable contribution to the process. Maeda launched an array of pioneering projects as well as introducing sophisticated research skills developed in other related areas. Maeda also established collaborative relationships with researchers and institutions in other countries on the basis of his many years of international experience.

After the TMIG's withdrawal from the leading role in the 1990s, social gerontological studies have been conducted by researchers belonging to the department of sociology or social work in universities. However, academic activities in this area are not as active as they used to be, nor can very few institutions organize longitudinal studies with large samples for many years as TMIG did. Several more years will be needed before ongoing separate activities can take a certain shape as a new trend.

Primary academic associations in this area are the Japan Socio-Gerontological Society and the Japan Society of Behavioral Science on Aging. Associations closely related to this area are the Society for the Study of Social Welfare, the Japan Society of Family Sociology, and the Japan Welfare Society Association.

Academic Studies

Seniors and Families

In Japan, caregiving (kaigo) has a connotation that "children as caregivers live together with old parents (doukyo)"

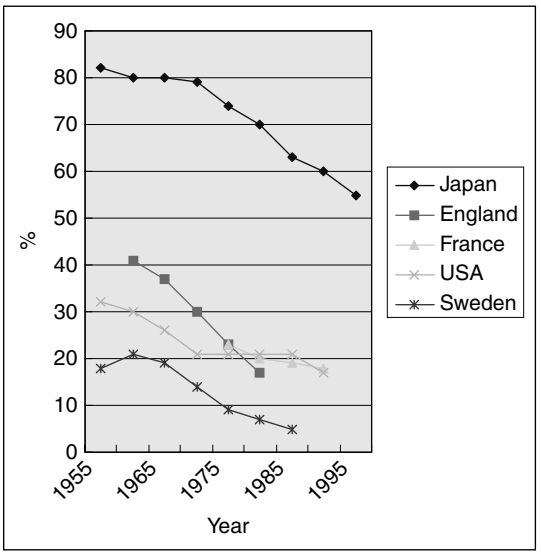

Figure 4 Percentage of those who are 65 years old and over living with their children *Source*: The Ministry of Health, Labor and Welfare (1996)

(Campbell, 2004). In the past few decades, however, the rate of seniors who have "doukyo" with their children is rapidly decreasing (Figure 4). This suggests not only the change of family structure but also the change in the notion of family and caregiving to old parents.

"Doukyo" has been considered as a sign that old parent(s) met their responsibility as parent(s) and children are fulfilling their responsibility of supporting their old parents in return by living together. It is also a sign of unchangeable love from children to old parents as well as the respect to relationships based on blood. When old parents are left alone without having "doukyo", the old parents feel ashamed while the children are considered immoral. However, the purpose of "doukyo" in these days is changing more for the convenience of the children; children save housing cost or daycare cost for their own children by having "doukyo" in the old parents' house (Naoi *et al.*, 1984; Okuyama, 1987).

One of the reasons for these changes of the "doukyo" culture lies in the improvement of financial conditions among seniors. Until the beginning of 1970s, it was said that "only one out of three old people, 60 years of age and over, could live on their own income" (Maeda, 1975). The situation stemmed from the fact that the compulsory retirement age was set between 55 and 57 in those days while the pension payment started between the age of 60 and 65. This yielded five to eight years during which retirees were left without an income. In addition, it was required to pay the premium for more than 25 years to receive the pension, and many retirees were not fulfilling the qualification. However, after the retirement age was increased to 60 years in the 1980s and the pension system became matured, the financial conditions of seniors dramatically improved. The seniors of these days obtained their houses before the so-called bubble economy when the prices were low, and they are now receiving full amount of pensions. In the meantime, younger generations suffer from expensive cost of housing and education of

their own children while supporting the disproportionately large number of seniors through the national pension system. As a result, stratification between the young and the old is increasing. For example, when comparing the monthly income after deducting tax, loans, and the cost for housing, education, food, water, gas and electricity, the households headed by those who are 65 years and over has 183 400 yen (1667 US dollars approximately), while the monthly income of the households headed by those 30–39 years old is 154 800 yen (1407 US dollars approximately), and the income of the households headed by members aged 40–49 is 165 500 yen (1504 US dollars approximately) (The General Affairs Office, 1999). Such difference in financial conditions of different generations is changing the role of seniors from financial dependents to financial supporters.

The way to have "doukyo" is diversifying as well. Strictly speaking, "doukyo" means old parent(s) and the family of a married child, traditionally the eldest son, live together under the same roof and share the same income. However, in these days, some families live under the same roof while old parent(s) maintain their financial independence, or old parents and the young family use different entrances or kitchens to avoid intervening with each other's privacy. Other families live separately at a very short distance, such as living next door to each other while sharing most part of their lives.

Along with these changes of family, the notion of "successful aging" is changing as well. Kodama *et al.* (1995) identified two different groups among seniors in terms of their attitude toward aging: traditional seniors who expect to enrich their aging process through intimate relationships with family members, and "new" seniors who enjoy social activities outside home, appreciate independenc, and pursue their own preferences and beliefs.

Social Activities

When the compulsory retirement age was set several years before the beginning of the pension payment, the purpose of "work" after retirement was to earn money. As financial conditions among seniors improved, the meaning of "work" in old age changed to an opportunity to maintain an active life. Previous studies support the notion that "work" helps to maintain good health and morale (Wada, 1984). However, those studies are cross-sectional, and the cause-effect mechanism is still unclear.

One of the recent topics is the process of adaptation to retirement of male workers, and its influence on their relationships with their wives. As a custom of the Japanese society, men with full-time jobs seldom stay at home; they leave home early in the morning and come home late at night. They frequently work even during weekends or go out to entertain their clients by playing golf and pursuing other activities. These male workers are forced to change such a lifestyle by compulsory retirement, usually to a more family oriented one. Wives, who have been leading a separate life from their husbands for many years, are faced with a sudden "restart" of life as a married-couple. Therefore, retirement of male workers in Japan is a critical life event in which both husbands and wives are required to make a tremendous effort to readapt to each other. Previous studies indicate that husbands complain more about decrease in human relations because of retirement. However, as years go by, husbands express more satisfaction than their wives about their retired life (Sodei, 1988).

Lifelong learning is another important topic. Japanese municipalities are sponsoring the Senior University Program (Rojin Daigaku) in which invited speakers give lectures a few times a month, normally. Usually, participation is free of charge, and a qualification is not required. Popular topics discussed in the lectures are health problems common to seniors, tips for living a long life, and hobby-related topics such as gardening, and so forth. Recently, PC training has been introduced as well as lectures on the public long-term care system and the problems of the public pension system. Previous studies report that these learning activities bring about positive influence on seniors both physically and psychologically. However, the studies are not only cross-sectional but also no comparison is made between participants and nonparticipants. Thus, the effect of learning activities is still not clear in a strict sense.

Volunteer activities are also receiving attention as opportunities for seniors to contribute to society on the basis of their many years of experience in society. In the 1990s, many public organizations attempted to organize relatively healthy seniors as volunteers to support frail seniors in the community. However, according to Maeda and Adachi (1992), about 90% of seniors are reluctant to participate in such activities. The study indicated that seniors wished to interact with younger people. They also hope to enjoy their later life, rather than undertake such serious responsibilities.

Burden from Caregiving

The existing public-service system does not provide enough support for frail seniors to maintain their independence in the community. The Long-Term Care Insurance, a newly installed system that will be described in a later part of this chapter, is not exceptional. In the meantime, the shortage of nursing homes is serious, especially in metropolitan areas. For example, in Tokyo, it is said that it would take up to 20 years for a patient to enter a public nursing home because of an extremely long waiting list! In such a circumstance, the family has no choice but to undertake the primary role of caregiving, and there are many families at present that serve as primary caregivers for more than 10 years.

The majority of the primary caregivers are married daughters or daughters-in-law. Their spouses are usually occupied with their jobs, and their support cannot be expected. However, recently, more husbands have started serving as primary caregivers when their wives become frail. Young sons who cannot find jobs under the poor economy are also entering as caregivers. They continue to depend on their parents by living together, and caregiving turns out to be their primary "job" as the parents grow old.

Academic approach to family caregiving has been focused on the development of scales to measure the seriousness

of the burden (Nakatani and Tojo, 1989; Mizoguchi *et al.*, 1995; Hattori, *et al.*, 2000). Standardized depression scales are also used to measure the burden of the family caregivers. The unique approach observed in Japan is to use the Chronic Fatigue Symptoms Index (CFSI) developed by Ogose (1991). CFSI was first developed to examine the chronic fatigue experienced by employees. However, it turned out to be widely used as a measurement to obtain comprehensive information on the burden experienced by family caregivers such as anxiety, depressive mood, exhaustion, irritation, general fatigue (low back pain, dim eyes, etc.), chronic fatigue (feeling tired when waking up in the morning, etc.), and physical symptoms (decrease of appetite, nausea, etc.).

As a new trend, some researchers are attempting to understand the positive aspects of caregiving experience (Nishimura, 2004). The viewpoint of social economists, in which caregiving is considered to be an exchange process, is gradually being introduced as well.

Social Services

Numerous "needs" surveys and studies on service use have been conducted in the past several decades. However, the system to provide long-term care for the elderly fundamentally changed in 2000, when the public Long-Term Care Insurance (LTCI), system, was installed. Many of the findings from the studies on public services conducted before 2000 are outdated.

Before LTCI, social services for the elderly were provided by tax through government or public agencies operating under a contract with the government. However, as the old population rapidly increased, the shortage of services turned out to be a serious problem since the availability of such public services was limited, and so was the amount of tax money to be spent for the services. In addition, the public-service system, operating on the basis of the Law of Social Welfare for the Elderly, which was established in 1963, was behind the times in many aspects. For example, the old system was not paying enough attention to the right of service users or accountability of government and public-service providers. LTCI was established as a resolution for the problems, through which a wide range of services are provided such as in-home help, a visiting nurse, day care, and institutional care. A semiprofessional position called *Care Manager* was also created in order to coordinate the services properly for each client. Half of the funds necessary to operate the system come from taxes and the rest are collected as premiums, which are compulsory payments for those who are 40 years and older. In addition, those who use services through the LTCI system are charged 10% of the entire actual cost of the services they use. LTCI promoted privatization as well. The government withdrew from service providing activities, while for-profit organizations, in addition to existing public agencies, were allowed to participate in the system as service providers. In this way, LTCI succeeded in increasing the amount of services provided as well as obtaining additional funds to support the expanded system.

Not many years have passed since LTCI has been installed, and solid outcomes based on sophisticated academic studies on LTCI are few, while anecdotal reports are uncountable. Basic statistics such as the number and health conditions of service users and the pattern of service use are collected in almost all municipalities, and are available to the public upon request.

Social Network/Social Support

Influenced by the trend of gerontology in the United States, numerous studies have been conducted on social networks and social support in Japan. The studies are focused on the development of scales, examination on the functions of social support, and the structure of support networks. Previous studies indicate that support networks of seniors in Japan primarily comprise of family members (Fukukawa *et al.*, 2002). This makes a contrast with the results in the United States, where seniors build intimate relationships both inside as well as outside of their families.

PSYCHOLOGY

Background

The founder of psychological studies on aging is Satokatsu Tachibana. His first paper on aging was published in 1926. Since then, he produced numerous papers in both domestic and international journals. In the 1960s, when geriatric psychiatry and social gerontology gradually obtained recognition from the society, psychology on aging was left behind. The turning point was 1972, when the Department of Psychology on Aging was established in the TMIG. The department undertook a leading role in defining psychological issues on aging and established methods to approach them.

The number of academic papers and presentations made in this area is increasing every year. Formerly, publications and presentations were made through the Japan Socio-Gerontological Society. Recently, academic communities that are not specialized in gerontology are more actively involved, such as the Association of Japanese Clinical Psychology, the Japanese Psychological Association, the Japanese Association of Educational Psychology and Japanese Society of Developmental Psychology. This trend indicates that old age is being considered as the final stage of personality development; thus psychological studies on aging is incorporated in developmental psychology rather than forming an independent area for it (Shimonaka, 2004, personal communication).

Academic Activities

Psychological studies on aging in the early days adopted the social psychological approach. Their interests were on the sources of happiness, loneliness, and subjective well-being of old people. The Department of Psychology on Aging at

TMIG conducted longitudinal studies on personality, self-image, anxiety, and cognition of the elderly. The primary findings from the longitudinal studies were that self-image became more positive while anxiety decreased as the subjects aged. It was also identified that widows recovered from the grief of losing their spouses within 2 years (Shimonaka and Nakazato, 1989; Sakaguchi, 2002).

How the society sees the seniors has been an important subject as well. "Nihon Shoki", the first history book published in Japan in 720, described seniors as heroes and heroines of wisdom who achieved longevity. However, in the sixteenth century, when Japan was divided into small provinces and there was constantly war among them, seniors became to be seen as useless drags. A saying which symbolized the negative image commonly shared about seniors in those days was, "Long life comes with a lot of shame". Buddhists advocated the idea of accepting "the shameful aging process" as a normal part of life instead of fighting against it. From the seventeenth to the end of the nineteenth century, there was no war inside the country. Under the peaceful environment, health promotion for a long life ("yojo-do") became popular. After the Second World War, democracy and individualism were introduced while industrialization and urbanization proceeded. As the extended family system was resolved in the process, the traditional culture of respecting seniors also eroded. As if to oppose the social changes, 15 September was designated in 1966 as a national day of "Respect for Seniors". In 1973, the Japan Railroad installed the system of "Silver Seat", in which certain seats in the trains were assigned for senior passengers to sit. In 1983, the Hyogo Prefecture passed the law to prohibit the use of word "old" to describe seniors in public, and "senior citizen" was adopted as an appropriate wording. In a short time, the same law was passed in the rest of the prefectures all over Japan. Shimonaka (1998) states that these movements could be interpreted as a way to "compensate for the loss of respect for seniors by installing formal systems".

Other topics in psychological studies on aging are as follows:

- clinical psychological approaches to deal with seniors with memory problems, such as, counseling, reminiscence (Matsuda *et al.*, 2002), and collage (Ishizaki, 2001);
- adaptation to a new task, such as institutionalization;
- caregiver's burden and coping problems;
- psychological characteristics such as cognitive functions and memory;
- grand parenting;
- influence of aging on personality and personal change at the terminal stage;
- stressful life events;
- personality traits commonly observed among centenarians.

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KEY POINTS

- Japan has experienced a rapid increase of old population in the past thirty years.
- Japanese geriatrics and gerontology studies have contributed to the understanding of the aging process, as well as the development of methods for effective interventions to the process.
- The constriction in the activities of the TMIG, in addition to the resolution of Yoikuin Nursing Homes and the Tokyo Metropolitan Geriatric Hospital, is wielding a serious impact on both practice and academic activities of geriatrics and gerontology in Japan.
- The future of geriatric medicine in Japan faces serious challenges. Especially, the poorly organized condition of the training system for geriatric practitioners raises a concern.
- The combination of the recent increase of stratification and the decrease of pension payment will make the middle class more susceptible to poverty in their old age. The issue of poverty among seniors was once overcome; however, it will surface again as a primary challenge of Japanese geriatrics and gerontology in the near future.

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Care of the Elderly in Israel: Old Age in a Young Land

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INTRODUCTION

Situated at the eastern end of the Mediterranean, Israel is a small country with a population of approximately 6.6 million covering only 20 700 square kilometers of territory. While still relatively young demographically (10% over age 65) in comparison to other developed states, from an absolute point of view, Israel has aged rapidly since the country obtained independence just over 50 years ago. Despite the pressures of waves of mass immigration, repeated war, and ongoing terrorism, an impressive set of institutions has been built to take care of the country's population in general and her elderly in particular (Clarfield *et al.*, 2000; Brodsky and Clarfield, 2001; Clarfield, 2000).

In this article, we will briefly describe Israel's demographic development, the organization and development of her health-care system, and the education of its formal caregivers. We will also touch on issues that make Israel unique from a gerontological point of view – such as the large proportion of Holocaust survivors among Israel's elderly and the situation of the Arab minority.

Demography

The population of Israel stands at just over 6.6 million, with nearly 80% being Jews and the rest Arabs (Muslim, Christian, and Druze). Israel has undergone a major increase in its relative proportion of elderly (65+) from less than 4% in 1948 to 10% in 2003 (Clarfield *et al.*, 2000; Brodsky *et al.*, 2004). Within the Jewish population, 11.3% are elderly, while in the non-Jewish population only 3.1% are over age 65 due to the much higher fertility rate among the latter group. Life expectancy at birth is among the highest in the developed world, especially for men, which stands at 77.5 years. Although, as would be expected, women have a higher life expectancy (81.5 years), Israel only ranks 16 in the world for women's life expectancy at birth while it ranks 6th for men (World Health Organization, 2004). This difference has yet to be adequately explained.

Despite the growth in the number of its older citizens, from a relative point of view, Israel is still one of the youngest of the world's developed countries primarily because of a relatively high fertility rate (2.9 children per woman in 2003). That said, the country has experienced an exponential increase in the absolute numbers of its older people due to a combination of both natural growth and immigration.

For example, while the general population increased 3.7 times during the past 50 years, the elderly population grew by a factor of 7.7, double that of the general population. The rate of increase of the older–old (aged 75 and over) is even more pronounced – 11.5. Thus, in Israel as elsewhere, not only has the general population been aging but the elderly population itself has been both increasing in numbers and growing older. The number of those aged 65 and older reached 670 000 at the end of 2003. It is projected that the proportion of elderly will remain stable up to 2010, but will rise to 12.7% of the total population by 2025 (numbering 1 176 000 persons) (Brodsky *et al.*, 2004).

Changes in levels of fertility and mortality alone cannot explain the rapid aging of Israeli society. Another unique characteristic that affects changes in the population's age structure is migration. Usually the elderly tend to be "reluctant movers" unless their motivation is strongly religious or emotional, or unless whole communities are on the move. The relatively high proportion of elderly persons in the waves of immigrants to Israel since the establishment of the country in 1948 is unique. On average, some 8% of all immigrants since 1948 were at least 65 years of age on arrival in Israel, and about 18% were between 45 and 64 (the middle-aged and

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aging cohorts). This has been an important factor in the process and pace of the increase in the numbers and percentage of the elderly in the Israeli population.

Of special note is the recent reemergence of large-scale immigration, primarily from the former Soviet Union (FSU), which began at the end of 1989. From 1989 to 2002, almost one million immigrants arrived from the FSU, including 155 000 individuals aged 65 and over (approximately 12% of the current immigration cohort). Today these recent newcomers represent more than one-fifth of the country's elderly. The absorption of this particular aged population, which arrived without economic resources, presents new problems and challenges to Israeli society and to its current social and health-care systems (Brodsky *et al.*, 2004).

Clearly, while it is predicted that the percentage of old people will remain relatively stable over the next two decades, the significant absolute increase will continue to strain the capacities of the country's health and social services.

With respect to the Arab population, its high fertility has ensured that the proportion of those over age 65 has remained low and will not reach more than 6% even by the year 2020. However, from an absolute point of view, like Israel's Jewish citizens, the number of Arab Israelis will grow significantly with a projected increase of 66% between the end of the twentieth century and the year 2010 (Brodsky *et al.*, 2004).

Beyond the Arab-Jewish divide, Israel's population is even more heterogeneous, with each group having its own demographic history. Although Jewish citizens comprise four-fifths of the overall population, they constitute 94% of the elderly. Also, with respect to this group, almost all (90%) were born abroad, two-thirds of them in Europe. Given the aging of the survivors of the European Holocaust, this group makes up just under one half of Israel's elderly today. These people bring a special challenge to both caregivers and policymakers (Brodsky *et al.*, 2003; David and Pelly, 2003).

The Health-Care System

In 1995, Israel's National Health Insurance Law was promulgated (Chinitz, 1995). This progressive legislation, which ensures the provision of both acute and rehabilitative care (in-patient and out-patient), is available to all legal residents with almost no out-of-pocket costs. In addition, a generous drug-benefits plan is available to citizens of all ages. The health system is funded via a progressive payroll tax (with a ceiling of five times the average wage) paid by the employee. Unemployed, the elderly ($\geq$60 years for women, $\geq$65 years for men), and those receiving disability and income support pay only a minimal tariff. These monies are transferred to the National Insurance Institute (*Bituach Leumi*), which then distributes them to each of the four sick funds according to a capitation mechanism. This system favors higher payments to the sick funds for those over age 65 and for those who suffer from a limited list of diseases (e.g. severe renal failure). The other half of the resources is supplied from general tax revenues.

Clinical care is organized and provided through one of four publicly financed and administered nonprofit sick funds (similar to American HMOs) mentioned earlier. These bodies are responsible for providing all of the acute and rehabilitative care to the whole population (Clarfield *et al.*, 2000; Clarfield, 2000).

DISABILITY AND LONG-TERM CARE SERVICES

Most relevant to the planning of long-term care services is the growth in the population of disabled elderly. Although the majority of older persons in Israel are independent, the changes that have taken place in the age, gender, and ethnic composition of Israel's elderly population have contributed to the increase in the absolute number and proportion of disabled elderly (who need assistance in personal care activities, such as dressing, washing, and eating). During the past two decades, the number of disabled elderly has grown 2.5 times, and in 2002, about 16% of older Israelis (including those living in institutions) were disabled in at least one activity of daily living (ADL). By the year 2010, the number of disabled elderly people is projected to increase by 31%, as compared to an expected 16% increase in the number of elderly. That is, the rate of increase of the disabled is double that of the total elderly population due to changes in its composition (Beer and Brodsky, 2002). On the other hand, there are initial indications that the new cohorts of elderly (especially the "young-old") are healthier than earlier ones (Clarfield *et al.*, 2004).

Institutional Long-term Care

Although the acute and rehabilitative side of care is highly socialized, with respect to institutional long-term care, the Israeli system is more analogous to the American Medicaid program (Clarfield *et al.*, 2000; Brodsky and Clarfield, 2001; Clarfield, 2000). Here, unlike that which pertains in acute and rehabilitative care, long-term institutional care is not covered by the above-described universal mechanism. Also, patients are placed at one of five levels of dependency with the institutions regulated by two Ministries: Health and Labour/Social Affairs. As is the case in the American system, those families that are able to purchase care from a licensed long-term institution (either for-profit or nonprofit) are expected to do so. However, given the high cost of such care, more than two-thirds of families turn to the Ministry of Health for a subsidy. (This can cover up to the entire cost of care, which is approximately 2500 USD per month.) However, co-payments are demanded according to a progressive system of accounting *by law* from the patient's spouse and children. Of interest is the fact that in the case of those categories of beds under the aegis of the Ministry of Labour and Social Affairs, even the resources and incomes of sons and daughters-in-law are included in the accounting of co-payments.

In comparison to most other industrialized countries, the majority of elderly people still lives or is cared for at home, with only 4.1% residing in a long-term care institution. Even among the disabled elderly, 78% still live in the community (Beer and Brodsky, 2002). It is clear that such a situation would be impossible without a great degree of family involvement, which is quite strong in Israel, an attitude fostered by both Judaism and Islam (Clarfield *et al.*, 2003). In addition, over the past decade, a number of formal services have been established, some quite innovative, meant to reinforce these social constructs and as such to help families cope with the burden of care.

Care at Home

Recent years have seen the rapid development of community and support services for the elderly who live at home. In the 1980s, forecasts of a significant growth in the number of disabled elderly raised fears that the cost of institutionalization would skyrocket if alternatives were not found. At the same time, an uneven distribution of funding for community and institutional services led to the desire for a more appropriate funding balance. All of these factors led to a range of efforts to develop community services (Naon and Strosberg, 1995).

Of the various models available, Israel chose to adopt the social insurance approach. In 1980, a 0.2% employee contribution to the National Insurance Institute was levied to create a reserve fund for implementing the law. By 1986, Israel's parliament, the Knesset, had completed the enactment of the Community Long-term Care Insurance (CLTCI) Law, and full implementation began in April, 1988.

The basic entitlement is for in-kind services, carefully delineated as a "basket of services" closely related to the direct care functions normally provided by families, such as personal care and homemaking. Benefits may also be used to purchase day care services, laundry services, absorbent undergarments for the incontinent, or an alarm system. Actual services are provided according to benefit levels set at 25% of the average market wage, with the severely disabled elderly receiving an additional 50% of this level (equivalent to about 10 or 15 hours of home care per week, respectively) (Brodsky and Clarfield, 2001; Naon and Strosberg, 1995).

Eligibility for benefits is not affected by any informal assistance an elderly person may receive from friends and/or family members. There is a means test for receiving benefits under the CLTCI law, but it is set at such a high level relative to the income status of the elderly that almost all of those who meet the clinical requirements are eligible for the entitlement. The less disabled elderly, who are not eligible for such services may still receive home care services from the social welfare system under a budget-restricted, income-tested program, which however provides fewer hours of care.

Home care (personal care and housekeeping services) is provided by semi-professional staff working for certified, licensed agencies. These agencies may be NGOs or for-profit agencies. The choice of a service provider is made by a local committee responsible for care planning, in consultation with the client and his family.

The first effect of the CLTCI law was to tremendously increase the resources earmarked for community care. This decision resulted in a more balanced allocation of public resources between institutional and community care. Prior to the law's implementation, expenditures for community services were limited, representing only 17% of public funds for long-term care (Naon and Strosberg, 1995). However, by 1994 (four years after the law's implementation) public funds for community care grew to constitute half of the public funding for long-term care.

This legislation has had a dramatic effect on the coverage of disabled elderly in the community. For example, the proportion of elderly receiving home care increased from 2% prior to implementation of the law to nearly 16–17% of the total elderly population (some 110 000 elderly in 2004).

Problems

Despite the range of services available, the situation in Israel results in many discontinuities between acute and long-term care as well as within the long-term care system. This problem among others was recognized more than 15 years ago and was studied comprehensively by the Netanyahu State Commission (Chinitz, 1995), which included a comprehensive examination of the whole health-care system. Among other things, this body recommended that within 3 years after the implementation of the National Health Insurance Law (in 1995), responsibility for long-term institutional care was meant to be transferred from the Ministry of Health to the patient's respective sick fund which, as mentioned earlier, already was responsible for acute and rehabilitative care for all ages. In this way, it was thought that one of the major discontinuities in the health-care system would be corrected. In addition, it was reasoned that following these changes, the sick funds would be more motivated to initiate programs that would encourage health promotion and prevention, geriatric assessment, and rehabilitation in order to keep the number requiring long-term institutional care (which would now be their fiscal responsibility) to an absolute minimum.

However, for many reasons (including primarily opposition from both the sick funds and the Treasury Ministry) this transfer of responsibility and jurisdiction has to date not come about (Clarfield *et al.*, 2000; Clarfield, 2000). Although the issue has been revisited several times since the Netanyahu State Commission (The National Institute for Health Policy and Health Services Research, 2002), this lack of implementation remains the single biggest barrier to taking the necessary steps required to improve integration of care for Israel's frail older population (Clarfield *et al.*, 2001).

Medical Education

There has been significant progress in geriatric education among all relevant health professionals over the last 20 years.

Geriatrics was recognized as a separate specialty by the Scientific Council of the Israeli Medical Association (IMA) in 1984. This act provided a professional basis for further progress and for the training of future generations of geriatricians of which there are now approximately 160 registered in Israel. (For comparison, this is almost the same number as, for example, in Canada, a country with five times Israel's population.)

There are three ways to specialize in geriatric medicine. In the first, somewhat analogous to the American model, after certification in either internal medicine or family medicine (5 years in both specialties), the physician is required to take an additional 2 years of geriatric training. Until several years ago, most geriatricians, especially those who now head the large geriatric centers or run academic departments, entered the field via the internal medicine route. However, of late there has been an increase in the number of candidates from family medicine.

In response to a perceived need for accelerating the number of physicians specializing in geriatrics, a "fast-track program" was initiated in 1993. This consists of a $4\frac{1}{2}$-year program, the first 2 years (post-internship) of which are in internal medicine followed by 2 years of geriatric fellowship and 6 months of research. There are 20 recognized geriatrics departments located in acute-care institutions or in one of the eight large geriatric teaching hospitals (which are analogous to American Veterans' Centers).

All training sites are inspected and accredited by the Israeli Medical Association. After successful completion of one of the aforementioned residency routes and after passing a two-stage board examination (including, as in Canada, an oral exam), the title "Specialist in Geriatric Medicine" is accorded (on recommendation of the IMA) by the Ministry of Health.

Unfortunately, most trainees in geriatric medicine, despite the demands of the formal syllabus, still have little exposure to normal aging, primary care, or community-based home care. Also, extensive out-patient work including formal geriatric assessment is still in its infancy in Israel.

Over the last 15 years, an interesting phenomenon has occurred. With the massive wave of immigration to Israel from countries of the FSU, approximately 9000 doctors came to the country, almost doubling the number of medical practitioners (Nire, 1999). Seizing an opportunity to kill two birds with one stone, the Ministry of Health and the Ministry of Absorption cooperated to fund training slots for many specialties, including geriatrics. Under the administration of an NGO, ESHEL (devoted to planning and development of services for the elderly in Israel), approximately 80 training slots for geriatricians have been funded throughout the country and these physicians are now beginning to practice.

In addition to the programs for the specialists in geriatric medicine there are two additional postgraduate programs that provide certificate training in geriatrics. One is held at Shmuel Harofe Hospital and has been offered annually since 1991. It began as a training course for immigrant physicians but for the last few years has been opened to all physicians interested in old-age medicine. More than 450 physicians, mostly from the long-term care sector, have taken this course.

The second setting for nonspecialist geriatric training is the postgraduate course provided by the Sackler School of Medicine of the Tel Aviv University. This program has been functioning since 1994 and is part of that faculty's continuing medical education curriculum. A postgraduate course in Geriatric Psychiatry is offered in the same educational framework.

With respect to undergraduate studies, geriatrics is offered by all four Israeli medical schools. Introductory lectures in geriatrics are given throughout the curriculum but the core teaching is based on a 2-week clerkship in one of the country's accredited geriatric units.

In some centers, there have been some innovative educational methods utilized. For example, at the Tel Aviv University, in accordance with a comprehensive approach to geriatrics, a special model has been developed as an assessment tool for medical students at the end of their clerkship. The tool combines summative with formative elements and provides an efficient way to assess the students according to what is referred to as the *five Cs*: clinical geriatrics, comprehensiveness, communication, coordination, and collaboration. A serious attempt is made to offer this evaluation in a nonthreatening and instructive manner. Another innovative approach has been the successful interdisciplinary model of teaching geriatrics to medical students created by combining geriatrics with epidemiology and preventive medicine.

With respect to the study of gerontology, two universities (Haifa and Ben Gurion University) have recently opened programs offering a Masters of Gerontology. These courses are not directed specifically toward physicians or nurses, although members of these professions do study in these programs.

SPECIAL ISSUES

Attitudes Toward Life and Death

In Israel, Judaism and to a lesser extent Islam have a strong formal and informal influence on the ethics and practice of health care. Of interest is the fact that the religion of Islam is also very close in many ways to Jewish philosophy on issues of end-of-life care (Clarfield *et al.*, 2003) as both religions place the highest value on the sanctity of life. For example in Judaism, one is enjoined to supersede all biblical commandments (except for three cardinal sins of idolatry, adultery, and murder) in order to save a life. Also, in addition to conventional medical care, rabbinical advice is often sought by those suffering from illness. In fact, the practice of consulting spiritual advisors in parallel with the conventional medical system has become quite widespread. Some might with justice consider this a form of alternative medicine. Both patient and family can receive advice (obviously of varying quality) according to which physician or medical center is considered to be expert in treating a particular disease (either in Israel or abroad). However, in many cases, this advice can interfere with appropriate medical decision-making. That said,

one could consider this voluntary transfer of decision-making power to fall under the rubric of respect for patient autonomy.

Regarding end-of-life care, *Halacha* (Jewish law) explicitly forbids any act of euthanasia or assisted suicide and, as mentioned earlier, leans strongly toward the preservation of life. According to this system of belief, food and fluids should always be provided to the dying patient and their supply is not considered to be "extraordinary" (as it is for example under Catholic law). In addition, for example, it is forbidden to discontinue drugs or oxygen or to withhold blood transfusions or antibiotic therapy (Marcus *et al.*, 2001), even if the physician considers the patient to have an incurable illness.

That said, however, when a patient does indeed reach the stage of "active dying" (*goses*) it is in fact forbidden to do anything to extend life and thus prolong suffering. Of course the debate usually revolves around when a patient has reached the situation of being a *goses* and this is not easy to define. As a result of this complex set of beliefs, it is not unusual in Israeli long-term wards to see an extensive use of tube feeding (either gastrostomy or nasogastric) even in patients with end-stage dementia (Bentur *et al.*, 1996; Clarfield *et al.*, 2005).

The Arab Elderly

As mentioned earlier, all of Israel's citizens regardless of ethnicity or religion are eligible for the services described in this article. For the most part, while discrimination has been described in some spheres such as the allocation of budgets for education or municipal infrastructure, health services are available equally to all. With respect to aging, the Arab population is still relatively young. However, a significant increase, both relative and absolute is expected in the number of elderly Arabs in the coming years. For example, at the end of 2003 there were about 42 000 Arab elderly, but their number is expected to reach 119 200 by 2025. This will represent a nearly threefold increase in absolute numbers. As this population ages, the number and percentage of people with chronic diseases and related disabilities will rise significantly (Brodsky *et al.*, 2004).

While the Arab elderly are somewhat younger than their Jewish counterparts, they tend to be more disabled and therefore have greater medical and nursing needs. An extremely important measure of the need for formal services is functional ability, especially the ability to live independently. The percentage of Arab elderly who are disabled and need help with ADLs is two times higher than that of the Jewish elderly population. Concomitant with demographic changes are forces that affect the ability of informal support systems to provide care. For example, the rising number of Arab women in the labor force together with changes in elderly peoples' living arrangements has increased the need for formal services to share responsibility for the elderly with families. As services are developed, questions arise regarding the extent to which they have been adapted to the culture and norms of Arab society and meet that society's unique needs (Azaiza and Brodsky, 2003).

Holocaust Survivors

One of the noteworthy characteristics of the elderly population in Israel is that it includes a significant proportion of those who suffered through and survived the Holocaust. It is estimated that between 40 and 50% are such survivors, and the percentage of survivors among the elderly born in Europe reaches about 75% (Brodsky *et al.*, 2003).

During the first years after the World War II, a high prevalence of physical and mental impairments was noted, but many of theses unfortunates either died or were placed in a long-term institution. It is therefore possible to note that many of today's community-dwelling survivors are examples of successful coping. Most dealt (at least on the surface) with their Holocaust trauma, built families, and adjusted well in their social and occupational lives. However, with increased aging, this traumatized group have had to cope with new challenges brought on by the vicissitudes of aging. In addition, this process, often accompanied by loss of family members and friends, can also accelerate and intensify past crises.

There are a number of areas in which elderly survivors often suffer from special difficulties, (see the excellent manual published by The Baycrest Centre for Geriatric Care in Toronto for a complete clinical description (David and Pelly, 2003)). Compared to the European-born elderly who are not Holocaust survivors, some differences have been found in the physical and mental health of these two groups. For example, among Holocaust survivors, particularly among those who experienced incarceration in the European ghettos, were in hiding, or forced into slave and concentration camps, there is a higher prevalence of illnesses such as osteoporosis, disc disease, and fractures (Menczel and Marcus, 2003). This clinical picture may result, at least in part, from nutritional and general deprivation during their youth, which influenced their state in older age and their quality of life. Thus, in older age, Holocaust survivors need extra attention to their special social, mental, and health needs.

Gerontological Organizations

In addition to the formal medical and nursing services available, Israel has a large nonprofit and NGO infrastructure. Several national bodies such as the research-oriented Myers-Brookdale Institute of Gerontology and ESHEL, the organization for planning and development for services for the elderly (both daughter organizations of the American Joint Distribution Agency), have initiated many innovative new services and models of care for older people. For physicians there is an active Israel Geriatrics Society, as well as a large Israel Gerontological Society and a dynamic Alzheimers Association. Other groups have formed of late, including organizations for stroke victims and those who suffer from Parkinson's disease, among others.

CONCLUSION

While Israel is still somewhat younger than other developed countries from a relative point of view, the absolute number of elderly Israelis, both Arab and Jew, has grown enormously over the last several decades and will continue to do so for the foreseeable future. In many ways, the health-care system for the elderly is quite organized and functions well. However, the discontinuities involved in the transitions within acute care and from acute to long-term care and the very large number of actors and jurisdictions responsible for ongoing care and supervision of the frail elderly remain a serious problem. Much attention has been paid to this issue but a solution is not on the horizon.

The Jewish and Islamic nature of Israeli society and health-care makes the country an interesting social laboratory to examine how different communities under the same formal system look after their elderly people. Israel is in many ways a dynamic, albeit stressed society. Despite this, care of the elderly in many cases is fair to good and in some places, even excellent.

KEY POINTS

- Israel, while still relatively young by Western standards, is rapidly aging with the absolute number of elderly having increased logarithmically over the past 50 years.
- While acute and rehabilitative care are covered by universal health care, long-term institutional care remains poorly integrated with the main system of care resulting in fragmentation, especially for the frail.
- Israel's Jewish/Islamic social structure, the fact that so many of its elderly are Holocaust survivors, and that it is a country of immigration makes it an interesting natural gerontological laboratory.

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Geriatric Medicine in China

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INTRODUCTION

The Elderly Population in China

In the past 50 years, China has made great achievements in controlling infectious diseases and improving public health. A direct indicator is the demographic transition from a young population into an aging population. The proportion of elderly people aged 60 and above has already crossed 10% in the year 1999. In the 5th National Population Census of 31 provinces, autonomous regions, and municipalities of mainland China in November 2000, the population was 1 265 830 000. There were 88 110 000 elderly persons aged 65 and over. This represents 7% of the population. The average life expectancy at birth is 69.6 years for males and 73.3 years for females. (Tables 1, 2, and 3) (National Bureau Statistics of China, 2004).

There are several special features regarding population aging in China. The number of elderly people in China is huge and represents 20% of the world's elderly population and 50% of the Asian elderly population. The growth in the elderly population is rapid. From 1982 to 1999, the proportion of elderly persons aged 60 and above increased from 7.64 to 10.1%. Such a demographic transition occurred within 18 years in China, whereas the same change takes a few decades in the developed western countries. China has now moved into an accelerated phase of population aging and is becoming an aging society in an underdeveloped economy. While the western countries have become both "old" and "rich", China has become "old" before getting "rich". This constitutes a burden to the economic growth. Another characteristic is the regional differences in the demographic transition. Population aging occurs more rapidly in the developed coastal cities than the underdeveloped inner rural areas within China. The urban cities showed higher proportions of elderly people than the rural areas. For example, Shanghai has the highest percentage while Qinghai province has the lowest percentage of elderly persons. Among the subgroups of the elderly population, the growth of the oldest-old population (aged 80 and above) is fast and at a rate of 5.4% per year. The oldest-old population in China has increased from 8 millions in 1990 to 11 millions in 2000 and will become 27.8 millions in 2020 (Lee, 2004; National Bureau Statistics of China, 2004). With an aging population, the prevalence of chronic diseases which include diabetes mellitus, hypertension, stroke, coronary heart disease, and chronic obstructive pulmonary disease has increased. For example, 1.5 million patients are newly diagnosed with stroke every year in China. Heavy medical expenses are required, and these diseases constitute an important burden of disease for China. Although the life expectancy of women is higher than men, the number of healthy elderly women is lower than that of healthy elderly men. Women survive longer, but are less healthy than men (Du and Guo, 2000; Lee, 2004; Ministry of Health of China, 2004; National Bureau Statistics of China, 2004; Woo *et al.*, 2002). The birth control and one-child policy has a great impact on the family size in China (Festini and de Martino, 2004). The size of the Chinese family has decreased from four- to five-person households to three- to four-person households in recent years. Family size is big in rural areas and small in city areas. This trend has been affecting the foundation of traditional family support of the elderly people in China.

As formal aged care services are quite limited, many older persons would mainly require their family members to support them. This is particularly true in rural areas. The functions of family support include financial support (income security), care-giving tasks (physical care) and comforting tasks (psychological care). Most of the younger persons in China still largely maintain that taking care of the elderly family members is their responsibility. However, more and more young people are unable to provide all the family support functions, and would require some assistance from the government, the policy makers, and community service providers (Du and Guo, 2000; Woo *et al.*, 2002).

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Table 1 China population in 2000

	Mainland China (1 November 2000; 5th National Population Census)	Hong Kong SAR (30 June 2000)	Macau SAR 30 (September 2000)	Taiwan (December 2000)
Total population	1 265 830 000	6 780 000	440 000 441 600 (2002)	22 280 000 22 605 000 (Dec. 2003)
Number of elderly (65 years and over)	8 811 000	745 800	34 003 (2002)	1 895 000
% of elderly (65 years and over)	6.96% (increase by 1.39% compared with 1990 Census)	11%	7.7% (2002)	8.52%
Average life expectancy at birth, years	All = 71.4	Male = 78.2	Male = 76.2	Male = 72.6
	Male = 69.6 Female = 73.3	Female = 84.1 (2001)	Female = 80.2 (2001) 78.6 for all (2002)	Female = 78.3

Note: Population of China in 2000: (including mainland China, Hong Kong SAR, Macau SAR, and Taiwan) was 1 295 330 000.

Table 2 China major cities' population in 2000

	Beijing (2000)	Shanghai (2000)	Hong Kong SAR (30 June 2000)
Total population	13 819 000	16 737 700	6 780 000 6 724 900 (2001)
Number of elderly (65 years and over)	1 155 000	1 924 836 (3 06 049 aged 80+ years)	745 800
% of elderly (65 years and over)	8.4% (increase by 2.1% compared with 1990 Census)	11.5% (65+: increase by 2.1% compared with 1990 Census; 80+ increase by 2.2% compared with 1990 Census)	11.1%

Table 3 Declining birth and death rates in mainland China

	Mainland China (Overall)		Beijing		Shanghai	
Year	Natural birth rate (per 1000 pop.)	Natural death rate (per 1000 pop.)	Natural birth rate (per 1000 pop.)	Natural death rate (per 1000 pop.)	Natural birth rate (per 1000 pop.)	Natural death rate (per 1000 pop.)
1949	36	20	–	–	–	–
1970	33.43	7.6	–	–	–	–
1980	18.21	6.34	–	–	–	–
1990	21.06	6.67	13.35	5.43	11.32	6.36
2001	13.38	6.43	6.1	5.3	5.02	5.97
2002	12.86	6.41	6.6	5.7	5.41	5.95
2003	12.41	6.40	–	–	–	–

Note: Natural Death Rate = Crude Death Rate

The Elderly Population in Hong Kong SAR, Macau SAR, and Taiwan

In 2004, 0.82 million persons in Hong Kong were elderly people aged 65 and over, which represented 11.7% of the total Hong Kong population. The proportion of the Hong Kong elderly will increase to 24% by the year 2031 (Census and Statistics Department HKSAR, 2002a). This increase will place an enormous demand for long-term care and health-care services for the elderly. The aging demographic change is related to a decrease in the number of births in Hong Kong (Census and Statistics Department HKSAR, 2002a; Chow and Chi, 1997; Chow, 2000; Hospital Authority HKSAR, 2003a; Hospital Authority HKSAR, 2003b). The elderly dependency ratio which is defined as the number of persons aged 65 years and over per 1000 persons aged between 15 and 64 years will increase from 382 in 2001 to 562 in 2031. The average life expectancy at birth was 78.2 years for Hong Kong men and 84.1 years for women in 2001 (Tables 1,2, and 4). Closely related to the health-care needs of the elderly is their life expectancy at and above 60 years. At the age of 60, the average life expectancy was 21.4 years for men and 26.0 years for women in 2001, and at the age of 80, the average life expectancy was 8.1 years and 10.6 years for men and women respectively. The increased life expectancy is related to the improvement in public health and nutrition, and is also related to an improved medical care for very elderly patients (Census and Statistics Department HKSAR, 2002b; Chow and Chi, 1997; Chow, 2000; Hospital Authority HKSAR, 2003a; Hospital Authority HKSAR, 2003b). However, improved survival may not mean normal health without disability or functional improvement.

Table 4 Declining birth and death rates in Hong Kong SAR, Macau SAR, and Taiwan

	Hong Kong SAR		Macau SAR		Taiwan	
Year	Natural birth rate (per 1000 pop.)	Natural death rate (per 1000 pop.)	Natural birth rate (per 1000 pop.)	Natural death rate (per 1000 pop.)	Natural birth rate (per 1000 pop.)	Natural death rate (per 1000 pop.)
1946	20.1	20.1	–	–	–	–
1956	37.0	37.0	–	–	–	–
1966	25.5	25.5	–	–	–	–
1976	16.9	16.9	–	–	–	–
1986	13.1	13.1	–	–	–	–
1990	12.0	5.2	20.5	4.4	15.5	5.6
1995	11.2	5.1	14.1	3.2	13.8	5.7
2000	8.1	5.1	8.8	3.1	11.7	5.7
2002	7.1	5.0	7.2	3.2	11.0	5.7
2003	6.9	5.4	–	–	–	–

Note: Natural Death Rate = Crude Death Rate

Elderly persons have multiple chronic diseases, functional impairments, and need for regular medical services (Chu *et al.*, 1998; Woo *et al.*, 1997).

Macau SAR is a small city of China. It has a population of 0.44 million people. The crude birth and death rates are both falling over the past decade and the population is also aging. In 2002, the elderly aged 65 and above constituted 7.7% of its population. The average life expectancy at birth for males and females are 76.2 years and 80.2 years respectively. (Tables 1 and 4) (Macau SAR Government, 2004).

Taiwan has also experienced a rapid demographic transition. The fertility rate has decreased from 5.9 children per woman in 1949 to 1.77 in 1997. Thus, the ratio of adult children to older parents will fall greatly in the coming years. A decline in the death rate has resulted in an increase of the average life expectancy at birth. From the year 1951 to 1998, the average life expectancy at birth has increased from 53.4 years to 72.0 years for males, and from 56.3 years to 77.9 years for females. These changes have led to an increase of the elderly persons (aged 65 and over) from 2.5% in 1950 to 8.1% in 1997. By projection, this percentage will increase to 9.86% in 2010 and 13.83% in 2020. The increase of the oldest-old group (i.e. 80 years and over) within the elderly population is very fast. In 1960, 9.2% of the elderly population belonged to the oldest-old group. By 2036, almost one-quarter (23.8%) of the elderly population will be in the oldest-old group (Barlett and Wu, 2000) (Tables 1 and 4).

POLICIES TOWARD AGING IN MAINLAND CHINA

Officially, the basic principle in China's aging policy is to maintain sustainable development by setting up a partnership of elderly support system involving the state, the community, the family, and the individual. The priorities in meeting the challenge of population aging in China are to develop China's economy, to set up an old age security system, to speed up the establishment of community-based old age care system, to set up legislative system in order to protect the rights of the elderly (i.e. the Law of Protecting the Rights of the Elderly of the People's Republic of China was enacted in 1996), to establish safety networks for the elderly, to raise the living standards of the elderly and to create an environment for healthy aging. In the past decade, China has set up five principles as the guidance for the work on aging. The principles are "Elderly people should be supported, have medical care, be contributive to the society, be engaged in life-long learning, and live a happy life". In 1994, the China Development Outline on the Work of Aging was formulated with a view to gradually upgrade the living standard of the elderly and to enrich their cultural life (Liang, 1995).

HEALTH OF THE ELDERLY IN MAINLAND CHINA AND HONG KONG SAR

In mainland China, the top killer diseases in the year 2003 included cancer, cerebrovascular diseases, respiratory diseases, heart diseases and injuries, and poisoning. Chronic diseases included hypertension, cerebrovascular diseases, and coronary heart disease. Diabetes mellitus is more common in the urban city areas than in the rural areas (Ministry of Health of China, 2004) (Table 5). All these fatal and chronic diseases occur predominantly in the elderly persons.

In the Hong Kong SAR, the top killer diseases in the elderly include cancer, heart diseases, and pneumonia while the chronic diseases include arthritis, hypertension, and diabetes mellitus (Chiu *et al.*, 1998; Chu *et al.*, 1998; Chu *et al.*, 2005; Lau and Lok, 1997; Leung and Lo, 1997; Woo *et al.*, 1997) (Table 6).

Health-care Services in Mainland China

China's health-care delivery system is organized in a three-tiered fashion. In the urban areas, this consists of street health stations, community health centers, and district hospitals. In the economically less developed rural areas, village stations, township health centers, and county hospitals are responsible

Table 5 Causes of death and common chronic diseases in China (all ages) (2003)

City	County
Top killer diseases in 2003:	Top killer diseases in 2003:
Male	*Male*
1. Cancer	1. Cancer
2. Cerebrovascular diseases (stroke)	2. Cerebrovascular diseases (stroke)
3. Respiratory diseases	3. Respiratory diseases
4. Heart diseases (incl. HT heart disease)	4. Heart diseases (incl. HT heart disease)
5. Injury and poisoning	5. Injury and poisoning
6. Diseases of the digestive system	6. Diseases of the digestive system
7. Endocrine, nutrition, and metabolic diseases (e.g. Diabetes mellitus (DM))	7. Endocrine, nutrition, and metabolic diseases (e.g. Diabetes mellitus (DM))
8. Kidney diseases (Nephritis, nephrotic syndrome, etc.)	8. Kidney diseases (Nephritis, nephrotic syndrome, etc.)
Female	*Female*
1. Cancer	1. Cerebrovascular diseases (stroke)
2. Cerebrovascular diseases (stroke)	2. Respiratory diseases
3. Respiratory diseases	3. Cancer
4. Heart diseases (incl. HT heart disease)	4. Heart diseases (incl. HT heart disease)
5. Injury and poisoning	5. Injury and poisoning
6. Endocrine, nutrition, and metabolic diseases (e.g. Diabetes mellitus (DM))	6. Diseases of the digestive system
7. Diseases of the digestive system	7. Endocrine, nutrition, and metabolic diseases (e.g. Diabetes mellitus (DM))
8. Kidney diseases (Nephritis, nephrotic syndrome, etc.)	8. Kidney diseases (Nephritis, nephrotic syndrome, etc.)
Common chronic diseases:	*Common chronic diseases:*
1. Hypertension (54.7%)	1. Hypertension (16.4%)
2. Diabetes mellitus (16.3%)	2. Gastroenteritis (10.5%)
3. Cerebrovascular diseases (13.0%)	3. Rheumatoid arthritis (8.7%)
4. Coronary heart disease (12.4%)	4. Chronic obstructive airway disease (7.3%)
5. Rheumatoid arthritis (8.4%)	5. Choleltih and cholecystitis (4.7%)
6. Gastroenteritis (9.8%)	6. Cerebrovascular diseases (4.4%)
7. Choleltih and cholecystitis (8.5%)	7. Intervertebral disc disease (4.0%)
8. Chronic obstructive airway disease (8.2%)	8. Peptic ulcers (3.8%)
9. Intervertebral disc disease (8.1%)	9. Coronary heart disease (2.0%)
10. Peptic ulcers (3.4%)	10. Diabetes mellitus (1.9%)

Note: Ministry of Health of China, 2004.

Table 6 Mortality and morbidity of the elderly in Hong Kong

Leading causes of death in the elderly in 2001:

1. Cancer
2. Heart diseases (incl. HT heart disease)
3. Pneumonia
4. Cerebrovascular diseases (stroke)
5. Chronic lower respiratory disease
6. Kidney diseases (Nephritis, nephrotic syndrome, etc.)
7. Diabetes mellitus (DM)
8. Injury and poisoning

Common chronic diseases:

1. Arthritis (34.2–61.4%)
2. Hypertension (32–33%)
3. Fracture (17.1%)
4. Peptic ulcers (13.5–15.4%)
5. Diabetes mellitus (10.7–12.4%)
6. Coronary heart disease (8.6–14.3%)
7. Hyperlipidemia (7.4%)
8. Dementia (6.1%)
9. Hyperthyroidism (6.1%)
10. Chronic obstructive airway disease (6.0–8.2%)
11. Stroke (3.8–6.3%)
12. Asthma (3.0%)

Note: Chiu *et al.*, 1998; Chu *et al.*, 1998; Chu *et al.*, 2005; Lau and Lok, 1997; Leung and Lo, 1997; Woo *et al.*, 1997.

for the health-care delivery. The doctors in the village stations receive only three to six months of training (i.e. not formal medical school training) after junior high school and receive an average of two to three weeks continuing education every year. Township health centers usually have 10 to 20 beds and are looked after by a physician with three years of medical school education after high school. They are assisted by assistant physicians and village doctors. County hospitals usually have 250 to 300 beds and are staffed by physicians with four to five years of medical training after high school. They are assisted by nurses and technicians (China Medical Association, 2004; Editorial Committee of China Health Annual, 2003; Ministry of Health of China, 2004).

The health-care cost for the elderly is an important problem for the poor and those in rural areas. If they cannot afford the cost of health-care, they will be denied access to care. In the olden days, the rural Cooperative Medical System (CMS) schemes primarily provided funding and organized prevention, primary care, and secondary health care for the rural population. After 1950, a mutual assistance mechanism was established to provide access to basic drugs and primary health care. During the Cultural Revolution (1966–1976),

the CMS was given political priority. The rural CMS then organized health stations, paid village doctors to deliver primary health care, provided drugs, and partially reimbursed patients for services received at township centers and county hospitals. China's relative success in extending health care to the rural population has played a key role in improving the health status of the population. However, CMS suffered from problems of poor management and a small risk-pooling base, contributing to the downfall of these early cooperative financing schemes after the initiation of agricultural reforms in 1980. The CMS has disintegrated in most rural areas and currently fewer than 10% of China's villages have CMS. In addition, many village doctors have left for farming or become private practitioners. Township health centers and county hospitals are largely financed by fee-for-service and out-of-pocket payment. Access to health care in many areas is now principally governed by the ability to pay for it and not the need for health care. Many of the elderly persons in villages will become bankrupt if they have a major illness and have to be hospitalized. For example, the cost of an average hospitalization would exceed the average annual income of 50% of the rural population. At present, the insurance coverage level of the primarily village-based community financing schemes in rural areas is severely limited. Poverty after an illness and the related treatment expenses continue to be a serious problem for the rural elderly as most of them are poor. Therefore, they are often deprived of the needed medical care because of the inability to pay. Regarding the rural CMS, reform is needed. In May 1997, the State Council issued a special document emphasizing that CMS reform is a major direction for China's rural health reform (China Medical Association, 2004).

For elderly persons who are retired government officials or workers from large corporations, the health-care cost will be paid from either the Government Insurance Scheme (GIS) or Labor Insurance Scheme (LIS), which have been effective in ensuring equity of access to health care. In urban areas, GIS and LIS will pay for the health-care cost for most elderly persons. Exceptions are those who do not belong to these two groups, they have to be financed by fee-for-service and out-of-pocket payment. Access to health care for these persons is determined by their ability to pay. In recent years, the government and other enterprises are facing increasing difficulty in supporting GIS and LIS medical expenditures. With the rapid introduction of high-technology medical services, increasing incomes drive up the demand for health care. Without an effective controlling mechanism on the medical service consumers or providers, China now faces a serious problem of inflation in medical costs. The primary weaknesses of GIS and LIS programs are the relative inefficiency in health resource allocation and health-care provisions as well as the lack of risk pooling across enterprises or across local governments. Each organization under GIS and LIS systems is self-insured. If an enterprise is running a deficit, it will not be able to reimburse the medical expenses of the employee or the retired elderly employee, rendering the individual uninsured (Woo *et al.*, 2002; China Medical Association, 2004).

Health care for the elderly needs governmental provision and support. However, the distribution of health-care resources including health-care professionals in China is very uneven. Geographical variations exist between cities and rural areas as well as coastal and inland areas in China. The gap is still growing with 80% of health-care resources allocated to the cities, out of which two-thirds are allocated to big hospitals. Primary health-care organizations and rural areas are severely insufficient. The rate of health-care utilization is very low, which is largely related to inadequate supply and access. The level of health-care resources in megacities like Beijing and Shanghai may match those in developed countries. However, primary health care is not adequately developed. The charging system for health-care is by insurance from government for government officials and employees of large companies. These are also applicable to retired older persons who have previously worked in government institutes or major companies. Ordinary elderly people without these insurance support have to pay the medical costs out of their own pockets. The financial subsidy policy of the government is usually not available and this is not reasonable (Lee, 2004).

Health-care financing reforms have started in some pilot cities recently. In 1994, Jiujiang in Jiangxi Province and Zhenjiang in Jiangsu Province were selected as pilot reform cities. A combination of individual saving account and social risk pooling forms the basis for the financing of medical expenditures. This model emphasizes individual responsibility with social protection through citywide risk pooling for GIS and LIS. These reforms have met with some success in controlling the escalation in medical costs and in expanding coverage to those who were previously uninsured or underinsured. This was a successful experience. In 1996, it was decided that the pilot scheme is to be extended to over fifty cities in 27 provinces and administrative regions (China Medical Association, 2004).

Community Health Services for the Elderly in China

According to the Chinese National Committee on Aging, China has limited resources to set up comprehensive facilities to meet the increasing needs of the elderly. However, community service is found to be an attractive way to complement the role of the family in caring for the elderly persons. Over the past decade, there has been a great development in community service. By 1997, there were 930 000 community service facilities, 5055 community centers and 1.01 million community service stations in the whole country – urban and rural areas. 85% of these facilities primarily serve the elderly persons in the local community. 5.4 million volunteers have provided service. The community service embraces several groups of service providers including care services for daily living (e.g. home help, lunch, household work, shopping, escort etc), cultural activities (e.g. activity centers, life-long learning, universities of third age), legal assistance (i.e. when the legal right of an elderly member is violated), and day care services. Day care services are provided by either home

for the elderly or day care centers. The latter also provide simple medical services like clinical checkup, intravenous saline treatment (as "health maintenance"), and family hospital beds. The medical service components are derived from the earlier street health stations and community health centers in the urban areas. "Doctors" in these centers usually receive basic training only and do not have formal geriatric medicine training (Zhang, 2003).

GERIATRIC MEDICINE IN CHINA AND HONG KONG SAR

Geriatric medicine has been defined as a branch of general medicine that deals with the clinical, rehabilitative, psychosocial, and preventive aspects of illness in elderly people. Despite an emphasis on the impact of the aging population, geriatric medicine has not been developed in China yet. Traditionally, there is a group of doctors who practice "Geriatrics" in China. They are responsible for the delivery of medical care to "old" and senior government officials in China. Most of these doctors are well trained and specialized in one particular organ-based specialty (e.g. cardiology, respiratory medicine, neurology). Their training and clinical practice in "geriatrics" in mainland China are different from geriatricians in other parts of the world. Their research works are primarily targeted at an organ-based approach which includes cardiac diseases in the elderly, dementia, osteoporosis, biological mechanisms of aging, and antiaging drugs. However, there is a lack of research in geriatric syndromes like falls or clinical models of geriatrics care for older persons.

MEDICAL EDUCATION AND TRAINING PROGRAMS IN GERIATRIC MEDICINE AND GERONTOLOGY

As the absolute number and the proportion of the elderly population in China increase progressively, services for the elderly would become a combined effort of the elderly individual, family members, professionals, and lay persons in Chinese society. Professional care in geriatric medicine and gerontology has an important role to play in any aging society. There is a great need to provide education and training programs in geriatric medicine and gerontology for doctors, nurses, social workers, and allied health professionals. This is grossly inadequate in China. There is only one undergraduate educational program on social gerontology at the tertiary education level at the People's University of China, which was started in 1994 (Du and Guo, 2000).

The curriculum of basic undergraduate medical training in the medical schools of China includes both the general and the shorter special diploma curricula. The duration of the general comprehensive curriculum is of 5 years usually, but may be 6 to 7 years in some schools. In terms of scope, these are comparable to primary medical training in other countries. In 1999, there were 21 university-based medical schools and 69 independent medical schools (Higher Education Office of China Ministry of Education, 2004).

High-school graduates may also study the special diploma programs, with training that usually last for 4 years. These medical programs are not comprehensive in training and each of them would focus on a special area only (e.g. oral health, hygiene, child health, physiology, pharmacology, chemistry, clinical medicine, physics, basic medical sciences, Chinese medicine, preventive medicine, medical imaging, acupuncture etc.). In 1999, there were 20 medical diploma schools and 15 colleges with medical diploma courses (Higher Education Office of China Ministry of Education, 2004).

Geriatric Medicine Educational Program in Mainland China

As described previously, geriatric medicine has been defined as a branch of general medicine that deals with the clinical, rehabilitative, psychosocial, and preventive aspects of illness in elderly people. Education in Geriatric medicine is lacking in most medical schools. In the undergraduate medical training in China, teaching of geriatric medicine is included in the curriculum of only 2.9% of the medical schools. Most doctors in China are not equipped with knowledge in geriatric medicine when they graduate from medical schools. This policy is not in keeping with the need of the aging population in mainland China and is different from many parts of the world. In Hong Kong SAR, United Kingdom, Europe, and other developed countries, geriatric medicine is included in the core teaching of the undergraduate medical curriculum. In the United States, 60% of medical schools have included geriatric medicine in the core or compulsory modules, while 40% has included this as an optional module (Higher Education Office of China Ministry of Education, 2004).

In mainland China, there is as yet no formal clinical postgraduate educational program for doctors or allied health professionals in geriatric medicine. This indicates that although China has paid great attention to family planning and population control, the university education system has not changed and prepared for the need of an aging society. Compared to the widespread availability of postgraduate medical training in geriatric medicine in overseas countries like United Kingdom, United States, Canada, Europe, New Zealand, and Australia, the absence of educational training program in geriatric medicine should be rectified (Chow and Chi, 1997; Chow, 2000; Chu and Lam, 1997; Higher Education Office of China Ministry of Education, 2004; Hong Kong College of Physicians, 2002; Woo *et al.*, 2002). China should establish the field of geriatric medicine and gerontology in the university training system at the undergraduate and graduate school levels.

Specialty status for doctors in China primarily follows their research degrees (e.g. master and Ph.D. degrees) as well as their publications in those specialty areas (e.g. geriatric cardiology, osteoporosis, basic science in aging mechanism, dementia). There is no formal clinical specialist training for physicians in a subspecialty (e.g. cardiology, neurology, or geriatric medicine). Thus, most professors in current geriatric departments in China usually have a research interest in diseases which are prevalent in old age (Luk, 2000; Zhu, 1993).

The Chinese Geriatrics Society has been publishing the Chinese Journal of Geriatrics since 1982. The papers published in the journal can be categorized into disease-based research findings, biological mechanisms of aging, and antiaging interventions. There is a lack of publication on clinical geriatrics services, geriatric assessment, models of geriatric care and interdisciplinary interventions. The summary report of the fourth committee meeting of the Chinese Geriatrics Society of the Chinese Medical Association emphasizes mainly research works on aging, antiaging, antiaging drugs, longevity, geriatric cardiology, geriatric respiratory diseases, dementia and molecular biology, and so on. The report also describes future problems, which included epidemiology research in diseases in the elderly, basic science research, clinical research on common geriatric diseases and health promotion (Wong, 1999). Unfortunately, problems due to the lack of clinical service in geriatric medicine and the need to train specialists in geriatric medicine in China are not yet realized. The current trend of continued development of pure organ-based specialists to look after frail geriatric patients who have multiple problems would be detrimental to the quality of care and the health-care cost in most geriatric patients. This will perpetuate fragmentation of care, neglect of atypical presentations of diseases in the elderly, unnecessary investigations, iatrogenesis related to the duplication of drugs and potential interactions related to multiple medical care providers.

Clinical Service in Geriatric Medicine

Geriatric departments have existed in China for a long time. The traditional role of doctors in these departments is to provide hospital care for senior government officials (working or retired). The doctors with specialty skills in this group may range from neurologist, cardiologist, intensive care physicians, urologist, and so on. The focus is still on organ-based hospital specialists. This is very different from the practice of geriatric medicine in other parts of the world (Chu and Lam, 1997; Fox and Puxty, 1993; Hall and Rowe, 1998; Isaacs, 1992; Lindsay and Barker, 1998; Swift, 1998). (*See also* **Chapter 161, Health and Care for Older People in the United Kingdom**; **Chapter 162, Geriatrics in the United States**; **Chapter 163, Geriatrics and Gerontology in Japan**; **Chapter 164, Care of the Elderly in Israel: Old Age in a Young Land**) The principles of geriatric assessment and interdisciplinary intervention are not practiced. Geriatric rehabilitation is also not available in clinical service programs of these departments.

THE HEALTH AND LONG-TERM CARE SYSTEM FOR THE ELDERLY IN HONG KONG SAR

All Hong Kong citizens are entitled to have inexpensive health- and social care services. Moreover, for those who are on Comprehensive Social Security Allowance (CSSA) Scheme, the service fees are waived. The latter scenario is very common among frail elderly patients in the hospitals. Together with an escalating health-care cost and an aging demography, the Hospital Authority (HA) is now having an annual budget deficit of HK$601 million (Hospital Authority HKSAR, 2004a).

The Social Welfare Department (SWD) has all along been responsible for the policy and funding of social services. At present, the social services for the elderly are categorized into community support (nonresidential) and residential care services for the elderly (Social Welfare Department HKSAR, 2004). In the past, long-term care services for the elderly referred primarily to residential care services, which are largely provided by the Nongovernmental Organizations (NGOs). Over the past decade, the private old age home industry has been developing rapidly and private old age homes now form the main service group for residential care of the elderly in Hong Kong. Meals delivery and personal care services are the key nonresidential home care services available to the elderly living in their own homes. The great demand for long-term residential care services has been a problem for many years and the magnitude of this problem is on the increase. At present, institutional care is quite commonly utilized and approximately 8% of the elderly in Hong Kong now resides in residential care homes for the elderly (RCHEs) and the hospital infirmary (Social Welfare Department HKSAR, 2004; Hospital Authority HKSAR, 2004b). The majority of the RCHEs in Hong Kong are the low-quality private old age homes, and a minority are government-funded care and attention homes and self-financing homes.

HISTORY OF DEVELOPMENT OF GERIATRIC MEDICINE IN HONG KONG SAR

On the basis of the British model, Hong Kong established its first geriatric unit in 1975. In the initial 10 years, the development of geriatric medicine was slow. However, in recent years, the importance of geriatric service to the elderly community has been gradually recognized. At present, there is at least one geriatric service per hospital cluster (Tables 7 and 8).

LACK OF A SYSTEMATIC APPROACH IN ACUTE GERIATRICS CARE IN HONG KONG SAR

The fundamental and serious problem in the present organization of hospital care for the elderly is a lack of systematic approach in the acute care for the elderly. While

Table 7 Geriatric service in Hong Kong Hospital authority by hospital clusters

Year	Cluster	Hospital	Unit/Ward/Team
1994	Hong Kong	Queen Mary Hospital (QMH)	Geriatric Team
1994	(HK) West	Fung Yiu King Hospital (FYKH)	Geriatric Department
2002		Tung Wah Hospital (TWH)	Geriatric Team
2004		Grantham Hospital (GH)	Geriatric Department
1990	Hong Kong	Rutonjee and Tang Siu Kin Hospitals (RTSKH)	Geriatric Department
1995	(HK) East	Pamela Youde Nethersole Hospital (PYNEH)	Geriatric Team
1996		Tung Wah East Hospital (TWEH)	Geriatric Team
1995		Wong Chuk Hang Hospital (WCHH)	Geriatric Department
1995		Saint John Hospital (SJH)	Geriatric Department
1996		Cheshire Home Chung Hom Kok (CCH)	Geriatric Team
1974	Kowloon East	United Christian Hospital (UCH)	Geriatric Ward
2000		Tseung Kwan O Hospital (TKOH)	Geriatric Team
1991		Haven of Hope Hospital (HOHH)	Geriatric and Rehabilitation Unit
1975	Kowloon West	Princess Margaret Hospital (PMH)	First formal Geriatric Department
1978		Caritas Medical Center (CMC)	Geriatric Department
1982		Kwong Wah Hospital (KWH)	Geriatric Unit
1994		Yan Chai Hospital (YCH)	Geriatric Team
1995		Our Lady of Maryknoll Hospital (OLMH)	Geriatric Team
1995		Wong Tai Sin Hospital (WTSH)	
1993	Kowloon Central	Queen Elizabeth Hospital (QEH)	Geriatric Team
1995		Kowloon Hospital (KH)	Geriatric and Rehabilitation Unit
2003		Buddhist Hospital (BH)	Geriatric Team
1985	New Territories	Prince of Wales Hospital (PWH)	Geriatric Team
2001	(NT) East	Shatin Hospital (SH)	Geriatric Unit
1997		Alice Ho Miu Ling Nethersole Hospital (AHMLNH)	Geriatric Team
1998		Tai Po Hospital (TPH)	Geriatric Team
1990	New Territories (NT) West	Tuen Mun Hospital (TMH)	Geriatric Department

Table 8 Geriatric services in the Hong Kong West Hospital Cluster

Acute hospital care	QMH (Integrated Model) GH (Direct transfer from Emergency Room)
Convalescent care	FYKH TWH GH
Geriatric rehabilitation beds	FYKH TWH GH
Long-stay infirmary beds for geriatric patients	FYKH TWH
Predischarge program and post-discharge support	QMH, TWH, FYKH, GH
Geriatric Day Hospital as day rehabilitation center	FYKH TWH
Geriatric Specialist Clinics	QMH Geriatric Specialist Outpatient Department QMH Memory Clinic QMH Falls Clinic QMH Nutrition Clinic FYKH Continence Clinic
Hong Kong West (HKW)	Outreach Geriatric Doctor Clinics in over 60 old age homes (Subvented Care and Attention homes, private old age homes, day care centers)
Community Geriatric Assessment Team (CGAT)	Visiting Medical Officer (VMO) under CGAT-VMO program Central Infirmary Waiting List (CIWL) clients preadmission assessment Domiciliary visits – medical, nursing, physiotherapy, and occupational therapy Educational and training program to carers and community elders Health education programs with community partners

a multidisciplinary, multidimensional geriatric assessment is frequently practiced in the extended care hospital, there is a general lack of acute geriatrics service in most acute care hospitals in Hong Kong. At present, only three out of 14 acute care hospitals have designated acute geriatric wards in the whole of Hong Kong (Table 7).

The number of elderly in the acute care hospitals is a huge case load. To be cost-effective, acute care for the

elderly has to be focused. To attain a cost-effective health-care model, targeting of the frail elderly patients in the acute geriatrics care program is necessary. The targeted geriatric patients would be physically, cognitively, and/or psychosocially frail. The settings of screening geriatric assessment would be at the sites where the frail elderly are present (i.e. medical, surgical, and orthopedic, and emergency room settings). Concurrent with acute treatment of the presenting medical diseases, geriatric assessment and intervention should be started simultaneously to prevent and revert functional decline.

The unit for development of acute care for the elderly should include several core elements of acute care for the elderly in its program: targeting of frail elders (i.e. in the emergency department, general medical, orthopedic, neurosurgical, and surgical wards with particular attention to those elderly who are residents from old age homes), comprehensive geriatric assessment, case-based conference by interdisciplinary team, and intervention. The interdisciplinary management should include a "Prehab" program to prevent functional decline with an appropriately designed acute care ward environment and then a "Rehab" program to revert functional decline and improve activity of daily living. Discharge planning (i.e. predischarge planning and postdischarge support with appropriate placement) with a case management approach should be implemented. Clinical outcomes must be optimized while unnecessary hospital admissions prevented (Palmer *et al.*, 1994).

Inadequate rehabilitation after acute illness in the frail elderly is also a problem and the waiting time for Geriatric Day Hospital (GDH) rehabilitation is long. Inadequate GDH transportation is another obstacle to provide adequate day rehabilitation for the frail elderly. Because of moderate disability, they usually require transportation support (e.g. Nonemergency Ambulance Transport) from home to GDH.

ISSUES IN PRIMARY HEALTH CARE IN THE ELDERLY IN HONG KONG SAR

For the general population, primary health care is largely provided by the private health-care sector, and the government is responsible for approximately 10% of this service. The latter is provided by the general outpatient clinic. In the elderly, the proportion of private doctor consultation is less than in the young and approximately 70% of them consult general outpatient clinic for primary health-care problems (Census and Statistics Department HKSAR, 2001). Most of the patients attending these clinics are either old or financially poor. Primary care providers are mostly private doctors who can manage episodic health problems well, but are inexperienced in detecting and managing chronic geriatric problems. For example, dementia is sometimes reassured as "normal aging phenomenon" without appropriate investigations and treatments.

Health promotion to improve lifestyles (e.g. quit smoking, healthy diet, exercise, etc), disease prevention (e.g. falls prevention and influenza vaccination for the elderly), and early chronic diseases identification and control are important. These measures would improve the health of the whole population and decrease geriatric health problems and the need for long-term care in the years to come. The Elderly Health Service (EHS) of the Department of Health provides health promotion program for the elderly members of their Elderly Health centers (Department of Health HKSAR, 2004). However, data regarding improvement of health status of the elderly in these programs have not yet been reported. Moreover, elderly citizens who are not members in these centers do not have access to these programs.

GERIATRIC HEALTH CARE AT RESIDENTIAL CARE HOMES FOR THE ELDERLY (RCHES) IN HONG KONG SAR

Those elderly living at home and alone constitute 12.4% of the over 65 year olds (11.2 and 13.6% for elderly men and women respectively) (Census and Statistics Department HKSAR, 2002b). While community and primary health cares are largely provided by private family doctors and general outpatient clinic (GOPC) doctors, specialist geriatric services at old age homes are provided mainly by Community Geriatric Assessment Team (CGAT) and partly by Community Health Nurses (CNS) (Leung *et al.*, 2000; Luk *et al.*, 2002). A new program of Visiting Medical Officers (VMOs) has been started in October 2003 to improve areas of infection control and provide *ad hoc* primary or geriatric medical care for frail elders in old age homes. Approximately 100 VMOs have been appointed as part-time HA staff to upgrade the previously inadequate primary and geriatric care in over 100 old age homes in the whole of Hong Kong (Hospital Authority HKSAR, 2004a).

SERVICE GAP AND DUPLICATION ISSUES FOR HEALTH AND LONG-TERM CARE OF THE ELDERLY

Multiple and continuous gaps in our traditional care models may lead to their "falling through the cracks" phenomenon (Coleman, 2003). The fragmentation of care would lead to frustration of the elders and caregivers and cause potential harm to patients, for example, being subjected to either "multiple repeated or similar drugs" (multiple doctors) or "no drugs" (waiting for new case appointment). The latter is a common transitional care problem for the elderly in Hong Kong.

In the community, the single frail elder commonly receives multiple health-care services (e.g. the private family doctor, VMO, orthopedic doctor, ophthalmologist, cardiologist, endocrinologist, etc.) as well as multiple social services (e.g. members of several multiservice or social centers for the elderly, home help services etc.). The current problems include fragmentation of care, service gaps, overlapping

of services, poor communication, and coordination. It is believed that an integrated geriatric health and long-term care team across both health and social sectors would be able to overcome these undesirable issues substantially.

Unfortunately, the current financing and public policy do not facilitate this development. Moreover, the present public health and social policy still lead to unhealthy competition for clients as well as creating some important gaps in services for the elderly. At present, separate service providers are under different budget holders in the Department of Health's Elderly Health Service (EHS of DH), Hospital Authority (HA), Social Welfare Department (SWD) and Non-Government Organizations (NGOs). Most elders would use the public health and social long-term care services. Only a small proportion of the elderly population seeks services from private hospitals, clinics, and social services. In general, the objectives and policies of different service organizations differ. The policy on service directions may also be different. In terms of collaboration between different elderly service providers, a service purchase model among different organizations is in operation, but this has great limitations in breaking the gaps or eliminating service overlaps. For example, the frontline staff has difficulty in working together as an integrated team despite overlapping of services (e.g. EHS of DH and Geriatric Service of HA). Loose collaboration is the practice at present, which is not ideal.

For the interface issue between public and private health sectors, there is a slow development. Communications have improved and private doctors can obtain discharge summary of their patients from HA if they have preregistered. The recent public–private collaboration with VMOs in the Caritas Evergreen Home is one of the successful pilot projects implemented by the author in the Hong Kong West (HKW) Hospital Cluster (Chu *et al.*, 2004).

The present organization of health care for the elderly indirectly gives rise to an overuse of hospital-care services as against community-care services. The trend for cost containment would shift hospital care from acute to subacute hospital care, and shorten the length of hospital stay in the acute care hospital per episode of admission. This is a consequence of merely concentrating only on the activity figures. There is no cost incentive to decrease unnecessary hospital readmissions. Moreover, there has been an overemphasis on specialty-led and organ-based disciplines, which are all very costly.

Thus, alternative health and long-term-care service models for the elderly with an appropriate health-care financing policy are needed urgently. Effective solutions should be explored and implemented in the near future to avoid catastrophic incidents in both health and social care services for the elderly.

The financial issue of the health-care system for the elderly in Hong Kong is inadequate financial resource for public health care of the elderly. Most of the elderly in Hong Kong are poor and obviously would choose to use the public health-care services (under Hospital Authority and Department of Health) rather than the private sectors. The financial condition of current and next generation older persons is definitely not good or optimistic.

RECOMMENDATION FOR AN INTEGRATED HEALTH AND SOCIAL CARE DELIVERY SYSTEM IN HKSAR

A comprehensive long-term and geriatric health-care program is needed for the elderly in Hong Kong SAR. This program can be subdivided into regional teams. The geriatric health and social long-term services must be fully integrated. We need to move the present interface and collaboration models further. Financial incentives are crucial for the success of this model. Merging different organizational structures to form an integrated long-term and geriatric care team is a cost-effective and sustainable way of providing targeted care to the frail elderly among the elderly population of Hong Kong.

CONCLUSIONS

The population of China is rapidly aging. Declining birth and mortality rates as well as 25 years of one-child policy are the main reasons for the phenomenon of fast population aging in China, particularly in urban cities like Shanghai, Beijing, and Hong Kong SAR. The practice of geriatric medicine with an interdisciplinary intervention is the most suitable clinical management approach for frail-older persons in China. Unfortunately, this has not yet started in most parts of China except the Hong Kong SAR. To cope with the needs of the aging population in China, there is a definite and pressing need to develop clinical geriatric service together with geriatric medicine educational programs throughout China. Research in local clinical geriatrics care models is also essential for proper evaluation of their effectiveness. In Hong Kong SAR, further improvement in the practice of geriatric care is needed. The fragmentation of health and long-term care services need to be rectified in the near future. Integration of geriatric services with social long-term care services is recommended.

KEY POINTS

- The population of China is aging and the proportion of elderly aged 60 years and above is over 10%.
- Geriatric medicine has not been developed in most parts of China except the Hong Kong SAR.
- Clinical geriatric service with an interdisciplinary team approach should be developed in China. Research in these clinical geriatric care models has to be performed simultaneously.

- Educational programs in geriatric medicine at the undergraduate and graduate levels and clinical training programs for doctors are greatly needed in most parts of China.
- The issues of inadequate health-care insurance for older persons in China need to be addressed. Contributions from the government, the older persons, and family are needed.

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Aging in Developing Countries

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THE IMPLICATIONS OF POPULATION AGING IN DEVELOPING SOCIETIES

Population aging has become a prominent topic as aging has emerged as a global phenomenon in the wake of the now virtually universal decline in fertility and, to a lesser extent, of increases in life expectancy. The theme is of immediate concern in developed countries, where aging is already well advanced and will continue, with serious consequences on every single aspect of life. It is also gaining importance in developing regions, where a number of countries have started worrying about the implications of population aging. With people in the developing world living longer and having fewer children, developing countries will have to be ready to meet the new health challenge of demographic aging. Medical advances and preventive health measures have meant significant progress against communicable diseases, which were once the main health threat in many such countries. But at the same time, the number of people with chronic and degenerative conditions has risen. Mortality rates from communicable disease in children under a year old were cut in half over the last 50 years. A decline in fertility rates from 3.1 to 2.4 children per woman followed. This coincided with the aging of the general population. The net result is that today, people over age 85 make up the fastest growing population group in these countries, increasing at a rate of 3 to 5% per year in some of them. The population over 65 years of age is growing at a rate of about 2% per year while overall population is growing at a rate of 1.3% annually. Not only are more people old now, but more people will get older. At the start of the twenty-first century, the average life expectancy in the region of the Americas is up to 72.4 years (WHO, 2001a).

With more elderly people living longer, chronic diseases and external causes have edged out communicable diseases as the main causes of death in many developing countries. They now account for about two-thirds of all deaths. Cardiovascular disease, cancer, injuries, and physical disability have become more prominent health problems. Endocrine problems such as diabetes and the metabolic syndrome are particularly frequent. Caring for an older population will mean a shift in the kind of health problems needing treatment. Another critical component is being sure that they get health care in the first place. Older adults living in isolated areas are more likely to lack permanent access to health care. Inequalities in people's risk of getting sick and dying, corresponds to inequalities in the distribution of resources. New health-care policies will need to address both sets of concerns. In this setting, preventive health continues to be important in old age to limit risks from factors such as environmental degradation, tobacco use, lack of physical exercise, violence, mental health problems, poor diet, motor vehicle accidents, and drug abuse (WHO, 2001b).

A long life should be everybody's right, but for older people in developing countries today, longevity can be a double-edged sword. Many older people never expected old age to be so stressful and difficult. For those who are poor, aging often means new burdens and worries about making ends meet. At the Second World Assembly on Ageing, governments signed the new International Plan of Action on Ageing (UN, 2002). But agreeing to the plan is only the beginning of a process. The key issue is how the plan is implemented and monitored. The challenge now is to mainstream aging issues into development processes and related international commitments. So far, aging is marginal in development debates. The International Development Targets and the UN's Millennium Development Goals (UN, 2004) largely ignore the question of how increasing numbers of older people can escape chronic poverty and be included in planning for a better future of communities and nations.

DEVELOPING SOCIETIES WILL EXPERIENCE SHORTER TIME TO REACH AGING STAGE AND WITH LESS RESOURCES

It is not our intention to discuss demographic or health data in great detail, but a summary of statistics on population and

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Table 1 Health-related and population-aging variables in developing and middle-income countries, compared with some developed countries estimates for 2000[a]

Countries	Developing and middle income																										Developed		
Indicators	Afghanistan	Argentina	Bangladesh	Bolivia	Brazil	Chile	China	Costa Rica	Côte d'Ivoire	Cuba	People's Republic of Korea	Ethiopia	Haiti	India	Indonesia	Iran (Islamic Republic of)	Kenya	Mexico	Nigeria	Morocco	Pakistan	Republic of Korea	South Africa	Tunisia	Turkey	United States of America	United Kingdom	Japan
Adult mortality (per 1000) females	376	92	252	219	136	67	110	78	494	94	192	535	373	213	191	139	529	101	393	113	198	71	502	99	120	84	67	44
Adult mortality (per 1000) males	437	184	262	264	259	151	161	131	553	143	238	594	524	287	250	170	578	180	443	174	221	186	567	169	218	147	109	98
Annual population growth rate (%)	4.8	1.3	2.2	2.4	1.4	1.5	1	2.8	2.4	0.5	1.1	2.8	1.7	1.8	1.5	1.9	2.7	1.7	2.9	2	2.6	0.9	1.8	1.5	1.7	1.1	0.3	0.3
Dependency ratio (per 100)	86	60	72	77	51	55	46	60	83	44	48	93	80	62	55	69	86	61	93	63	83	39	60	55	56	52	53	47
Percentage of population aged 60+ years	4.7	13.3	4.9	6.2	7.8	10.2	10	7.5	5	13.7	10	4.7	5.6	7.6	7.6	5.2	4.2	6.9	4.8	6.4	5.8	11	5.7	8.4	8.4	16.1	20.6	23.2
Total fertility rate	6.9	2.5	3.7	4.1	2.2	2.4	1.8	2.7	4.9	1.6	2.1	6.8	4.2	3.1	2.4	3	4.4	2.6	5.7	3.2	5.3	1.5	3	2.2	2.5	2	1.7	1.4
Healthy life expectancy at age 60 (years) females	5.8	16	8	10	12.6	15.7	14.3	15.6	8.5	15.5	12.1	7.5	8.5	10.9	12.5	11.4	9.1	15	8.2	10	8.7	16	10.4	12.6	13.4	16.8	17.4	21.4
Healthy life expectancy at age 60 (years) males	7.1	13.2	8.8	9.8	10.7	13.1	11.8	14	8.6	14.5	11.1	7.7	7.8	9.9	11.6	11.3	9.3	14.5	8.4	9.9	9.8	12.3	9.1	11.4	11.2	15	15.3	17.6
Healthy life expectancy at birth (years) females	32.5	65.9	47.9	51.4	59.2	67.4	63.3	66.4	38.9	66.7	56	35.1	44.9	51.7	58.4	58.6	40.1	65.3	41.1	54.5	46.1	68.8	43.5	61.7	60.5	68.8	71.4	76.3
Healthy life expectancy at birth (years) males	35.1	61.8	50.6	51.4	54.9	63.5	60.9	64.2	39.1	65.1	54.9	35.7	41.3	52.2	56.5	59	41.2	63.1	42.1	55.3	50.2	63.2	43	61	56.8	65.7	68.3	71.2
Healthy life expectancy at birth (years) total population	33.8	63.9	49.3	51.4	57.1	65.5	62.1	65.3	39	65.9	55.4	35.4	43.1	52	57.4	58.8	40.7	64.2	41.6	54.9	48.1	66	43.2	61.4	58.7	67.2	69.9	73.8
Life expectancy at birth (years) females	45.1	77.8	60.8	63.6	71.9	79.5	73	78.8	48.4	77.5	67.2	44.7	56.1	62.7	67.4	69.9	49.6	76.2	51.4	70.4	60.7	78.3	52.1	73.4	72.5	79.5	79.9	84.7
Life expectancy at birth (years) males	44.2	70.2	60.4	60.9	64.5	72.5	68.9	73.4	46.4	73.7	64.5	42.8	49.7	59.8	63.4	68.1	48.2	71	49.8	66.1	60.1	70.5	49.6	69.2	66.8	73.9	74.8	77.5
Life expectancy at birth (years) total population	42.8	73.7	61.6	62.2	68.4	76.1	70.8	76.4	46.2	76.8	66.1	47.5	53	60.6	65.4	68.3	49.7	74.2	51.6	69.3	61.2	74.6	51.2	70.9	68.9	76.8	77	81.3
Percentage of total life expectancy lost females	27.8	15.2	21.2	19.1	17.6	15.2	13.2	15.7	19.7	14	16.7	21.4	20	17.5	13.5	16.2	19.1	14.3	20.1	22.7	24.1	12.1	16.5	15.9	16.5	13.4	10.6	9.9
Percentage of total life expectancy lost males	20.5	12	16.2	15.6	14.8	12.4	11.6	12.6	15.6	11.6	14.8	16.6	16.9	12.7	10.9	13.3	14.5	11.2	15.5	16.3	16.6	10.3	13.3	11.8	14.9	11.1	8.7	8.1
Social security expenditure as % of general health expenditure	0	59.5	0	66.7	0	71.8	50.7	90.2	0	0	0	1	0	0	7.5	40.6	0	67.7	0	7.6	39.6	77.3	0	57.3	28.4	33.9	0	83.5
Total expenditure on health as % of GDP	5	8.9	3.6	5.2	7.6	6.8	5.3	6.9	6.2	7.1	2.4	3.2	4.8	5.1	2.7	6.4	8.7	5.7	3	4.7	4.1	5.9	8.7	6.2	5	13.1	7.3	7.7

[a]These figures were produced by WHO using the best available evidence. They are not necessarily the official statistics of Member States.

Source: Table produced by the author from data available at the World Health Organization website: http://www3.who.int/whosis/menu.cfm?path=whosis,bod,burden_ statistics&language=english.

aging for developing countries is given in Table 1. These data are drawn principally from the WHO World Health Report 2001a, Statistical Annex. The data are therefore presented on a broadly comparable basis.

As it can be shown from this data, all these countries are facing the rapid growth of an aging population, although, in practice, their cutoff ages for defining "older people" are not the same. Indeed, for various purposes internally (retirement ages, pensionable age, granting of certain benefits), individual countries specify different chronological ages. For example, the age requirement for entitlement to elderly services and care in both Thailand and Malaysia is 60 years of age, while in Hong Kong, Korea, and Singapore it is 65, and in Mexico 70. Hong Kong and Singapore both have lower retirement ages in some sectors, at 55 (increasing to 60) in Singapore, and at 60 in Hong Kong, in many companies and the public sector. Definitions aside, the chronological aging of the population in most countries is obvious: in Hong Kong, 11% of the population is aged 65+; in Singapore, Thailand, Korea, and Mexico, it is 7%; and in Peru or Malaysia, it is 4% – all substantial increases on the previous decades' figures.

The factors underpinning the increase in the aging populations are similar across the countries. A major reason for this demographic aging is a very low fertility rate. Added to this are gradually increasing life spans. The life expectancy at birth of males and females in Hong Kong is 77 and 82 years respectively, while comparable figures in Singapore are 76 and 80, and in Malaysia, 70 and 75, and in Mexico 70 and 74.

There are also quite high elderly dependency ratios in these countries, and while dependency rates are not perfect, they are often taken as an indication of potentially increasing burdens both on the economically active population and on governments and their economies, especially in the health and welfare sectors. In many ways, increasing dependency ratios, like increasing life expectancy, as they reflect population aging, show the success in social and economic policies, good health and nutrition, modern welfare services, and a good standard of living for the population.

Demographic aging in these countries is very much influenced by the previous explosive demographic growth, and the ensuing rapid fertility lowering (Liao, 1996). This has resulted in a fast and explosive population aging. Furthermore, the growth of the elderly in these regions happens in a context of poverty, large heterogeneity, and profound inequity. Besides, in all less developed nations, at the same time, the extraordinary growth of the young population and of those of working age has to be managed. Between the year 2020 and 2040, these countries will show age structures approaching those of the developed world today. Only 20 years are left to gather resources that can be devoted to the care of the elderly and to develop an infrastructure for the same purpose.

Current demographic trends (UN, 2003) show that the differences between regions are considerable at the present time: a 15-point gap exists between the percentage of elderly people for the least developed countries and the more developed regions in 2000. For example, Latin America is moving toward patterns similar to those of developed regions. In this context, it is clear that population aging of the kind that raises serious economic and social issues in the more developed countries is not such a distant prospect in many developing and middle-income countries and is already a matter of concern for many others, particularly in Asia and Latin America.

The social and economic dimensions of this phenomenon depend as well on dynamics of the younger population. If this population grows as fast as, or faster than the older population, then the needs of the aged will probably be disregarded. From this perspective, what matters is relative growth of both segments of the population. This data from the UN allows projections that show how, with few exceptions, the rates of increase of the aged population during more recent periods are higher than the increase of the total population, and that these rates have been increasing steadily. This shows how rapid aging in these countries has been present, though unnoticed, for a long time.

While in developed countries, the current reality is that of an aging population that is healthier and better educated than ever before, and of whom 60% are neither disabled nor dependent (Robine and Romieu, 1998), in developing countries the analysis of the situation reveals many problems that make it more difficult to care for an emerging aging population in which illiteracy, poverty, poor social and family support prevail and lead to a poor self-care capacity. In such a context, finding the means with which to accomplish a "compression of morbidity", helping an aging population with 13–16 years of additional life expectancy at age 65 to remain active and robust until the last years of life is the biggest challenge to public health for the twenty-first century (Gutiérrez-Robledo, 2002).

Furthermore, a disturbing hypothesis has been stated, suggesting that massive improvements in survival such as those occurring in Latin America during the sixties, and concentrated within a few years after birth are likely to induce important changes in the mean and variance of the frailty distribution of the elderly population (Palloni *et al.*, 2002). It is well known that this fact alone could account for increases in the prevalence of disability as well as for slower improvements in mortality at older ages than would otherwise be expected. So, elderly health status and functional limitations are likely to have worse distributions than those observed among the elderly in more developed contexts. If this hypothesis proves to be true, then the aging process in the region will be characterized not only by its rapidity and dimension but also by an "expansion of morbidity", leading to a huge demand on health services.

In such conditions, countries in the region would be facing the "failure of success": as their populations attain longer life expectancies, they will be unable to support their health status and avoid dependency because of lack of resources and specific services. Nevertheless, at the same time, they will be facing an opportunity for creative social planning. If policy makers understand the immediacy and implications of all these phenomena, and the connections between population aging, early life health status and economic growth, the actual

lack of infrastructure would open the way to the development of alternative, community-based care systems.

The case of Sub-Saharan Africa's elderly population deserves special consideration. Even though population aging is not as large as in other regions of the world, it must be considered as a potential cause for concern, since the largest increase in the number of elderly in the world between 1980 and 2000 will occur in Asia and Africa. The most rapid growth is expected in western and northern Africa whose elderly populations are projected to increase by a factor of nearly 5 between 1980 and 2025. A distinct feature of the aging situation in Africa is that a large proportion of the elderly people live and work in the rural areas. It is estimated that by the year 2020, approximately 64% of Africa's elderly will live in areas defined as rural. Also of significance is the fact that most of these elderly will be women. Africa has experienced an unprecedented proliferation of political unrest and civil strife. These and other economic hardships have caused millions of Africans to flee their countries, and at present, African refugees top the list in the world. Elderly persons have special difficulties coping with the hazardous and stressful journeys and are overwhelmed with the process of adjustment to new life. Many who choose to remain suffer from hardship, as there is hardly anyone left young enough to cultivate food and provide care and protection.

There is no doubt that the greatest constraint facing African countries with respect to planning for aging is the dearth of data on populations over age 60 years. Several areas of research deserve higher priority in order to get a more general view of aging (Apt, 1995).

DEVELOPING SOCIETIES WILL EXPERIENCE DIFFERENT INTERGENERATIONAL TRANSFERS

The economics of aging has been analyzed mainly in developed countries. In the very different context of developing regions with large informal sectors, flexibility of labor participation patterns, large nonmonetized economy, and lack of institutionalized pension systems, analyses so far have been much less detailed. Attention has been focused principally on the negative consequences of aging such as the problems regarding economic support for older people who no longer participate in the labor force, or do so with low productivity; and problems regarding elderly health care, like the financing of facilities and services and their adaptation to changing needs. But the economics of aging in developing countries must be examined in the context of broader demographic changes, of which aging is only one single aspect. A balanced, comprehensive view of the implications of those changes is needed. During the demographic transition that these countries are now undergoing, the decline of fertility causes not only an increase in the proportion of older people, but also, conversely, a reduction in the proportion of younger people. Of particular interest is the proportion of people under 15 years of age, as they are also dependent, even though to a lesser extent. So, we must place projected aging within the context of overall age dependency. In recent decades, the most significant change in age structures in developing countries has been the reduction in the proportion of young people due to fertility declines: the proportion aged 0–14 has been declining in all the developing regions since 1970–1975. It will continue to decline, and the resulting reduction in numbers will be roughly as large as the increase in the number of older people. This shift, and possible reduction in the total burden of dependents per person in the active age-groups, in turn, opens opportunities to redirect investment in health and human development. The period during which the age dependency ratio declines has been described as a "window of opportunity". This shift implies changing needs and, therefore, requires adaptations in health and social investment programs. For instance, as the overall costs of education for the society decline during this process, resources could be diverted to partially solve the additional health costs of aging (Schulz *et al.*, 1991).

For some old people, life will be better in the twenty-first century, for many it will be worse, for most there will be, seemingly, little change. Human societies, of which the old are an integral part, are subject to economic, social, and political pressures. Two-thirds of the world's elderly in this century live in developing countries, the majority being very poor. The main underlying cause of ill health in most of these countries, poverty, will be relieved only very slowly – if ever. Poverty and economic crisis adversely affect mortality rates among the elderly, in women more than men, and the strength of that association has been increasing over time (Wang *et al.*, 1997). In 1992, tightening of the embargo on Cuba increased the mortality in people older than 65 by 15%. The 1995 economic crisis in Mexico had a similar effect (Cutler *et al.*, 2000). The elderly constitute a particularly vulnerable group in times of economic crisis. The health of the elderly in Latin America is likely to be particularly sensitive to economic trends, and the present supply of health services may not be wholly effective in preventing this response. Present trends indicate that the gaps between rich and poor will widen both within and between countries, and will be a long lasting, if not permanent feature of rapidly changing economies (Davies, 1999). As developing countries struggle to cope with their economic problems, the aged individual is marginalized. The manifestations of poverty are much more severe for the aged. Rural poverty leaves older people alone in the village to look after themselves, while the family migrates to urban areas in search of jobs. In the middle of competing priorities at the national and family levels, the welfare of the elderly is usually given low or no priority.

The current health of younger generations can impact on older persons in a number of ways if they are expected to be earners as well as carers. A specific issue occurs in some countries where there is an impact from the morbidity and mortality of intermediate generations, for example, from HIV/AIDS, which is likely to significantly affect Thailand, Myanmar, the Philippines, and perhaps China (HelpAge International, 2002). As has been noted, the most unfortunate older people can be those who live utterly alone or with young, dependent grandchildren, yet with no middle

generation. Such a scenario is, unfortunately, increasingly common in some African countries and may appear in the Asia–Pacific region as well (Gorman, 1999).

DEVELOPING SOCIETIES WILL EXPERIENCE MORE NEGATIVE ATTITUDES TOWARD AGING POPULATIONS

Old age poverty is too often presented as a matter of special pleading rather than a basic human right. In economics, poverty among older people is accepted as a norm; in health, routine discrimination against older people is tolerated; while in personal security, violence against older people is perceived as no one's business.

Policy on aging has to be based on equal rights for older citizens. In practice, older people are not treated equally before the law – national and international legislation to protect people from violence is often not applied in cases of violence against older people. Older people report that they view old age with anxiety and fear, not only because of worsening poverty, but because of increasing dependence on others and consequent vulnerability to physical, sexual, and psychological abuse. Welfare services frequently discriminate against older people. Where health and social services are offered, they often exclude older people, whether formally, by setting age limits, or informally, through negative staff attitudes. Most poor people work into very old age and, therefore, have the same requirements as other groups for employment, credit, development assistance, education, and training schemes. Yet credit is often denied on grounds of age, and there is an upper age limit on most loan schemes. Poverty, social exclusion, and discriminatory attitudes toward old age violate the human rights of older people. The UN Principles for Older Persons, for instance, do not have the status of legally enforceable rights.

DEVELOPING SOCIETIES WILL EXPERIENCE GREATER EXPECTATION OF GOVERNMENTAL PROGRAMS BUT MORE PROBLEMS DELIVERING SERVICES TO THE AGING POPULATION

The elderly, with their greater need for health care, put considerable strain on systems of health care in all societies and provide additional urgency to the search for solutions. The ideal of healthy aging requires that the elderly share the general facilities available to the population at large, and also receive additional care to meet their special needs. These include the social and physical environments, the promotion of healthy lifestyles, and the provision of medical and nursing care. Few professionals choose to care for the elderly, and as the majority of the world elderly are women, their low status in developing countries will continue to be a major barrier to their health as they age. Poverty is the greatest single cause of ill health at all ages and while its reduction is not strictly a role of the health sector, it is certainly a prerequisite, for its persistence will continue to adversely affect any health intervention (Lloyd-Sherlock, 1997).

Global aging impacts on policy in two ways. First, good policies can easily be undermined if they fail to take account of the radical demographic shifts that are now under way. The changing shape of populations creates new opportunities and challenges. Appropriate policy recognizes the valuable human resource represented by increased numbers of older people, supports their role in enhancing the quality of our societies, and protects their right to live in decency to the end of their lives. Secondly, there are powerful economic, social and ethical grounds for a fundamental shift in policy and opinion on older people in aging societies. Countries cannot afford to ignore the contribution to economic and social development made by millions of older people. More importantly, as a matter of equity and citizenship, the needs of older people have to be addressed in the context of human rights. The neglect of older people's most basic rights, to food, shelter, health care, and a voice, must end. The price of neglecting older individuals and the challenges of aging populations is increasing poverty; not only for those who are now old but also for younger generations. An opportunity for all of us to manage our own future will be lost unless determined action is taken now (Phua and Yap, 1998).

EPIDEMIOLOGIC TRANSITION: THE EXPANSION OF CHRONIC MORBIDITY

In 1971, Abdel Omran first proposed the concept of epidemiological transition (Omran, 1971). Today, this approach in population studies is widely used. Nevertheless, this concept is probably outdated, as it has become clear that the evolution of the epidemiological profile in different regions of the world follows no single pattern. In Latin America's experience, this transition shows some particular characteristics such as multiplicity; there is not one single way to follow but several possible roads – and vulnerability of the transitional course (Palloni, 1990). In these countries, the improvement of living standards has not been uniform for the population as a whole and the vulnerability of the poor sector is growing as a consequence of economic programs that have not favored them. Negative consequences are manifest in a greater morbidity and mortality in those vulnerable groups. So, morbidity patterns are not uniformly shifting toward degenerative disorders as infections still take a heavy toll on our elderly – tuberculosis is a particular case as its incidence is rising – and the evolution of chronic and degenerative disorders suffers a heavier influence of nutrition in its pathogenesis and outcome as is the case with diabetes whose high prevalence is associated with an even higher prevalence of other coronary risk factors, both associated with an increased risk of functional impairment (Lerman *et al.*, 1998).

The aging process exposes individuals to increasing risks of illness and disability. The key factors affecting the health

profile of the elderly are incidence and timing of onset of chronic illnesses and disability, magnitude of rates of recovery, and mortality. But in poor countries, lifetime exposure to health problems means that many people enter old age already in chronic ill health. People can be frail and functionally impaired much earlier. This is particularly so for women who, after years of hard physical labor, poor nutrition, and many pregnancies, are on the threshold of old age by the end of their reproductive years. For older people in the developing world, personal health consistently ranks alongside material security as *a priority* concern. Physical health is for many poor people their single most important asset, bound up with the ability to work, to function independently, and to maintain a reasonable standard of living. Illness in old age is, therefore, an ever-present threat. Many older people live in fear of illness, for they cannot afford to be ill. Despite its importance to older people, health care is inaccessible to many. Hospitals tend to be concentrated in urban centers, far from the rural areas where many older people in developing countries still live. Even those who live in cities and towns can often only reach health facilities by using public transport, which is expensive, crowded, and not adapted for easy access. Treatment is often unaffordable for older people, even where it is nominally free of charge. Where fee exemption policies exist, older people could not benefit because of lack of information, shortage of supplies, and poor management. The negative attitude of health staff toward the treatment of older people is also a powerful factor dissuading many from seeking treatment (Palloni *et al.*, 2002).

The challenges to health systems are twofold. The first is to postpone the onset of disease as long as possible, and the second, to provide adequate services when people develop fatal or disabling illnesses. The World Health Organization (Yach *et al.*, 2004) estimates that, by 2020, chronic diseases, along with mental health disorders and injuries will make up 70% of the health-care needs in developing and newly industrialized countries. Older people form a significant part of this caseload. If unchecked, chronic diseases might pose a serious threat to the future solvency of health care and social protection systems. The challenges for developing countries are particularly formidable because of the speed of population aging, and the prevalence of absolute poverty and infectious diseases. There is a third and more fundamental constraint. Health spending in many developing countries is a tiny fraction of what is needed to meet these challenges. Per capita spending on health care in many countries of Sub-Saharan Africa, for example, is under 3% of the GDP (see Table 1), and that is skewed toward urban areas. So, as life expectancies and the possibility of exposure to risks for chronic health problems rise, chronic conditions become more prevalent and this happens during a longer period of time. Chronic conditions presently comprise the major health burden in developed countries, and trends for developing countries forecast a similarly concerning situation. Noncommunicable conditions and mental disorders accounted for 59% of total mortality in the world and 46% of the global burden of disease in 2000. The disease burden will increase to 60% by the year 2020; heart disease, stroke, depression, and cancer will be the largest contributors. Low- and middle-income countries are the biggest contributors to the increase in the burden of disease from noncommunicable conditions. In China or India alone, there are more deaths attributed to cardiovascular disease than in all other industrialized countries combined. These diseases share key risk factors: tobacco use, unhealthy diets, lack of physical activity, and alcohol use, all of these very often, during a lifetime. The current burden of chronic diseases reflects past exposure to these risk factors, and the future burden will be largely determined by current exposures. Moreover, in developing countries, chronic diseases have not simply displaced acute infectious ones; rather, such countries now experience a polarized and protracted double burden of disease. Moreover, if these countries thrive successfully, as economic development occurs, tobacco use and obesity (and presumably other risk behaviors) will increase. Eventually, uptake of risk factors will lead to onset of disease. Mortality and morbidity from chronic disease would subsequently decline along with continued economic development. Thus far, only some of the Organization for Economic Cooperation and Development countries have achieved these declines, which have been associated with consumption behavior, while declining mortality from chronic diseases is associated with very high levels of social and economic development. Thus, in the absence of policy actions, consumption of tobacco, alcohol, and foods high in fat and sugar increases along with gross national product, followed by associated increases in chronic diseases decades later. This contrasts with infectious diseases, which generally decline with economic growth. Chronic disease risk rates do not begin to fall yet and demand an integrated approach to their prevention, surveillance, and control (WHO, 2002).

HEALTH AND WELL-BEING OF THE ELDERLY IN DEVELOPING AND MIDDLE-INCOME COUNTRIES

Information is still scarce in this setting. Some more data on the subject is available in the Latin-American region. In 1998, Pan American Health Organization (PAHO) conducted a multicentric Study on Aging, Health, and Well-being (SABE) (Peláez *et al.*, 2003; MIAH, 2004) in seven major cities of Latin America and the Caribbean. According to the SABE survey, the prevalence of chronic conditions vary in the region: hypertension was reported by one out of every two persons 60 years and older; the lowest percentage was reported in Mexico City (43%) and the highest in Sao Paulo (53%). One out of five persons reported having heart disease. In most cities, at least one out of three older adults reported having arthritis. Diabetes was highest in Bridgetown and Mexico City, with 22% of older persons reporting it. The percentage of persons reporting having had a stroke is over 8%. Older men were less likely to report having arthritis and hypertension, but were just as likely as women to report having heart disease and diabetes. In the United States, a study of a much older population found that about 45% of persons aged 70 years or older had hypertension, 21%

had heart disease, 58% had arthritis, and 12% diabetes. The prevalence of stroke in this age-group was 9%. In Canada, 33% of persons 65 years or older reported having hypertension, 16% had heart disease, 47% had arthritis, and 10% had diabetes.

The SABE survey found that approximately one out of every five persons 60 years and older, in the combined sample, reported having some difficulty with the basic activities of daily living (bathing, dressing, using the toilet, eating, getting in and out of bed, and walking across a room). Included in this number were those who needed assistance in order to perform an activity as well as those who were unable to do the activity at all. Since the data obtained by the SABE survey concerns only elders living at home, it is difficult to estimate the true levels of disability without comparable data obtained from long-term care facilities or group homes. Anyway, these are very high levels of prevalence of activities of daily living (ADL) and instrumental activities of daily living (IADL) impairment and point to needs that, in the changing social and political contexts of these countries, may well require practical solutions quite different from the traditional ones. From this data, it seems clear that disease is more prevalent, begins earlier, and disability spans for a longer period of time. So, the correlation between a growing life expectancy and compressing morbidity is not yet present in Latin America, for as we have shown, risk of morbidity is higher and morbidity tends to be more devastating, with a higher risk of functional impairment.

Some other questions about the epidemiological transition in these countries remain open: To what extent do the successive cohorts of elderly people become either frailer or more robust? Will the "emerging" morbidity and mortality causes be the same when compared with fully developed countries? Can treating chronic diseases reverse disability? Are the elderly able to benefit from health and social interventions in this context? Answers are urgently needed in order to develop adequate long-term policies.

Provision of Services and Care

In broad terms, services and care for older persons can be considered under three categories: social security, health care, and social services.

Social Security

To ensure that the basic needs of older persons are met, the governments of some developing countries provide direct financial assistance, although this tends to be very limited. For example, Hong Kong has an Old Age Allowance of approximately US$80 per month, as an asset and income-tested benefit for its citizens aged 65 and over, known colloquially as "fruit money" due to its minimal value. It also has a means-tested Comprehensive Social Security Assistance Scheme, starting at US$325 per month for older persons (aged over 60) with some disability, rising to $558 for poorer older people needing nursing care. Mexico City, likewise, aims to guarantee a minimum living standard for its older adults through its newly codified 2000 Basic Livelihood Security Law, which built on the existing public assistance law, and its small "Elder Pension". On the other hand, some societies emphasize on provident fund schemes to provide income security for their retired workers. For example, in Malaysia, formal sector workers participate in a range of government and private sector pension schemes, but these are not compulsory for the self-employed, amongst whom the participation rate is low. These people will, therefore, have to rely largely on their own resources in old age. Such is the case as well for many countries in Latin America (Gill *et al.*, 2004).

Health Care

Health care comprises a wide range of services, at the primary care level, ranging from clinics to increasingly specialized hospitals and institutions. In many of the developing countries, in addition to western-style allopathic medicine, with mainly a disease-oriented nature, there is also an important parallel, and sometimes connected, system of traditional medicine, particularly in Asian countries. Older persons in Latin America often find traditional sources of health care a great comfort and culturally acceptable. Such traditional health care is mainly available through the private sector.

When in need of formal conventional health care and services, older adults, in all the societies under discussion, tend to rely mainly on publicly provided government facilities, particularly for hospital and rehabilitative services. This is because few older persons have the resources or insurance to pay for private sector medicine, although there are exceptions, such as people with special coverage, retired armed forces personnel, and some civil servants in some countries as Mexico. By and large, however, the older population will at present rely on out-of-pocket primary care, or if in need of hospital care, they turn to the public sector.

Most developing countries provide at least basic hospital services for their older populations, even if these are sometimes crowded and difficult to access. Many have already implemented, as is the case for Mexico, or at least have plans to introduce, insurance schemes to lessen the financial burden of medical services. Korea and Malaysia have also recently developed such a scheme (Gutiérrez-Robledo, 2002; Philips and Chan, 2002).

The health status of the current and future cohorts of older persons in these countries is also very important. At present, as noted above, expectation of life at birth is generally extending. As it has been said, there is no compelling evidence as yet as to whether there is a compression of morbidity in these regions, or a longer life and a worsening health status; seemingly, this is unfortunately the case (Palloni *et al.*, 2002; Vita *et al.*, 1998). This is clearly a very important question for policy makers, and it will underpin decisions about the sort of community and institutional services that are needed. Indeed, it will influence the nature of the medical and nursing skills and the training needed in

the future, as well as many other issues. As a result, research needs to be conducted and epidemiological data needs to be systematically gathered as soon as possible.

The solution to the health problems of older persons requires more than access to a physician. It requires a change in the culture of health, and a public health approach to health education, health promotion, early detection of problems, and appropriate resources to provide community-based care and rehabilitation. There is a need for human resources to be trained to understand the different health needs of an aging population. Systems should be flexible and should provide coordinated services that are organized according to population needs and community resources.

The study of health determinants reveals that there is a wide range of factors that contributes to the health of older adults or puts them in situations of risk. These determinants rarely exist separately and thus rarely benefit from one-dimensional solutions. Therefore, multiple sectors and partners must collaborate to address interrelated risk factors and safeguard factors that promote active aging and prevent or delay the onset of chronic disease. Main risk factors are: social isolation and poverty; malnutrition and sedentarism; stress, anxiety, and depression.

Social isolation and poverty contribute to morbidity and negative health outcomes and reduce the ability of older persons to access information and assistance, as needed. Multisectoral approaches should alleviate poverty, educate older persons to understand their rights, and promote health literacy. There is mounting evidence of the importance of active living and proper nutrition to help prevent and alleviate disease and chronic conditions, boost the positive effects of rehabilitation, reduce the potential for falls and injuries, and help manage other risk factors. Diet and exercise play a positive role in maintaining function and preventing disability. Screening for malnutrition and targeting the identified nutritional needs with a variety of community interventions for the neediest are cost-effective means of strengthening the capacity of elders to adhere to wellness prescriptions and practices. In addition, a variety of programs are essential to promote elder participation in organized physical activities and exercise. The prevalence of mental health problems among elders contributes to misuse of medications, alcohol abuse, and self-destructive behavior, and reduces the capacity of the individual to care and manage health problems before they become disabling or life threatening. Considerable improvements have been made in the treatment of depression and anxiety, but the lack of coordination of primary health care and community mental health services results in a situation in which the mental health needs of most elders are often not met. Local strategies designed for the timely detection and treatment of depression, anxiety, and dementia in older persons are to be developed, including training mental health and primary health workers, as well as peer group counselors, to address the mental health needs of elders (PAHO/WHO, 2002).

In most of these countries, health-care systems are still designed to provide acute illness care. They lack a population-based, community health orientation that is focused on enhancing the capacity of the individual and the community for improving health, detecting early problems, and handling and managing chronic diseases with the least costly and most effective approaches. Public Health in most developing countries has not developed an integrated community approach to promote health and well-being in the older population. Much of the work to be done requires multisectorial collaboration: to alleviate poverty, promote healthy eating, physical and social activity, and to provide a coordinated system of care for older persons. Primary health-care systems in these countries need tools and resources to reorient or reorganize services to meet the complex health needs of older persons. The current method of organizing and financing primary health care with existing human resources cannot respond to the health needs of aging persons, even if additional resources are added to the services. Primary health-care needs population-based approaches, including prevention, early detection, and patient empowerment for self-management of chronic diseases. It also requires networking with community resources and other disciplines. This approach also needs human resources that are capable of moving beyond curing acute episodes, to understanding the need for a collaborative process involving the treating physician, other members of the health-care team, the patient, and other partners in the management of complex health problems. Effective care also requires effective monitoring of adherence and patient education. Training of primary health-care teams for care of the elder should be considered a priority and provided with resources. Training programs should be developed for teaching self-care or self-management for elders and families dealing with chronic diseases or complex health problems (Barry, 2002). There are evidence-based educational programs that teach the necessary skills for self-care and provide models for psychological support for elders. These resources should be adapted to the needs of elders who are very poor and who have low levels of education. There is a need to integrate social and health-care services to promote a continuum of support for older persons in danger of loosing autonomy. The performance of primary health care can be improved if linkages are made to community resources relevant to health promotion, prevention, treatment, management, rehabilitation, long-term care, and palliative care of the elderly population (PAHO, 2002a).

For this purpose, explicit guidelines and protocols for screening and assessing the physical, functional, emotional, and cognitive health of elders should be developed or adapted as it has been done by the Merck Institute for Aging and Health (MIAH, 2005).

Norms and standards for community-based programs such as adult day-care services, home care, foster adult homes, and assisted living facilities need to be developed and implemented. The public sector, NGOs, and the private sector need to form alliances for the development of age-friendly community services (WHO, 2004). However, the state must guarantee a minimum standard of quality care to protect the dignity and well-being of disabled and frail older persons.

Countries are beginning to experience the challenges posed by the care of frail older persons, and need to

learn from the mistakes of those who have in the past, prioritized the institutional approach to long-term care and are now searching for better models of community-based long-term care. For example, during the past decade, the Governments of Canada and the United States have explored the development of more appropriate, as well as cost-effective, community-based alternatives to nursing homes. This has led to increased funding for home care and community day-care services and has limited the growth of nursing homes. The costs related to long-term care and palliative care will become a major issue in most of the developing countries during the next decade. Foresight in developing appropriate community models while the demand is still relatively low will avoid major problems during the next two decades when the demand could overwhelm the system (Brodsky, 2002).

Countries with more lead time at their disposal now have the possibility of planning well ahead for the necessary adaptations. In this perspective, they should define long-term strategies to partly reorient public investment efforts as well as training programs, set up public mechanisms for welfare where feasible, and foster or assist with the development of targeted initiatives and institutions in the civil society.

Social Services

This third category of services involves provision of services and assistance in kind, as well as housing or specialist accommodation for older persons. The range and depth of services developed in the countries under discussion are varied according to their different contextual needs. Some social services, such as recreational services, are generic and serve all ages, while others are more focused on older persons and include services such as institutional care, day care, personal care, and home help services. Issues related to the status and morale of older persons are sometimes also covered, and can include promoting the employment of older persons. Unlike other countries, Mexico, Korea, and Singapore increasingly emphasize employment of elders, Singapore in part because of predicted potential labor shortages.

The need for specialist or adapted forms of accommodation to enable some older persons to continue living in the community and to avoid institutionalization is widely recognized. Therefore, given the nature of demographic aging in the countries in this chapter, with large percentage increases expected in the number of older persons, coupled with social changes that are diminishing family care abilities, it is not surprising that housing forms a major plank in most social services and welfare policies. These range from policies to promote aging *in situ* and community care, to the provision of long-stay residential and hospital units with day-round nursing care. Home care and associated support is clearly crucial here. Most countries, specifically aim part of their housing policy for older persons on strategies to enable families to keep living with or near elderly relatives. These strategies include allocation of housing units nearby for children and elderly parents, and more rapid allocation of public housing when older relatives are included. It is strongly predicted that these types of initiatives will gain in importance, as the public sector tries to maintain family care and coresidence or residence nearby, for older people and their younger relatives, and to foster traditional values such as filial piety. In addition, policies to enable unrelated older persons to live together are also being attempted and may well expand as widowhood and longevity increase (Sokolovsky, 2000).

Unanimously, all countries recognize the importance of the family that cares for older people, particularly long-term care and financial support. These still depend greatly on family and the informal sector, the governments, while setting the scene, are the last resort provider of care at the moment, although this is clearly changing. The traditional Asian value of "filial piety", a two-way duty of care and responsibility between parents and children, is emphasized, especially among the Chinese society. These values prevail as well under different manifestations in most countries in Latin America. This assumes that older people will be cared for by families and communities, which is encouraged and promoted as the norm of the society. The family is seen as the key caring unit of society, and in some countries this has been embodied in law, for example, in Singapore, in the Maintenance of Parents Act in 1995, and in Mexico in the Older Adult Law in 2000.

This reliance on family care is a great strength and something of which these societies may justifiably be proud. However, its uncritical acceptance, and more importantly, the continuing expectation that families in the twenty-first century will be able to continue their functions as carers for older persons has been identified as *a potential weakness* (Ng *et al.*, 2002). This is particularly so when children are made to feel guilty if they are not able to take full care of their parents, however old or frail, and when their own domestic and economic circumstances make such care difficult. In some cases, the unbending expectation that families will be the primary caregivers has been seen to have actually deterred the development of coherent policies and effective public services for older persons. As a result, there is now growing pressure for these expectations to be amended. There must be services and other forms of assistance available, so that families can continue to shoulder what may become an increasingly heavy burden if left to them. While families undoubtedly do still have a very important caring function in all the countries under discussion, the ability of older persons to choose where they would like to live and with whom is also important. This will grow with future older cohorts, who will be better educated and better off than many of today's older persons. If asked where they would like to live, many older persons state that they would like to do so with their children, but this is an ideal. In reality, many older persons prefer their independence, and for personal reasons do not actually want to live with their children and risk intergenerational conflicts.

A number of practical factors militate against the family's easy continuation of care. First, many families are split because of migration for work and because of social issues such as bereavement or divorce. Second, family sizes are decreasing and will be even smaller in the future, reducing

the number of children to share the social and economic responsibilities of care for elderly parents (Arriagada, 2004). The combined effects of these two factors mean that many future older persons may not have any children living nearby on whom they can rely. Third, housing space is at a premium and, in most middle-income country's cities, dwellings large enough to accommodate multigenerational families are becoming rarer and very expensive. Fourth, economic circumstances and social choice mean that many more women, the traditional carers for elderly parents or parents-in-law, are working and are not available as constant free carers. Last but not least, as noted above, many older persons themselves would prefer the freedom to live independently, perhaps near their children and grandchildren. This aspect, the welfare of older persons, is very important. Many do not wish to live in the same house as their children and do not wish to be perceived as burdens on them, especially in hard economic times (Sokolovsky, 2000).

All these factors operate in various combinations in the countries covered by the chapter. They heavily underscore the urgent need for policies and provisions to be developed, which will help families and will not place crushing burdens on them. The family as a caring institution is a resource and needs nurturing and support.

POLICY ISSUES

Following the former considerations, several issues have been raised: How to strengthen the informal support of the family, which is weakening because of the evolution that we have described? Is there any possibility of developing a social security for those in the informal sector? How do these countries protect the interests of the aged as they restructure their economies in the era of globalization? Are there any lessons to be learned from developed countries in these issues?

Overcoming marginalization is a main issue, poverty is its main instigator; economically it implies being at the periphery; politically, it means being out of decision making; and socially, it means being cut off from the appropriate life and culture of the society. Empowering the elderly throughout and ensuring elderly people's participation in society as a need means the avoidance of marginalization. The crucial issue is the avoidance of poverty. Mutual support structures could provide older persons with more control over their own lives but such organizations will not be able to satisfy elderly people's basic needs. Improving social services is also an urgent need, for the aging situation will generate a tremendous demand for social services. Some of this will be very basic such as food and shelter, others not so basic, as is dealing with disabilities. In order to improve these services, the first step is probably to recognize aging as an emerging and significant issue; secondly, to consider that a large majority of elderly people will have neither savings nor access to social security benefits; and third, to recognize that their need of social services are high and ranging from basic to rehabilitative services. The development must be based on the existing informal support system for the aging and the existing social service infrastructure. In this context, adult day-care centers can be developed with little additional input. Most countries cannot afford to develop specialist geriatric services. Special provisions will have to be made in the existing health system in order to prepare primary care professionals in the field of geriatrics (Gutiérrez-Robledo, 2002).

Planning for the health care of the elderly in less developed nations is already a must as aging and health care are already significant emerging policy issues in these countries. National policies on aging are developed in a complex set of contexts: sociocultural, political, economic, and international. The international context, in particular, is becoming increasingly important, as research and knowledge of the types of services and provisions for older persons that exist in different parts of the world become known. Also very important is the sociocultural context, as most of the countries under consideration regard older persons with traditional respect, even if this is not always translated into care and resources. The family is also widely regarded as the main and acceptable, indeed expected, provider of care and financial support. This is both a strength and a weakness in the development of these policies.

The desired objectives of public policy on aging would be to promote an optimal physical and mental functioning, lowering the incidence of chronic diseases and disabilities throughout, making available enough resources specifically devoted to this purpose, promoting intergenerational transfers in every possible level, promoting elderly empowerment through the combat of poverty, their engagement in decision making and in productive activities. At the same level, optimal health care of the elderly would require universal access to primary medical care and population-specific interventions, with an emphasis on health promotion and disease prevention, as well as development of home and community care. In every level, patient participation must be encouraged (Walker and Naegele, 1999).

Although the details of care and service provisions are different among countries, the nature and philosophy reflected in their implementation are, in many ways, more or less similar in all. This fact offers some insights that may be useful for planning and improving the policies and care for aging populations.

Although the growth of the aging population, and the need for policies with a longer-term perspective, is apparent, not all countries have a clear policy on aging. From this perspective, the International Plan of Action on Ageing 2002 contains a number of important points to be considered, including the concept of "secure aging" and several priorities that could seem daunting and ambitious (UN, 2002). But such ambition reflects the neglect that population aging has faced until relatively recently. The well-being of older people is clearly linked to that of their families and the wider community. Sound policy needs to recognize that aging populations have the same potential for investment as other age-groups.

In the same line of thought, and in a much more specific perspective, the Merck Institute for Aging and Health, together with the Pan American Health Organization have proposed a set of goals on the basis of the available information for the Latin-American region. Many of these goals can be proposed as well for other developing and middle-income countries in different regions of the world (MIAH, 2004).

Health policy makers need to be aware that today's older persons are in many ways an interim generation. Future programs must anticipate the emergence of older persons in the coming decades who will know and demand their rights, unlike the present generation, many of whom are humble and regard the state as the paternalistic authority. Many of tomorrow's older persons will be fitter, better educated, and wealthier. They will expect and demand responsive, high-quality services and provisions. Any national policy on aging that does not take this into account will be fatally flawed. However, a major challenge for the coming decade is likely to be how to develop quality services for future generations in a setting of scarce resources and while dealing with the needs of poorer and often less healthy people.

KEY POINTS

- Developing societies will experience a shorter time to reach the aging stage, and with less resources.
- They will experience more negative attitudes toward aging populations.
- Medical advances and preventive health measures have meant significant progress against communicable diseases, but at the same time, the number of people with chronic and degenerative conditions has risen.
- The aging process in such a context exposes individuals to increasing risks of illness and disability.
- Future programs must anticipate the emergence of older persons in the coming decades who will better know and demand their rights.

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Geriatrics from the European Union Perspective

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INTRODUCTION

Europe has a landmass of 9 938 000 sq. km (3 837 000 sq. miles), 6.7% of the total land area on earth, with varied climate, cultures, and populations. Unlike the United States, it is not a federation of states with a unifying governmental structure. However, the European Union (EU) does provide a certain amount of integration between the Member States in terms of laws, trade, and governmental policies. There remain areas where each Member State has the final say.

The European Union is a complex structure with the Council of the European Union being the main decision-making body. The Council is where ministers from each Member State can commit their government to various EU policies. The Council of the European Union and the Parliament, where members are elected directly by voters in each state, are the bodies responsible for European laws. The European Commission, based in Brussels, Belgium, is the civil service of Europe split into various directorates, each of which has an appointed political head combined with an overall Commission President. The Commission has responsibility for proposing legislation, implementing agreed policy, enforcing EU law and representing the European Union at international level (http://europa.eu.int/abc/index_en.htm, 2005).

From 1 May 2004, the European Union expanded to 25 Member States, having been 15 prior to the expansion. Although various enlargements have occurred from the original six states over the last 30 years, this is the single biggest expansion since its inception, increasing its population by 20% and its land area by 23%. This expansion brings in states from the Baltic, Eastern, and Mediterranean Europe. The population of the European Union will now number some 450 million with 150 million aged over 50 years.

DEMOGRAPHY

The European Union compiles statistics, thorough its agency Eurostat (http://europa.eu.int/comm/eurostat/), from Member States regarding a number of population and health-related parameters. However, these are collated rather than collected, so there can be problems with the uniformity of their collection not only in terms of completeness but also their comparability.

Bearing the above in mind, it appears that Europe's population has been aging steadily. In EU15 (the Member States before the recent expansion), because of falling birth rates and rising life expectancy, the number of people aged 65 years and over is projected to increase from 61 million in the year 2000 to 103 million in 2050. The proportionate increase in the very old, aged 80 years and over, is even more dramatic, going from 14 million to 38 million in the same time period. In 2003, EU15 was thought to have 16.8% of its population 65 years and over. The expanded European Union (EU25) has a slightly lower figure of 16.3%. These global figures disguise major variations across the European Union, for instance, Ireland had only 2.6% aged 80 years and over in 2003, while Sweden had 5.3%. Similarly, although, life expectancy at 60 years is 19.6 years for males and 23.8 years for females in EU25 in 2003, this varies in males from 15.2 years in Latvia to 20.9 years in Sweden and for females from 20.4 years in Latvia to 24.3 years in Sweden (European Commission, 2004).

In parallel with these changes, the working population, at least in EU15, over the same time frame is projected to decrease significantly (see Figure 1). This demographic time bomb has considerable implications for health and social care across the European Union.

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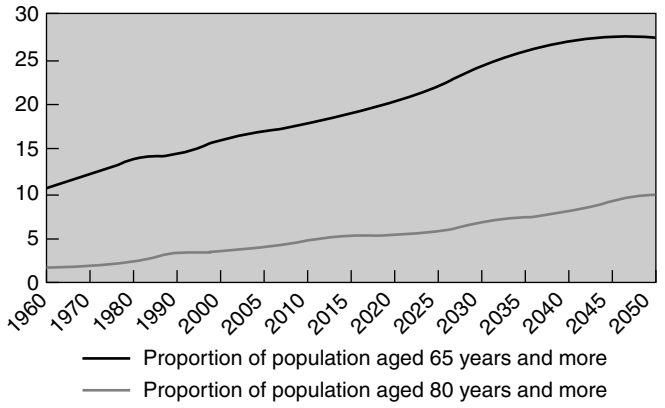

Figure 1 The aging EU population (Eurostat, population structure indicators (1960–1990), baseline scenario projection (2000–2050))

HEALTH AND HEALTH SYSTEMS

In EU15, all the of the Member States have systems in place that offer complete, or near complete, rights to health care for people residing within their borders. These are financed in two broad ways, either through general taxation, or utilizing systems based on occupational health insurance. Both systems limit their liability to pay the full cost of treatments such that expenditure borne by households amounts to between 20 and 30% in the majority of Member States. The difference is made up either through direct contributions or via supplementary private insurance, for example, France. It is however clear that public sector funding makes up a significant proportion of health expenditure in all the EU Member States: this proportion being lowest in Greece (56%) and rising to nearly 84% in the United Kingdom.

This reliance on a degree of financial participation may adversely affect some groups' access to health care as they are unable to afford the costs. This is particularly true of older people who may have both lowered incomes and considerable comorbidity. Thus, some Member States have enacted methods to target older people either by reducing their financial liability or ensuring that they are regularly screened by relevant health professionals.

In common with other developed countries, the Member States see the need to recruit staff appropriately trained in the needs of older people and also to create post-acute rehabilitation facilities to assist a multidisciplinary approach to treatment with the goal of reablement and settlement in the community. Unfortunately, often these rehabilitation sites are adrift from main acute centers in the mistaken belief that rehabilitation can wait till the conclusion of an acute episode of care.

In contrast, long-term care is seen mainly as a social risk. This seems to devalue it in many eyes and forgets that the primary reason for the need is multiple disabilities related to chronic ailments such as dementia and cerebrovascular disease. The responsibility for such care is often left to the family or untrained carers. Changes in epidemiology and demography make this an increasingly untenable situation. Almost all Member States are trying to share the costs of long-term care provision through insurance schemes and there is a move away from institutional to home-based care. In parallel, there is a drive to quantify quality standards for health care in general and long-term care in particular. As many states predict a need to increase health-care expenditure between 0.7 and 2.3 percentage points of gross domestic product (GDP) over the next 50 years, due to demographic changes, it can be seen that finance is a major issue for most governments. According to the Organisation for Economic Co-operation and Development (OECD) Health Data from the 4th Edition in 2002, it has been calculated that total health expenditure in EU15 in 2000 ranged from 6.6% in Finland to 10.6% in Germany. This contrasts with 13% in the same period in the United States.

The health needs of each country within the European Union still vary enormously (Whitehead, 1999) and will become more skewed with the generally poorer countries that have recently joined. For instance, the World Health Organization (WHO) standardized death rate per 100 000 population for ischemic heart disease varies from only 76.4 in France to 352.8 in Slovakia in 1999. Similarly, the incidence of tuberculosis ranges from only 4.8 per 100 000 population in Sweden to 88 in Latvia in 2001. This compares with 5.8 per 100 000 population in the United States in the same year.

HEALTH TRENDS

Life expectancy has been steadily growing in the European Union in the last century, and this trend has not stopped in recent years (Table 1). When a European citizen is 65 years old, he/she may expect to live more than 18 years into "old age". This means that diseases and disabilities of old age are steadily increasing. Changes in lifestyles, risk factor management and health care have pushed for a slow but steady reduction in the main cause of mortality in this age group: diseases of the circulatory system (a 24.9% reduction from 1990 to 2001). Stroke, a very frequent cause of disability in the elderly, has also decreased. However, mental health disorders (particularly dementing diseases and depression) seem to be increasing fast during the same time period, not only in mortality but also in morbidity.

One of the main problems researchers are faced with when studying illness in the elderly in the European Union is the lack of good morbidity data across Europe. Health statistics are available for communicable diseases, for health habits and lifestyles, and for disease-related mortality. However, there are no reliable data regarding geriatric diseases and syndromes (stroke, dementia, hip fracture, heart failure, diabetes, or other diseases) (Berr *et al.*, 2005). Data are fragmented, come from different years and sources, are gathered with different criteria, and are not systematically collected. Good age-specific data are especially sparse. Efforts have been recently undertaken by the statistical

Table 1 Health trends in 25 Member States of the European Union

	1990	2001
Basic demographic indicators		
Population, millions	44.04	45.22
% of population aged 65+ years	14.03	16.03
Mortality indicators		
Life expectancy at birth, years	75.54	78.19
Life expectancy at age 65, in years	16.63	18.17
SDR[a], diseases of circulatory system, 65+ per 100 000	2694.81	2022.07
SDR, ischemic heart disease, 65+ per 100 000	966.04	762.02
SDR, cerebrovascular diseases, 65+ per 100 000	720.23	529.12
SDR, malignant neoplasms, age 65+ per 100 000	1105.66	1049.17
SDR, mental disorders, and diseases of the nervous system and senses	134.92	179.01
Health-care resources		
Hospitals per 100 000	3.76	3.20
Hospital beds per 100 000	807.08	619.74
Acute-care hospital beds per 100 000	524.02	422.69
Physicians per 100 000	291.07	338.77
General practitioners per 100 000	96.44	97.82
Nurses per 100 000	730.44	773.87
Health-care utilization and costs		
Average length of stay, all hospitals	14.16	9.79
Average length of stay, acute-care hospitals only	9.55	6.99
Outpatient contacts per person per year	6.85	6.40
Total health expenditure, % of gross domestic product	7.27	8.81
Total health expenditure, $ per capita	1184.39	2030.81

World Health Organization, 2004.
[a]SDR, standardized death rate.

agencies of the United Kingdom and Belgium to define standards for the creation of a good database. However, research and progress in this area is urgently needed.

These changes have transformed the paradigm of health care. Health-care systems were once developed for the care of single, acute diseases, usually unexpected, with cure and self-sufficiency as usual outcomes. However, elderly patients usually have multiple, chronic morbidities (sometimes with acute exacerbations), where disease course can be expected, with dependency as a very frequent outcome. Unfortunately, health systems in Europe, very efficient for acute care, have only evolved slowly and in a very irregular and heterogeneous mode to be able to manage chronic diseases in dependent people. This lack of efficiency may explain why per capita health expenditure increases sharply after the age of 65 and even more sharply after the age of 80.

In the last two decades, the number of hospitals and hospital beds has been diminishing, especially those used for acute care, while the number of general practitioners, nurses, and primary care units has not grown at the same rate. Intermediate and long-term hospital beds have suffered a slower reduction, and rehabilitation and palliative care services for older people are scarce and irregularly distributed, not only between countries, but also within different areas of the same country.

Geriatric medical care is also extremely diverse within the European Union (Hastie and Duursma, 2003). Geriatric medicine is accepted in many European Countries, as a subspeciality of Internal Medicine. It is officially accepted by the European Union, but it is not yet available in every country: only 15 of the 25 countries have, in 2004, established the mechanism for mutual recognition of the speciality (Table 2). However, this list may not offer a fair picture of geriatric medicine in Europe. In some countries (Belgium, Germany), geriatric medicine has a wide distribution with hospital departments and specific geriatric training programs, even when mutual recognition has not been achieved. In other countries, geriatric medicine is not accepted as a separate speciality and is very poorly developed. European geriatricians are working hard to promote recognition of the speciality and development of geriatric medicine departments in every EU country.

One may expect that a medical speciality department would be somehow similar around Europe, so that similar up-to-date procedures will be applied to any patient admitted to a medical department of a hospital, that is, cardiology or gastroenterology. However, this is not true for geriatric medicine. Excellent geriatric departments exist in most EU countries, but citizens living in different places will have different access rights to these departments, and a significant proportion of older people in the European Union will not have access to geriatric medicine. This is not due to lack of evidence, as very solid evidence exists about the benefits of most levels of geriatric care, but to discrimination against old people by political decision makers. Primary care is universally available for the older population, but many general practitioners are not prepared to manage this special population due to a lack of academic

Table 2 Mutual recognition of geriatric medicine in the European Union

Belgique –	
België – Belgien	
Česká republika	Geriatrie
Denmark	Geriatri eller alderdommens sygdomme
Deutschland	
Eesti	
Ελλάς	
España	Geriatria
France	
Ireland	Geriatrics
Italia	Geriatria
Κύπρος	Γηριατρική
Latvija	
Lietuva	Geriatrija
Luxembourg	
Magyarország	Geriátria
Malta	Ġerjatrija
Nederland	Klinische geriatrie
Österreich	
Polska	Geriatria
Portugal	
Slovenija	
Slovensko	Geriatria
Suomi – Finland	Geriatria – geriatric
Sverige	Geriatrik
United Kingdom	Geriatrics

leaders and continuing professional development in geriatric medicine.

The growing numbers of older people and the reduced ability of weaker family networks to care for them, when they depend on others, are also increasing the need for long-term care in different settings (home care, long-stay units or nursing homes). Such care has not been regularly covered by health systems, so it is not even a universal right within the European Union, in contradistinction to acute health care. In many cases, it depends on private systems or the recently termed "*medical-social sector*". Nursing home use and availability is also diverse across the European Union: rates are close to 10% for people 65 or older in some northern countries (Sweden, Holland) and lower than 3% in some Mediterranean countries (Spain, Portugal), with a gradient from north to south that is not only explained by economic reasons but also depends more on people preferences and family networks.

IMPACT OF THE EUROPEAN UNION

The public health policy and the promotion of a high level of human health is a relevant part of the EU Treaty. The prime responsibility for health systems, under the Treaty, falls to the Member States. Most recent developments in the care of older people, however, have been fostered by the European social policy agenda. In March 2000, the European Council in Lisbon set out a ten-year strategy (the Lisbon Strategy), a commitment to bring about economic, social, and environmental renewal in the European Union to make it the world's most dynamic and competitive economy. Under this strategy, social policies that ensure sustainable development and social inclusion are being fostered. These policies are based, in many cases, in an improved cooperation between Member States, respecting the principle of subsidiarity. The Lisbon Strategy is being reviewed yearly at the EU spring meetings. A major review in the area of health care of the elderly is scheduled for spring 2005.

Following the Lisbon meeting, the Gothëborg Council, (2001) asked for an initial report on orientations in the field of health care and care for the elderly, in conformity with the open method of coordination (a method used to improve coordination in some policy areas, allowing Member States to challenge common problems, defining their own national strategies, and benefiting from experiences of other Member States). This is a milestone, as never before have EU countries tried to establish a common strategy toward geriatric care.

This request resulted in a report from the Commission (COM 723 final, December 2001).[1] The report carefully analyzed the impact of demographic aging on health-care systems; expenditure, the growth of new technologies and treatments, an improved well-being and a better standard of living, the diversity of national systems, and the contribution of the European Union. Three long-term objectives were established: accessibility, quality, and viability. Access to health care is a fundamental right and an essential element of human dignity that must therefore be guaranteed for all EU citizens, regardless of income or wealth. The need for special protection is recognized for dependency and old age. Quality implies a search to reduce diversity and variation and look for "best practice" standards. Financial viability is needed to sustain health and social systems of care in the future.

Since then, Member States provide information on how they deliver the three suggested objectives. Their information was reflected in a joint report from the Commission and the Council on supporting national strategies for the future of health care for the elderly (March 2003). The European Parliament confirmed the validity of the three key objectives for the renovation of health care and long-term care.

Very recently, the Commission issued a new report (COM 304 final, April 2004) that sought to outline a common framework to support Member States in the reform and development of health care and long-term care using the open method of coordination. The report proposes common objectives for health-care provision that would add to similar ongoing coordinating processes in three social policy areas: pensions, social inclusion, and employment. The most relevant aspects of this document related to geriatric medicine are outlined in BOX 1.

BOX 1 Recent EU Action Lines Related to Geriatric Medicine[2]

- Health systems have a role in combating the risk of poverty and disease, contributing to social cohesion and fighting the consequences of demographic aging.
- The principles of accessibility of care for all (taking into account the needs and difficulties of the most disadvantaged groups and individuals), high-quality care for the population (which keeps up with the emerging needs associated with aging) long-term financial sustainability of this care have to be met.
- The provision and funding of health and long-term care are key elements of the economic and social modernization strategy of the European Union.
- To meet the challenges posed by demographic trends and technological progress, it is vital to have a sufficient number of trained professionals and to give them quality jobs.
- Demographic aging will mean more age-related illnesses and more people in long-term care; and a growing number of old people living alone. The response to the needs of this population group will include developing a wide range of services, including care at home, and specialized institutions, as well as closer coordination between care providers.
- The social protection systems need to be reformed in an integrated and coordinated way to meet these

challenges. Health and elderly care is one of the areas where coordination in the field of social protection should be streamlined.
- Access to high-quality care based on the principles of universal access, fairness, and solidarity must be ensured, providing a safety net against poverty or social exclusion associated with ill health, accident, disability or old age, for both the beneficiaries of care and their families. Particular attention will have to be paid to persons requiring long-term or expensive care, to those with particular difficulties accessing care and those on low incomes. Financial and physical accessibility of care systems for disabled persons has to be ensured, and specific care for elderly people offered, based in particular on closer coordination between the social services, primary carers, hospital services, and specialized institutions.
- The system should be properly funded in order to meet the new challenges posed by aging, changes in society and technological progress. Responsibility for the organization and funding of the health care and elderly-care sector rests primarily with the Member States.

Member States – including the new ones – will present "preliminary reports" covering the challenges facing their systems at national level, current reforms, and medium-term policy objectives by March 2005. They will be analyzed by the Commission, so that their views and contributions can be taken into account when the joint objectives of the streamlined social security process are established. This streamlining will lead in 2006 to an initial series of "development and reform strategies" in health care and long-term care for the period 2006–2009. The conclusions of the assessment of these strategies will be presented in the Joint report on social protection and social inclusion in 2007.

This acknowledgement of the European Commission is a promising step for geriatric care. Nevertheless, it must be remembered that the Commission can only suggest action lines, which have to be agreed and implemented by Member States. European and national organizations of geriatric medicine specialists have a long way to ensure that their older patients have the best multidisciplinary care in the most optimal setting.

CHALLENGES FOR THE EUROPEAN UNION

Although these recent advances are appealing, geriatric medical care in Europe is still challenged by governments, patients, colleagues, and other parties. Table 3 summarizes some of the challenges that have to be met in the future. Although, some of them depend on political compromise by decision makers, geriatricians will have to prove their ability to offer a broad research base, academic leadership, and efficient health care to their oldest patients Duursma *et al.*, (2004).

Table 3 Challenges for geriatric medical care in the European Union

- Demographic aging.
- High degree of variability in geriatric health-care systems between countries and within regions.
- Lack of resources allocated for acute health care, rehabilitation, and long-term care of elderly individuals.
- Competition with other specialities.
- Lack of social support systems and weak coordination with health-care systems.
- Urgent need for specific guidelines and evidence-based practice for older people and geriatric syndromes. Good research networks are also lacking.
- Lack of expertise and formal education in general geriatric medical care of primary-care physicians.
- Geriatric medicine is not officially accepted in some European states.
- Few academic leaders.
- Agism in patients, professionals, and politicians.

New EU countries face the special challenge of improving geriatric care in the face of competing interests by other national budget-demanding projects, with lower incomes than other EU countries. A change in the perception of aging as an opportunity, not as a problem, has to be fostered in many of these countries.

NOTES

[1] This and other related documents can be found in most European languages at http://europa.eu.int/.

[2] Extracted from "*Modernizing social protection for the development of high-quality, accessible and sustainable health care, and long-term care: support for the national strategies using the "open method of coordination"*". EU COM 304 final, April 2004.

KEY POINTS

- The European Union has 25 Member States.
- The demography of older people is varied and health trends differ.
- Systems of care are not fully developed in all Member States to cope with an increasing older population.
- There is a recognition of the need to give the population access to an appropriately trained health-care workforce.

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Delivery of Health Care in India

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HISTORICAL BACKGROUND

Ayurveda (Ray, 1994) was the system of medicine in the Indian subcontinent and its description is as old as *Sanatan Dharma (Hindu Religion). Dhanwantri,* the physician of Gods and Goddesses practiced only *Ayurveda*. The three other books (Upoddhat, 1994) in Ayurveda which became famous are *Charak-Samhita* (Upoddhat, 1994), *Sushurta-Samhita*, and *Kashyap-Samhita.* The Indian medicines were derived from *herbs.* Old age, old-age ailments, and antiaging measures (rejuvenation) have been described in the above medical literature.

After *Mahabharatha* (the great battle between members of two dynasties), the invasion of the Indian subcontinent by foreign powers began. This introduced other systems of medicine and led to cessation of researches and growth of *Ayurveda*. This continued under British rule, which lasted for 150 years. With the British Empire came the *System of Modern Medicine*, which is still the most popular system in India and is being followed by the majority of the society. This also has the blessings and support of the government.

With independence (1947), India inherited a population infested with diseases, poor sanitation, and an unplanned health support system. Diseases like *tetanus neonatorum, cholera, plague, puerperal sepsis, malaria, small pox, gastroenteritis,* and so on, used to take a heavy toll. Death in all age-groups was very common, but more so in neonates, infants, and children. The fury of epidemics was curtailed by the involvement of world bodies such as World Health Organisation (WHO). With education and also the improvement in per-capita income, the health scenario started improving. The death rate came down, life expectancy increased, and the population, especially that of older persons started rising. At present, approximately 86 million, that is, 8.6% of the total population is of geriatric age-group (above 60 years).

Indian scenario 1947 to 2003 (Life expectancy at birth)

1947: Life expectancy 34 years
2002: Life expectancy 64 years

Health awareness improved and so did the availability of medical facilities. Earlier, the attention was on bread earners only, but by the end of the last millennium, health of the elderly also became a topic of concern. Soon, medical men as well as lay public realized that what was earlier being discarded as old-age ailments and seen with a pessimistic attitude now needed changing. Medical and health needs of people aged more than 60 became an issue for which one looked toward the West for clues. This propagated development of geriatric medicine. A major turning point in the recognition of the potentials of the problem of aging in India was the "Vienna International Plan of Action on Ageing" adopted by the World Assemble on Ageing (United Nations, 1983). In 1982, the WHO had implemented several worldwide programs for the elderly by adopting the theme "Add life to years", which was followed by *Active Aging* and *Healthy Aging*. The Alma-Ata Declaration of WHO in 1978 introduced the notion of incorporating the needs of older persons within systems of primary care under the rubric of "Health for all" (United Nations, 1988) by the year 2000. A boom in the sociomedical activities came in 1999 by the declaration of Dr Koffi Annan in United Nations Assembly as the *International Year of Older Persons.*

DEMOGRAPHY OF AGING (PONNUSWAMI, 2003; KUMAR, 1997)

In India, persons 60 years and above are considered as elderly. At the beginning of this century, the number of

Principles and Practice of Geriatric Medicine, 4th Edition. Edited by M.S. John Pathy, Alan J. Sinclair and John E. Morley.
 ISBN: 0-470-09055-3

elderly was 12 million only, which doubled in the next 60 years, making their number 24 million by the year 1961. This number rose to 56 million by the year 1991. The figure for the year 2001 and projected figure for 2016 are 70 million and 112 million respectively. The decadal growth rates in 60+ age-group from 1951 to 1961 have remained above 26% and are about 5 to 8% higher than that for the total population. There has been a major increase in life expectancy at birth with a consequent impact at 60 years of age. Expectancy of life at birth has risen by more than 10 years from 49.7 years during 1970 to 1975 to 60.3 years during 1991–1995. Over this quarter century, life expectancy at 60 and 70 years has also shown significant rise from 13.8 and 8.9 years respectively to 16.2 and 10.6 years. In 1991 census data, it was observed that of the 78% of the elderly that lived in villages, there were 930 females to every 1000 males in 60+ age-group (see Figure 1), 34% of them were widowed (15% males and 54% females), 52% were illiterate, and 39% were working (60% males and 16% females).

Women normally outlive men and there are always more widows than widowers. From the point of view of geriatric management in India, we divide the above in three segments:

Young Elderly: 60–64 years
Middle Elderly: 65–70 years
Old Elderly: 71 years and above.

This division has been done because it influences all the three aspects relating to elderly care, that is, social, financial, and medical aspects. Considering that the young elderly are still fit to work and socially well adjusted in the younger generation, the age of retirement was raised (in the government jobs/PSUs) from 55 to 62 years in various capacities. The Supreme Court judges of India retire at the age of 65. This division is important from medical aspects also because people in the young elderly age-group were required to be absolutely fit and working, hence their medical and health needs had priority over the other two age sets.

Currently, there are 24 million elderly in the young elderly age-group and males outnumber females, contrary to the second and third groups.

HEALTH AND MORBIDITY

The leading cause of death in old age in India is cardiovascular diseases (CVD). Earlier in life, infections are still the leading causes of death, but among older people most deaths are due to noncommunicable diseases (Goha Roy, 1994). The Indian Council of Medical Research (ICMR) has attempted to compile data on morbidity from different sources.

- The total number of blind persons among the older population was around 11 million in 1996, 80% of them due to cataract (Angra *et al.*, 1997). The consequences of blindness are not limited only to physical disability that ensues, but also impinge on economic, social, and psychological domains of the affected individual's life. The calculated economic costs for maintenance of the blind is Rs 432 000 million, and loss of productivity is Rs 86 400 million over a decade. Nearly 60% of older people are said to have hearing impairment in both urban and rural areas. The hearing loss and resultant communication problems adversely affect the well-being of older people (Kacker, 1997).
- In 1996, the number of people with hypertension among the elderly population was nearly nine million. The prevalence rate of coronary heart disease among the urban population was nearly three times higher than the rural population and the estimated number of cases was around nine million in 1996 (Shah and Prabhakar, 1997).
- An estimated five million elderly people were diabetic and the prevalence rates were about 177 and 35 per 1000 for urban and rural dwellers respectively.
- A crude estimate of the prevalence rate of strokes is about 200 per 100 000 persons. Older persons surviving through peak years of stroke (55–65 years) with varying degrees of disability are already a major medical problem (Dalal, 1997).

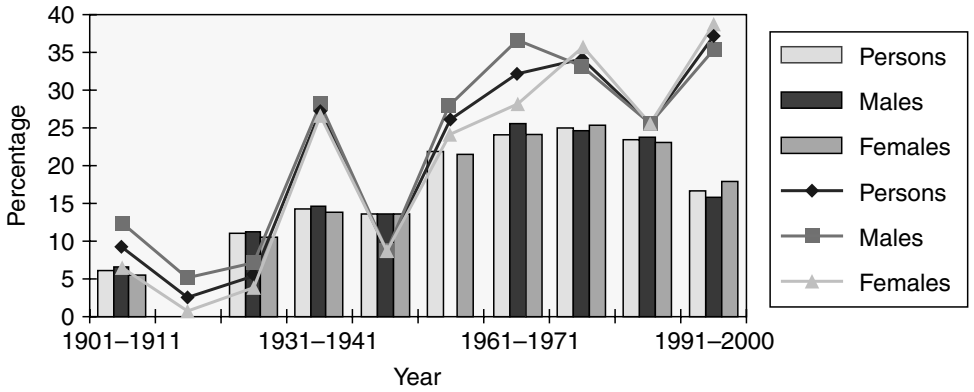

Figure 1 Decadal variation (percentage) in general population and elderly population (60+) by sex-wise – India (1901–2001)

- Population-based cancer registries were initiated by the ICMR in 1982. The number of older persons with cancer in 1996 was 0.35 million. The reports show that in coming years, as the number of aged increases, the problems associated with cancer in older age will require greater attention and resources.
- Age-related changes in the immune system render people susceptible to a variety of infections and tumors. Though tuberculosis-related mortality has declined, it is still not eradicated effectively and the prevalence rate is reported to be higher in the older age-group (Dey and Chaudhury, 1997). Adverse reactions and major side effects to anti-tuberculosis therapy have been reported in as much as 40% of the cases.
- Disabilities arising from aging assume greater significance as a large segment of this population is below the poverty line. Undernutrition is also common in this population (Srivastava *et al.*, 1996). Elderly people in low socioeconomic groups, in urban slums, or those living alone are at higher risk of poor dietary intake (Wadhwa *et al.*, 1997). The nutrients least adequately supplied in the diet of the aged Indian are calcium, iron, vitamin A, riboflavin, and niacin. Health is a key contributing factor to quality of life and is therefore closely associated to low socioeconomic conditions (Bali, 1997).

DISEASE PATTERN IN ELDERLY

Forty five percent of the elderly have a chronic disease. The 10 most common diseases are *hypertension, cataract, osteoarthritis, chronic obstructive airway disease, ischemic heart disease, diabetes, benign prostatic hypertrophy, dyspepsia, constipation, and depression.*

There is not much difference in the disease pattern between the rural and urban elderly. There are limited epidemiological studies about disease patterns in elderly. They are by Angra *et al.* on *cataract*, Dalal PM on *stroke*, Dey *et al.* on *infections*, Kacker SK on *hearing loss*, Srivastava *et al.* on *nutrition*, (Venkoba Rao, 1997) on *psychiatric problems*, and (Gupta, 1997) on *hypertension in elderly*.

Chronic diseases in elderly

Hypertension	*Cataract*	*Osteoarthritis*
Chronic obstructive airway disease	*Ischemic heart disease*	*Diabetes*
Benign prostate hypertrophy	*Dyspepsia*	*Constipation*
	Depression	

Rural elderly have apprehensions and apathy about contacting doctors of modern system of medicine. They mostly thrive on indigenous systems of medicine. Hence, they are usually brought to hospitals in the advanced stages of diseases. The five most common killer diseases in rural elderly are *bronchitis and pneumonia, ischemic heart disease, stroke, cancer, and tuberculosis*.

SOCIAL ISSUES AND HEALTH

Old age in India is associated with several social problems. They are social isolation, poverty, apparent reduction in family support, inadequate housing, impairment of cognitive functioning, mental illness, widowhood, bereavement, limited options for living arrangement toward end of life because of dependency due to physical or mental disease.

All these problems have an impact on the quality of life in old age and health care at the time of need. In traditional Indian societies, joint-family system used to take care of most of these social issues. In the INDO–UK Workshop in 1995, it was concluded that revival of the joint-family system would be the most befitting solution to the problems of elderly in India.

INDO – UK workshop 1995 (Sharma, 1999, 2004)

Joint-family system

However, with industrialization, urbanization, and disintegration of traditional joint family, older people in India are likely to face major social problems. In the absence of well-organized social support networks similar to that available in developed societies, the scenario appears gloomy. It is expected that in a not too distant future, the elderly in the organized sector will be opting more and more for living arrangements similar to that in developed societies namely old-age homes and senior citizen homes. For the elderly in the unorganized sector, the options remain limited due to poverty and destitution in the absence of family support. Nevertheless, family and the community provide the most important support for elderly persons in India. It is thus necessary to strengthen the traditional family system through community education and social interventions.

THE INFRASTRUCTURE

Social

In ancient times in India, the village was the unit and agriculture was the main profession. The system of joint family existed and it was not uncommon to see a family of four to five generations living together under the same roof. The head of the family was respected most and his opinion on account of his age, authority, and experience was considered valuable. The elderly were looked after well with devotion and dedication by the younger generation. The social support from the family was quite adequate and the need for support by the community or the government/ruler was rare. The

financial, social, and emotional support was always provided by the younger family members and medical needs were also covered by them as and when required.

With industrialization and urbanization, the social problems started occurring in the form of migrations, leading to increasing numbers of nuclear families. The age-old joint-family system started cracking. Elderly people became unsupported in rural areas. In the urban area, the elderly suffered because of the changing economy. By the time people reached the age of retirement, they had exhausted their financial resources and savings in constructing a house, bringing up children, getting them educated, getting them married, and in fulfilling social obligations. The elderly who were not prepared for this transition became penniless and suffered the most especially when their children migrated for jobs and so on. The urban elderly were also divided economically into rich, middle class, and poor elderly.

The government came forward and made some *old-age homes* for the poor and destitute elderly. Old-age homes were also made by some Nongovernmental Organizations (NGOs) and individuals. The total number of old-age homes in India is about 2000. The government created some social schemes and brought out *constitutional and legal provisions*.

Constitutional Provisions (Ponnuswami, 2003; www.parliamentofindia.nic.in)

In the constitution of India, under various clauses, certain rights have been guaranteed to elderly citizens:

- Item 9 of the State List and Items 20, 23, and 24 of the Concurrent List relate to provision of old-age pension, social security, social insurance, economic and social planning, and relief to the disabled and the unemployed.
- Article 41, Directive Principles of State Policy (Fundamental Rights and directive Principles of State Policy, 1950), has particular relevance to old age social security. It directs that the State shall "make effective provision for securing the right to work, to education, and to public assistance in case of unemployment, old age sickness and disablement, and in other cases of undeserved want, within its limits of economic development and capacity".
- Article 41 is reinforced by Section 125 1(d) of the Code of Criminal Procedure, 1973 under which every person having sufficient means is required to provide for his parents who are unable to maintain themselves.
- Section 20 (3) of the Hindu Adoption and Maintenance Act, 1956, makes it obligatory on the part of the person to maintain his aged or infirm parents.
- Fundamental Right Article 16 (2) – Equal opportunity in matters of public employment.
- Article 21 – Protection of life and personal liberty. No person shall be deprived of his life or personal liberty except according to procedure established by law.
- Article 38 – State to secure a social order for the promotion of welfare of the people.
  - The State shall strive to promote the welfare of the people by securing and protecting as effectively as it may a social order in which justice, social, economic, and political, shall inform all the institutions of the national life.
  - The State shall, in particular, strive to minimize the inequalities in income, and endeavor to eliminate inequalities in status, facilities, and opportunities not only amongst individuals but also amongst groups of people residing in different areas or engaged in different vocations.
- Article 39(a) – Adequate means of livelihood.
- Article 39(b) – Right to ownership and control of material resources to subserve the common good.
- Article 39(c) – Ensures equal pay for equal work.
- Article 39(e) – Citizens not being forced by economic necessity to enter a vocation unsuited to their age or strength.
- Article 39A – Equal justice and free legal aid – The State shall secure that the operation of the legal system promotes justice, on a basis of equal opportunity, and shall, in particular, provide free legal aid, by suitable legislation or schemes or in any other way, to ensure that opportunities for securing justice are not denied to any citizen by reason of economic or other disabilities.
- Article 42 – Provision for just and humane conditions of work and maternity relief. The State shall make provision for securing just and humane conditions of work and for maternity relief.
- Article 43 – Living wage, etc., for workers – The State shall endeavor to secure, by suitable legislation or economic organization or in any other way, to all workers, agricultural, industrial, or otherwise, work, a living wage, conditions of work ensuring a decent standard of life and full enjoyment of leisure, and social and cultural opportunities and, in particular, the State shall endeavor to promote cottage industries on an individual or cooperative basis in rural areas.
- Article 44, Uniform civil code for the citizen – The State shall endeavor to secure for the citizens a uniform civil code throughout the territory of India.
- Article 47 – Raising the level of nutrition and the standard of living of its people and improvement of public health. The Concurrent List covers social security, social insurance, employment, invalidity, and old-age pension.
- Entry 24 in list III of schedule VII in constitution of India deals with welfare of laborers including condition of work, liability for workmen compensation, provident funds, invalidity, old-age pension and maternity benefits.
- Himachal Pradesh assembly passed Parents Maintenance Bill 1996, according to which, parents who are ignored by their children are to be given maintenance. In addition, to make it obligatory for errant wards not taking care of their aged parents, the bill aims at simplifying the procedure by authorizing the subdivisional officer (Civil) for fixing maintenance and additional commissioner as the appellate authority so that decisions can be taken and cases disposed of promptly, bringing justice and relief to older persons without loss of time.

Legal Provisions (Frontline from the Publishers of The Hindu, 2001)

As per the letter number F.No.20-76/99-SD, dated 3/11/99 of Ministry of Social Justice and Empowerment (SD Section), Government of India, the Honorable Chief Justice of India Shri R. K. Anand has advised chief justices of all the High Courts in the country to accord priority for the cause list for cases involving elderly persons and ensure their expeditious disposal.

- Section 88B of Finance Act 1992 (Income tax Act 1961) – Provides rebate of income tax to senior citizens who have attained the age of 65 at any time during the relevant previous year. From 1998 to 1999, tax rebate under Section 88B shall be as follows:
  - The amount of income tax before giving any rebate under Section 88, 88B and 88(1) or
  - Rs 10 000 or 40%, whichever is less (Rebate is available from assessment year 1998 to 1999 even if total income is above Rs 1 20 000).
- Section 80D (Finance Bill 1999) – An assessee is entitled to a deduction upto Rs 15 000 with effect from year 2000–2001, where assessee, his/her spouse, dependent parents, or any member of the family is a senior citizen (above 65 years), and medical insurance premium is paid to effect or keep in force an insurance in relation to him or her.
- Section 80DDB (Finance Bill 1999) – Provides a separate deduction to a resident assessee being an individual or Hindu undivided family member for expenditure incurred for medical treatment for the individual himself or his dependent relative, irrespective of disease. The deduction shall be limited to Rs 40 000 and in case of senior citizen, a fixed deduction of Rs 60 000 will be available.
- The Finance Act of 2000 provides a rebate of Rs 15 000 in income tax (as against Rs 10 000 in earlier years) for all senior citizens above the age of 65.
- Delhi Rent Control Act 1995 (Act No. 33 of 1995) – Section 24 explains the right to recover immediate possession of premises to accrue to members of the armed forces, and so on.
  - Where a person
    (1) is a released or retired person from any armed forces and the premises let out by him, his spouse, or his dependent son, or daughter are required for his own residence, (2) is a member of any of the armed forces and has a period of less than one year preceding that date of his retirement and the premises let out by him, his spouse, or his dependent son, or daughter, are required for his own residence after his retirement, he, his spouse, or his dependent son, or daughter, at any time, within a period of one year before the date of his retirement, apply to the Rent Authority for recovery of immediate possession of such premises. Section 25 explains the right to recover immediate possession of premises to accrue to Central Government and State Government employees. (3) is a retired employee of the Central Government or of a State Government and the premises let out by his spouse, or his dependent son, or daughter, are required for his own residence, such employee, his spouse, or his dependent son, or daughter, within one year from the date of his retirement or within a period of one year from the date of commencement of this Act, whichever is later, can apply to the Rent Authority for recovery of immediate possession of such premises. (4) is an employee of the Central Government or a State Government and has a period of less than one year preceding the date of his retirement and the premises let out by him, or his spouse, or dependent son, or daughter, are required by him for his own residence after his retirement, he, his spouse, or his dependant son, or daughter may at any time within a period of one year before the date of retirement apply to the Rent Authority for recovery of immediate possession of such premises.

Medical

Medical and health is a state subject. The Central Government as well as all the 28 State Governments have their own health ministries and Directorates of Health.

Flow Chart of Medical Infrastructure in India (see Figure 2)

Central Government

The Central Government has a Ministry of Health and Family Welfare and a Directorate of Health services; these bodies look after the medical and health needs of Central Government employees. They are also in charge of liaisons with world bodies like WHO, United Nations International Children's Emergency Fund (UNICEF), and so on, and control the funds of these bodies to the central as well as state health directorates.

Central Government Health Scheme (CGHS). This was started on 1 May 1954 on the pattern of National Health Service (NHS) of United Kingdom. The objective was to provide medical services to Central Government employees; however, certain other categories like journalists, judges, account services, post and telegraph, and autonomous bodies like the Delhi Police were also included in the scheme. CGHS covered the above category of people in 22 cities in India. There was a nominal contribution from the employees against which the services like consultation, investigations, medicines, in-hospital treatment, surgeries, and implants were provided. The employees were *referred* abroad in case suitable treatment was not available in this country. All the dependent family members and people retired from these services were included in this medical coverage. In the year 2000, the government took a bold decision to put many

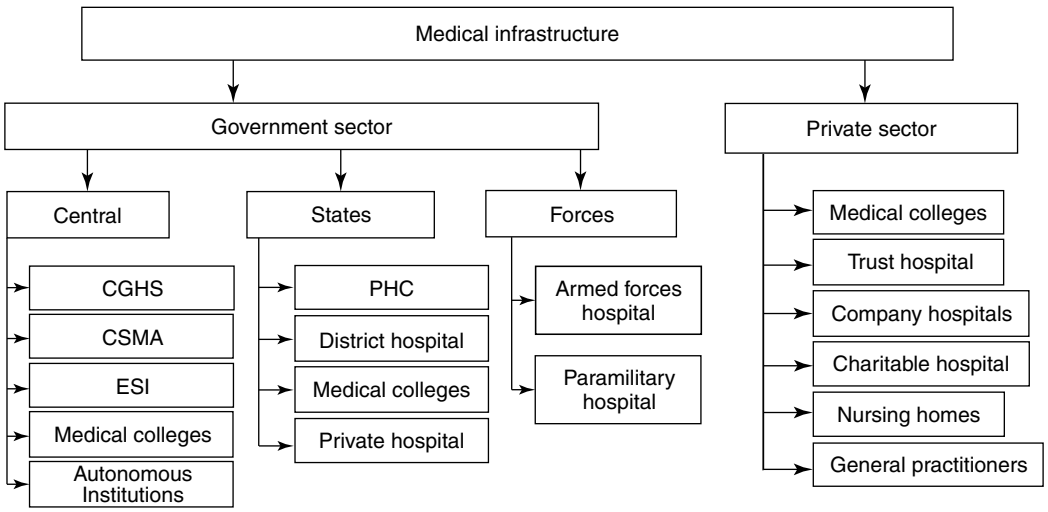

Figure 2 Medical infrastructure in India

private hospitals/institutions on the CGHS approved list for medical treatment.

Central Services Medical Assistance (CSMA). This was similar to CGHS but did not provide coverage for the retired and the elderly. It was limited to serving employees only, who, if posted at places outside the 22 cities, were allowed to opt for a nearby city where the CGHS infrastructure existed.

Employees State Insurance Corporation (ESI). Under the Ministry of Labour, this medical scheme was started to provide medical coverage for the labor class. Under this scheme, ESI hospitals and dispensaries were set up on a large scale. Elderly and retired persons continue to enjoy medical facilities under this scheme.

State Governments

All the 28 State Governments in India have the same three-tier system for providing health facilities. There are nearly 28 000 primary health centers (PHC) located in villages where primary care is provided free of cost. There are 575 district hospitals in these states where the patient is referred for secondary health care. In these states, there are hospitals attached to medical colleges as well as other hospitals that provide tertiary care. The State Government employees as well as the general public can avail treatment from all these places.

Public Sector Units. There are 258 public sectors under Central Government which have their offices, factories, refineries, plants, and so on, throughout the country. Their employees get medical aid from the hospitals and dispensaries owned by these public sector units (PSUs). There are provisions for referring them to government as well as private institutions in case of need.

Armed Forces and Paramilitary Forces

In each command, there is a command hospital and some smaller hospitals in the Indian Army. There are similar facilities for the Navy and Air Force. There is a large Research and Referral Center now being attached to a medical college under the Directorate of Armed Forces Health and Medical Services at New Delhi. There is already one medical college for armed forces at Pune. There are hospitals with paramedical forces like Border Security Force (BSF), Central Reserve Police Force (CRPF), Indo-Tibetan Border Police (ITBP), and so on.

Private Sector

In the last two decades, the private sector has developed considerably to provide health care and has exceeded the government infrastructure for health. There are tertiary care hospitals and research centers owned by various trusts, private companies, and also companies who have floated shares. Most of these large centers have been approved for treatment of government employees. There are also private nursing homes and clinics owned by private practitioners.

The private sector has become a significant partner with the government in health-care delivery.

Nursing

Nursing is an integral part of geriatric care. In India, the following courses in nursing have geriatrics as a part of teaching.

- Three-year diploma course for Nursing where the basic qualification is $10 + 2$ (Schooling).
- Bachelors Degree in Nursing (B.Sc Nursing): This is a 4-year course.

- Masters Degree in Nursing (M.Sc. Nursing): This is a 2-year course after Bachelors Degree.
- M. Phil (Nursing): This is a 1-year course if done full time, but is a 2-year course if done part time.

The above facilities are available in RAK College of Nursing at New Delhi and also at Manipal Academy of Higher Education in Karnataka.

Ph.D. (Nursing): This is a 3 year course at Rajiv Gandhi University of Health Sciences, Bangalore; SNGT Women University, Mumbai; RAK College of Nursing, New Delhi; Jawahar Lal University, New Delhi; PGI, Chandigarh; and Punjab University.

PLANNING GERIATRIC SERVICES (WHO EXPERT COMMITTEE, 1974)

As per the health-care planning by Government of India in 1952, there was a three-tier system.

1. Primary care level (at village level)
2. Secondary care level (at district level)
3. Tertiary care level (in cities).

Primary care level is at the level of PHCs of which there are nearly 28 000 in this country. Health being a state subject, all these centers are funded and governed by states in India. However, the Central Government and world bodies do give them help from time to time under various programs. The doctors posted to PHCs are being encouraged to attend Continued Medical Education (CME) programs in geriatrics medicine.

Secondary care level is at the level of District Hospitals, which now number almost 600 and are also controlled by states in the above fashion. The specialists here are encouraged to upgrade themselves in geriatric medicine. Geriatric services are being introduced into these District Hospitals in the following manner:

Steps of geriatric care (WHO expert committee, 1974)

1) Outpatient	*2) Inpatient*
3) Domiciliary	*4) Community*

At the tertiary care level, the centers are under control of the state, Central Government, NGOs, and other autonomous bodies. In the last two decades, private and corporate sectors have developed and improved substantially in health-care delivery and in the past one decade, the government has collaborated with the private sector, resulting in a better coordination between government and private sectors rather than rivalry/competition. Geriatric out patient departments (OPDs) and services are being conducted in these institutions.

With the rapid modes of transport, faster communication, changing economy, and so on, it is only arbitrary to keep these three distinctions. Beyond reasons related to administration and finances, secondary care level has largely merged into tertiary care level. I would therefore directly comment about such care levels which can be suitably modified depending upon resources and need.

DEVELOPMENT OF GERIATRIC MEDICINE

Government

Geriatric medicine has not been part of the undergraduate medical curriculum till recently. This gave no exposure to appropriate teaching in geriatric medicine to the medical and paramedical personnel produced in India till the late 1990s. "Vienna International Plan of Action on Ageing" adopted by the World Assemble on Ageing (UN, 1983) helped the initiation of geriatric services in India.

The Central Government in the year 1995 organized a workshop on geriatric care. This was a joint venture of the Government of India and the Government of Britain. The Ministry of Health and Family Welfare and ICMR participated on behalf of the Government of India. The problems were identified and the quantum was accessed and weighed against resources. It was concluded that revival of the joint-family system is the only solution to the geriatric situation in India at the moment.

In 1999, with WHO support, the Government of India carried out an exhaustive exercise to bring out learning material for medical and paramedical personnel. During the same exercise, an attempt was made to create resource personnel (medical) for geriatric care. Several government sponsored programs to create learning material for paramedics giving geriatric care were started. One such program was by NICE (National Initiative on Care of Elderly by the Ministry of Social Justice and Empowerment).

At this juncture, MCI introduced geriatric medicine into the medical undergraduate curriculum so as to give some exposure to MBBS students.

Institutions like the Medical College of Madras, which introduced an MD Degree in Geriatric Medicine, gave a lead to the teaching institutions, which was followed by Banaras Hindu University (BHU). The OPD services, geriatric units, and geriatric departments were started by many medical college hospitals as well as tertiary care hospitals. The doctors in government and armed forces were encouraged to undergo training in geriatrics.

NGOs

The main NGOs who played a significant role in sensitizing and updating doctors in India are the Geriatric Society of India (GSI), Indian Medical Association (IMA), and Indira Gandhi National Open University (IGNOU).

Geriatric Society of India (GSI)

The GSI was formed in the year 1980 with the main objective "to sensitize, train, and update Indian doctors in the field of Geriatrics". GSI organized CME programs at regional, national, and international levels. GSI organized its annual conferences jointly with the Association of Physicians of India (API) till 2002 when it finally separated from API for its independent scientific programs. GSI has organized International Conferences in the year 1999, 2001, and 2002. It has also awarded fellowships to the doctors who had made significant contributions in the field of geriatric medicine. The society supported Dr O.P. Sharma for bringing out the learning material "Geriatric Care in India". This became the first textbook on Geriatrics in India, which gives comprehensive coverage of Indian elderly in 77 Chapters spread over 750 pages. In the year 2004, Dr O.P. Sharma brought out another textbook "Geriatric Care" covering Geriatrics in 85 Chapters (Sharma, 2004). The society encouraged opening of OPDs for elderly care in government as well as nongovernmental institutions and gives technical help for this purpose. It also encourages medical and relief camps for elderly. GSI stimulates and supports research in the field of geriatric medicine.

Indian Medical Association (IMA)

IMA is the largest NGO of doctors in India. It works through its 1600 branches spread over the length and breadth of country. IMA, through its branches and through its academic wings (Indian College of General Practitioners, IMA Academy of Medical Specialities and IMA AKN Sinha Institute), is involved in CME activities. Geriatric medicine is a part of the activities of the CME. In 2002, the IMA AKN Sinha Institute started a PG Certificate Course in Geriatrics. Every year, about 250 doctors take up this course.

Indira Gandhi National Open University (IGNOU)

In 2001, IGNOU decided to start a Distant Education course in Geriatrics. It took one year to produce modules and the full course has now been commissioned. The first batch comprised 250 students.

Association of Physicians of India (API)

API is the voluntary body of physicians who carry out CME activities all over the country. API is considering geriatric medicine in all of its programs. The Indian College of Physicians is awarding scholarships under its Sponsored Training Program (STP) in geriatrics.

Medical Council of India (MCI) (Medical Council of India, 1995)

MCI is the watchdog of medical education in India. It had not included Geriatrics in the medical curriculum till late 1990s. Inspired by WHO declarations and repeated projections of rise in the number of elderly, MCI added Geriatrics in its revised undergraduate curriculum. The All Indian Institute of Medical Sciences (AIIMS) was one of the first few institutions to stress the teaching of geriatric medicine in the undergraduate curriculum. The example of the Madras Medical College is a lead in considering an MD in geriatric medicine. The department of Geriatric Medicine in BHU, Varanasi was one of the biggest to be set up in a medical institution.

NATIONAL POLICY OF THE AGED

A national policy for old persons was formulated in January 1999, which covers the dimensions of social, economic, and health security. The Union Ministry of Social Justice and Empowerment is the nodal agency for implementation. A national council for Older Persons has been constituted to implement the policies and programs for an aging population.

Key Elements of the Policy

1. To achieve integration between the young and old and develop a support system, formal and informal, to increase the potential of the families to take care of the aged persons.
2. Tapping human resources among elderly people.
3. Expansion of old-age pension scheme to include the private sector, subsidize health-care network with private sector involvement, increased standard tax deduction for senior citizens, legislations on parents' right to be supported by their children, regulatory authority to monitor pension funds, easy access to housing loans, and special provisions in the Indian Penal Code for protection of older persons.

The health services will be provided through primary, secondary, and tertiary-level government institutions, by nonprofit organizations including trusts and charitable institutions, and also private medical care.

Facilities for specialization in geriatric medicine will be provided in the medical colleges.

Hospices for chronically ill and deprived elderly will be set up.

Training and orientation will be provided to medical and paramedical personnel working at various levels of health-care facilities.

Primary health-care system to be strengthened and orientated to be able to meet the health needs of older persons.

There should be proper distribution of services in rural and urban areas and a much better health administration and delivery system.

High priority to health insurance to cater for the needs of different income groups in society with varying contributions and benefits.

Trusts, societies, and voluntary agencies promoted by way of grants, tax relief, lending at subsidized rates to provide free beds, medicines, and treatment to very poor elderly citizens with reasonable user charges for the rest of the population.

Private nursing homes and hospitals will be directed to offer discounts to older patients and public hospitals will have separate counters and convenient timings with facilities of geriatric wards.

Mobile medical unit of health services, special camps, and ambulance services will be encouraged to ensure accessibility and use of hospital services.

ELDERLY CARE COVERAGE

Elderly people obtain medical and health benefits from the following bodies:

1. Central Government – Central Government Health Scheme (CGHS)
2. State Government Health Services
3. Armed Forces Health Services
4. Public Sector undertakings
5. Employees State Insurance Corporation (ESI)
6. Mediclaim and Health Insurances

Retired personnel (age of retirement 60 years $\pm$ 2 years) have medical coverage ranging from partial to total coverage in Central Government, State Governments, armed forces, paramedical forces, industries, private entrepreneurs, and self-taken insurance coverage.

Health-Care Facility

- Sunday clinics at various hospitals in Delhi exist to enable senior citizens to get medical care easily.
- Geriatric ward and OPD (once a week) exist in municipal hospitals in Mumbai and Government hospitals of Chennai and Kerala.
- Free intraocular lens (IOL) is given for cataract surgery in Gujarat. However, in Maharashtra Rs 600 is to be paid.
- The mobile medicare unit (MMU) program is the program implemented by Help Age India to provide basic essential medicare at the doorstep of needy and underprivileged elderly in India.
- Free health-care checkup camps organized by government or social organizations.
- Medical Insurance Scheme (Mediclaim). This policy has been available since November 1999 to persons aged between five and 80 years. The sum insured varies from Rs 15 000 to 500 000 and premium varies from Rs 201 to Rs 16 185 per person per annum depending upon different quantums of insured services and age-groups. The cover provides for reimbursement of medical expenses incurred by an individual toward hospitalization/domiciliary treatment, hospitalization for any illness, injury, or disease contracted or sustained during the period of insurance.

Group Medical Insurance Scheme

The group Mediclaim policy is available to any group/association/institution/corporate body of more than 100 persons, provided it has a central administration point. The basic policy under this scheme is Mediclaim only.

Jan Arogya

The Jan Arogya scheme is primarily for the larger section of the population with an age limit of 70 years who cannot afford the high cost of medical treatment. The limit of cover per person is Rs 5000 per annum. The cover provides reimbursement of medical expenses incurred by an individual toward hospitalization/domiciliary hospitalization for any illness, injury, or disease contracted or sustained during the period of insurance.

Others

- The National Council for Older Persons has been constituted to provide guiding steps as well as feedback on the policies for welfare of elderly persons.
- Rupees 30 lakhs shall be provided to eligible institutions for construction of old-age homes/multiservice centers for older persons.
- Financial assistance up to 90% is provided to NGOs for establishing and maintaining old-age homes, day-care centers, MMUs, and for providing noninstitutional services to older persons.
- Special consideration has been given to elderly in telephone and banking services. Various helplines have been instituted.
- The National Consumer Redressal Commission (Legal aid Program), 5th Floor, A Wing, Janpath Bhawan, New Delhi, has been providing free legal aid in court or other matters.
- The National Institute of Social Defense, launched a project NICE in year 2000, which provides cost-free technical training on the care of elderly.

For success of various schemes and initiatives for the welfare of elderly people as described, effective implementation and continuous follow-up are required. Welfare of elderly citizens of rural areas requires reinforcement and strengthening of the ability and commitment of the family to provide care. Improvement in intergenerational relationships, care of destitute elderly, and promotion of productive aging (using wisdom and experience of elderly people) should be specially emphasized, besides efforts involving multiple sectors, thereby helping elderly individuals to live with dignity and self-esteem with the feeling of being wanted.

KEY POINTS

- The population of Elderly persons is rising significantly in India.
- There are both medical as well as social needs of Indian elderly which require attention.
- There is an urgent need to develop geriatric medicine.
- The infrastructure for Medical care of elderly persons needs expansion.
- The government and NGOs will join hands and become partners in geriatric care.

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Geriatrics in Latin America

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INTRODUCTION

The present status of geriatric medicine in Latin America reflects the demographic history of aging in the region and the diverse schemes for delivering health services to older adults. This chapter addresses these issues within the context of the various academic initiatives under development in the region and discusses the future outlook of geriatrics in Latin America.

Demography and Health Conditions in Latin America and the Caribbean

Latin America and the Caribbean are aging at an accelerated pace. Declining fertility rates combined with steady improvements in life expectancy over the latter half of the twentieth century have produced dramatic speed in the aging of the population. The number of persons 60 years and older in Latin America and the Caribbean is currently about 44 million. An expected annual rate of growth of 3.5% in this population during the first two decades of the century will bring the total of persons 60 years and older to close to 100 million. This number will grow to 168 million by the middle of the twenty-first century. Currently, older persons represent 8% of the total population in Latin America and the Caribbean. By 2025, 14% of the population in Latin America and the Caribbean will be 60 years of age and older (UN Population Aging). However, not all countries in the region are aging with the same momentum or have the same speed of growth. In Table 1, individual countries are presented with three indicators of aging: the proportion of the population above age 60, C(t), the mean age of the population, A(t), and an indicator of the availability of support among the younger generations, L(t). The first indicator is a conventional measure and needs little introduction. The second is also straightforward, *albeit* much less used, but of extreme utility to understand patterns of growth of the older population. The third, L(t), defined as a ratio of adult to older adults, is a crude indicator of kin availability and of constraints in the patterns of the living arrangements of older persons. Altogether, these indicators suffice to characterize the demographic nature of the growth of the older population (Palloni *et al.*, 2002).

A cross-sectional survey sponsored by the Pan American Health Organization (PAHO) during 2000, Aging, Health, and Well-being (SABE) in seven major cities of Latin America and the Caribbean documents that chronic disease is rapidly becoming the new epidemic of developing countries.[1] Hypertension was reported by one out of every two people 60 years and older; the lowest percentage was reported in Mexico City (43%) and the highest in Sao Paulo (53%). One out of five persons reported having heart disease, with the exception of elders in Bridgetown (12%) and in Mexico City (10%), where heart disease was reported less frequently. In most cities, at least one out of three older adults reported having arthritis. However, arthritis appeared to be most significant in Montevideo (48%), Buenos Aires (53%), and Havana (56%), where the proportion was closer to one out of every two elders. Diabetes was highest in Bridgetown and Mexico City, with 22% of older persons reporting it. The percentage of persons reporting having had a stroke is over 8%. Older men were less likely to report having arthritis and hypertension, but were just as likely as women to report having heart disease and diabetes.

In population studies, self-assessed health serves also as a summary measure of health that is well correlated with objective health indicators (Beaman *et al.*, 2003). In the SABE survey, the question: "Would you say that your health is excellent (=4), very good (=3), good (=2), fair (=1) or bad (=0)?" is consistent across cities, providing an aggregate value of the individual's objective health condition. Self-assessment of health is a relatively easy indicator that has been used in surveys throughout the world and is recognized as an important predictor of mortality (Idler and Benyamini, 1997). In SABE, the absolute levels of

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Table 1 Values of the proportion of the population above age 60 [C(t)], the mean age of the population [A(t)], and the ratio of adults to older adults [L(t)] for 1950–2025: countries in Latin America and the Caribbean, and United States (calculations by Dr Alberto Palloni using the United Nations database, 1999)

Country	1950–1955			1990–1995			2020–2025		
	C(t)	A(t)	L(t)	C(t)	A(t)	L(t)	C(t)	A(t)	L(t)
Argentina	7.0	25.5	4.95	12.9	31.3	3.03	16.6	35.6	2.89
Bolivia	5.6	24.2	4.65	5.8	23.9	4.34	8.9	29.3	3.97
Brazil	4.9	23.5	5.16	6.7	27.4	4.31	15.3	35.0	3.24
Chile	6.9	25.4	4.52	9.0	29.6	3.72	18.2	36.2	2.69
Colombia	5.6	24.2	5.02	6.2	26.1	4.19	9.7	33.4	3.28
Costa Rica	5.7	24.3	4.22	6.4	26.4	4.27	14.3	33.8	3.09
Cuba	7.3	25.8	4.51	11.7	33.1	3.30	25.0	42.2	2.44
Dominican Republic	5.2	23.8	4.59	5.6	25.7	4.50	14.2	34.2	3.25
Ecuador	8.1	26.6	3.65	6.1	26.9	4.16	12.6	36.5	3.53
El Salvador	4.8	23.4	4.71	6.0	24.9	3.73	10.1	31.7	3.88
Guatemala	4.3	22.9	5.19	5.1	22.1	4.29	7.4	27.2	4.54
Honduras	3.9	22.5	5.40	4.5	22.3	4.57	8.6	29.4	4.17
Mexico	7.1	25.6	3.89	5.9	25.4	4.21	13.5	34.2	3.43
Nicaragua	4.1	22.7	5.15	4.3	21.7	4.61	8.4	28.4	4.35
Panama	6.5	25.0	4.34	7.3	27.1	3.89	10.5	35.2	3.13
Paraguay	8.9	27.4	3.54	5.4	24.7	4.32	9.4	29.9	3.79
Peru	5.7	24.3	4.66	6.1	27.0	4.29	12.6	36.8	3.56
Uruguay	11.8	30.2	3.37	16.5	34.2	2.69	18.4	37.3	2.57
Venezuela	3.4	22.0	7.00	5.7	25.6	4.61	13.2	33.2	3.32
Barbados	8.5	27.0	4.06	15.3	33.3	2.49	23.2	41.5	2.49
Jamaica	5.8	24.4	5.16	9.2	27.6	2.87	14.9	35.1	3.21
Trinidad	6.1	24.6	4.67	8.7	29.0	3.61	17.4	38.7	2.91
Puerto Rico	6.1	24.6	4.10	13.2	32.7	3.06	20.5	38.2	2.60
United States	12.5	30.8	–	6.6	35.6	–	24.7	40.6	–

Source: Aging in Latin America and the Caribbean, 2002. Unpublished article prepared for the Pan American Health Organization.

prevalence of poor/fair health is quite high, no city has a total summary score equal to 2.0 (Figure 1).

In addition to having poor health, one of every five persons 60 years of age and older in the research cities reported having some difficulty with the basic activities of daily living (bathing, dressing, using the toilet, eating, getting in and out of bed, and walking across a room). Included in this number were those who needed assistance in order to perform an activity as well as those who were unable to do the activity at all. The most common limitation among both men and women aged 60 years and older was walking across a room.

The majority of older persons living in urban centers in Latin America and the Caribbean have access to a primary health-care center. Over 50% of those interviewed by the SABE survey reported that they had visited an ambulatory care provider in the four months prior to the interview and at least 60% received a prescription. Of those who received prescription, over 80% had to pay for this prescription in Buenos Aires, Sao Paulo, and Havana; 69% in Montevideo, 38% in Mexico DF, and 20% in Bridgetown. Ten percent to 20% of elders who received prescriptions were unable to obtain the prescribed medication.

Trends in Health-care Delivery

The lack of health-care professionals trained to provide acute and chronic care for older persons in Latin America and the Caribbean is creating a major dilemma for the region. The two mega countries in the region, Brazil and Mexico, in combination have over 20 million persons 60 years old and over, approximately 42% of all elders in Latin America and the Caribbean. Brazil has only 20 hospitals with geriatric services and Mexico has a total of 12. The lack of organized services targeting the care of older people means that medical education continues to ignore the training of physicians in geriatric medicine. The lack of trained personnel to care for the complex and difficult conditions of older people results in a systematic exclusion of older adults from appropriate care. Therefore, when the health-care system cannot provide treatment, support or care for chronically ill and disabled older adults; families take refuge in homes for the elderly, or board and care homes that are staffed by untrained caregivers, and segregated from the mainstream of public health functions. In addition, because the majority of older adults do not have a pension and those who have a pension, it is not sufficient to cover the cost of living; the family typically finances the cost of private care. Therefore, the development of private nursing homes has lacked an economic incentive to develop professional solutions to the chronic care of older persons with disabilities.

The Evolution of Geriatric Medicine in Latin America

Costa Rica, Chile, Cuba, and Panama are the only countries that have a specialized geriatric hospital; these hospitals vary in the number of services provided and in the degree of complexity that they are able to handle. Costa Rica appears

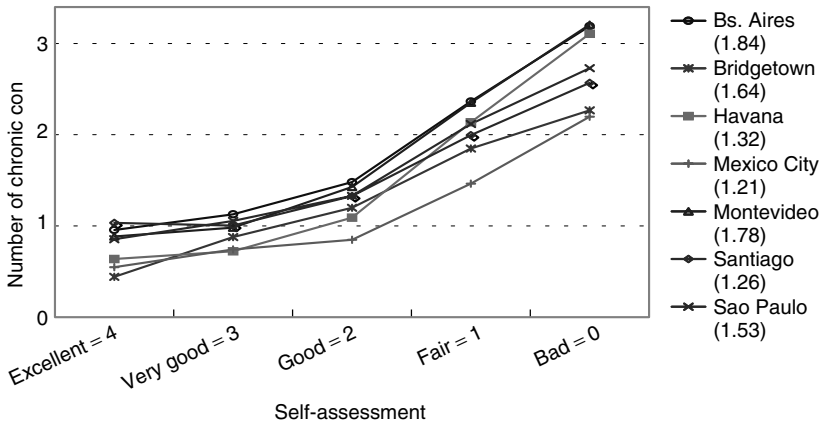

Figure 1 Self-assessed health according to number of chronic conditions (including depression) by city (*Source*: SABE Survey/PAHO – 2000 in Pelaez *et al.*, 2003. © PAHO)

Table 2 Availability of geriatric training and services in selected cities of Latin America

Country	Formal University training in Geriatrics[c]	Geriatric unit	Geriatric medicine department	Geriatric hospital	Day hospital	Home care
Argentina	Yes	Yes	Yes	No	Yes	Yes
Brazil	Yes	Yes	Yes	No	Yes	Yes
Costa Rica[b]	Yes	Yes	Yes	Yes	Yes	Yes
Colombia	Yes	Yes	Yes	No	Yes	Yes
Cuba	Yes	Yes	Yes	Yes[a]	Yes	Yes
Chile	Yes	Yes	Yes	Yes[a]	No	Yes
Ecuador	Yes	Yes	No	No	No	Yes
El Salvador	Yes	Yes	No	No	No	Yes
México	Yes	Yes	Yes	No	Yes	Yes
Panama	Yes	Yes	Yes	Yes[a]	No	Yes
Peru	Yes	Yes	Yes	No	Yes	Yes
Uruguay	Yes	Yes	Yes	No	No	No
Venezuela	Yes	Yes	No	No	Yes	Yes

Source: Survey done by Dr Fernando Morales-Martínez (2004).
[a]Inpatient service only (subacute care). [b]Costa Rica does have a geriatric hospital with a comprehensive service (Day hospital, outpatient home visiting, and inpatients). [c]Geriatricians with University training in recognized academic centers.

to offer the most comprehensive program. The teaching of Geriatrics has evolved during the past two decades in many countries of the region. Teaching University hospitals with Geriatric services are found in Argentina, Brazil, Chile, Costa Rica, Colombia, Cuba, México, Panama, Peru, Puerto Rico, Uruguay, and Venezuela. The teaching of Geriatrics in the medical education of general practitioners and family medicine has not become standardized, and if it occurs, it is not well documented. The development of geriatrics in nursing schools and allied health faculties is even less developed. Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, and México have developed training programs for some allied health professionals (see Table 2).

Latin American Academy of Medicine on Aging (ALMA)

Latin American Academy of Medicine on Aging (ALMA) (in Spanish *Academia Latinamerican de Medicina del Adulto Mayor*) was created in 2002 by a group of Geriatric Faculty Members from Latin American and Spain with the support of the Pan American Health Organization, the Merck Institute of Aging and Health, and the guidance of the European Academy of Medicine on Aging. The mission of ALMA has been adapted to meet the needs of Latin America. ALMA is the premier organization providing leadership in the development of health services for older adults; improving quality of care, and advocating for the training of health-care professionals in the basics of geriatric medicine. ALMA has a distinctive public health agenda in addition to the academic agenda for strengthening geriatric teaching in the region. ALMA has offered a yearly program since 2002, rotating through different Latin American countries. Each ALMA program includes an intensive course for teachers of geriatrics in a selected topic; a public health forum with public health authorities in the country where the course is delivered; and a primary care workshop on a topic of geriatric care. Thus, in each ALMA program, the message of Geriatric Medicine is provided to different audiences. The III program of ALMA was held in September 2004

in San José, Costa Rica, and the theme was Nutrition and Aging.

ALMA has also undertaken the task of developing and promoting uniform guidelines for the teaching of geriatric medicine in general medical education (Cano *et al.*, 2005). It is developing practice guidelines in collaboration with the Pan American Health Organization and will soon have an interactive web site to organize and manage geriatric knowledge for the region.

The Costa Rican Case

The University of Costa Rica offers Speciality in Geriatrics Medicine and Gerontology after graduating a medical doctor, with a 5 years duration program; the first 2 years are straight Internal Medicine and the following 3 years are Geriatrics and Gerontology within the National Geriatrics Hospital. At present, there are 43 geriatricians and 28 medical residents. The program graduates four geriatricians every year and admits six new medical residents every year.

Costa Rica is located in Central America and has a history of commitment to peace and health. The country has not had an army since the middle of last century and officially abolished the army by a new constitution in 1948. Instead, Costa Rica allocated a major portion of its budget to a program of universal education, universal access to medical services, and social security. All residents have a constitutional right to receive health care from a system of national hospitals providing curative care; provincial centers providing treatment and prevention programs, and community health centers providing primary health care to the whole population. Community health workers make home visits to local residents, maintain ties with families, conduct socioeconomic surveys, give talks in schools, and collaborate with community health committees, elected by local residents, to set priorities for communal health.

In 2004, infant mortality was 9.1 per thousand live births and life expectancy at birth was 78.5 years. General mortality was reduced by 38%. Life expectancy at 60 and 80 has continued to increase since the early 50s (Table 3).

Programs for the Elderly

In response to the challenges of an aging population, Costa Rica has made important progress in the development of public policies, plans, and programs to promote health, provide care, and strengthen the well-being of older adults.

Table 3 Life expectancy in Costa Rica

	1950		2000		2003	
	M	F	M	F	M	F
60 years	14.85	18.84	20.9	23.7	21.7	24.5
80 years	5.22	5.95	8.3	9.33	8.46	9.47

Source: Population Estimates, Instituto Nacional de Estadistica y Censos de Costa Rica. www.inec.go.cr and Centro Centroamericano de Poblacion, University of Costa Rica. www.ccp.ucr.ac.cr

National Council for the Elderly

In 1999, the Legislation established the National Council for Older Persons. The National Council is the technical committee that is accompanied by the Council of Notables established for outstanding older persons in the community. Both the Technical Council and the Council of Notables advise the President and propose policies, plans, and programs for older adults in the country. The council aims to represent, involve, and evaluate actions of public agencies and private institutions and to seek resources for the implementation of priority programs.

The council is administratively located in the Ministry of the Presidency. The President of the Republic designates the coordinator of the Council.[2] Representatives of the following Ministries form the Council: Health, Labor and Social Security, National Planning, Education, Joint Institute for Social Assistance, and representatives of the main nongovernmental agencies working with older adults in the country.

Medical care for older adults in Costa Rica includes preventive care, acute care, rehabilitation services, and long-term care facilities. Preventive care is directed primarily at the healthy elderly population (see Figure 2).

Acute care is provided in the first instance through a network of polyclinic and health centers. The first level refers patients either for outpatient assessment to the day hospital or to the outpatient department of the general hospital, or for inpatient care to the geriatric hospital. The majority of patients are discharged back to the community under the care of the staff in a polyclinic or health center, with additional service arranged prior to discharge as required. Follow-up care and respite care may be provided at the day-care center.

The National Council for Older Persons has a Secretariat to coordinate the activities of its representative institutions. The Secretariat is responsible for documenting initiatives relevant to the elderly: formulating a national plan with particular programs and specific strategies: analyzing and assessing existing programs; and developing new models of practice. The Secretariat also develops programs related to health and human services, education and employment, family support, and sanitary assistance.

The National Council and Technical Secretary employ a participatory planning process that involves public agencies, private institutions, and the local community. The planning process emphasizes the development of organizations and communities and includes a national campaign to increase public awareness, improve public attitudes, and recognize the rights of the elderly in society. The planning document itself emphasizes the involvement of public agencies and private institutions, collaboration in agency administration; participation in local community committees, development and dissemination of information on the social, political, economic, and psychological aspects of aging, education, and training at the community level, and research to promote health.

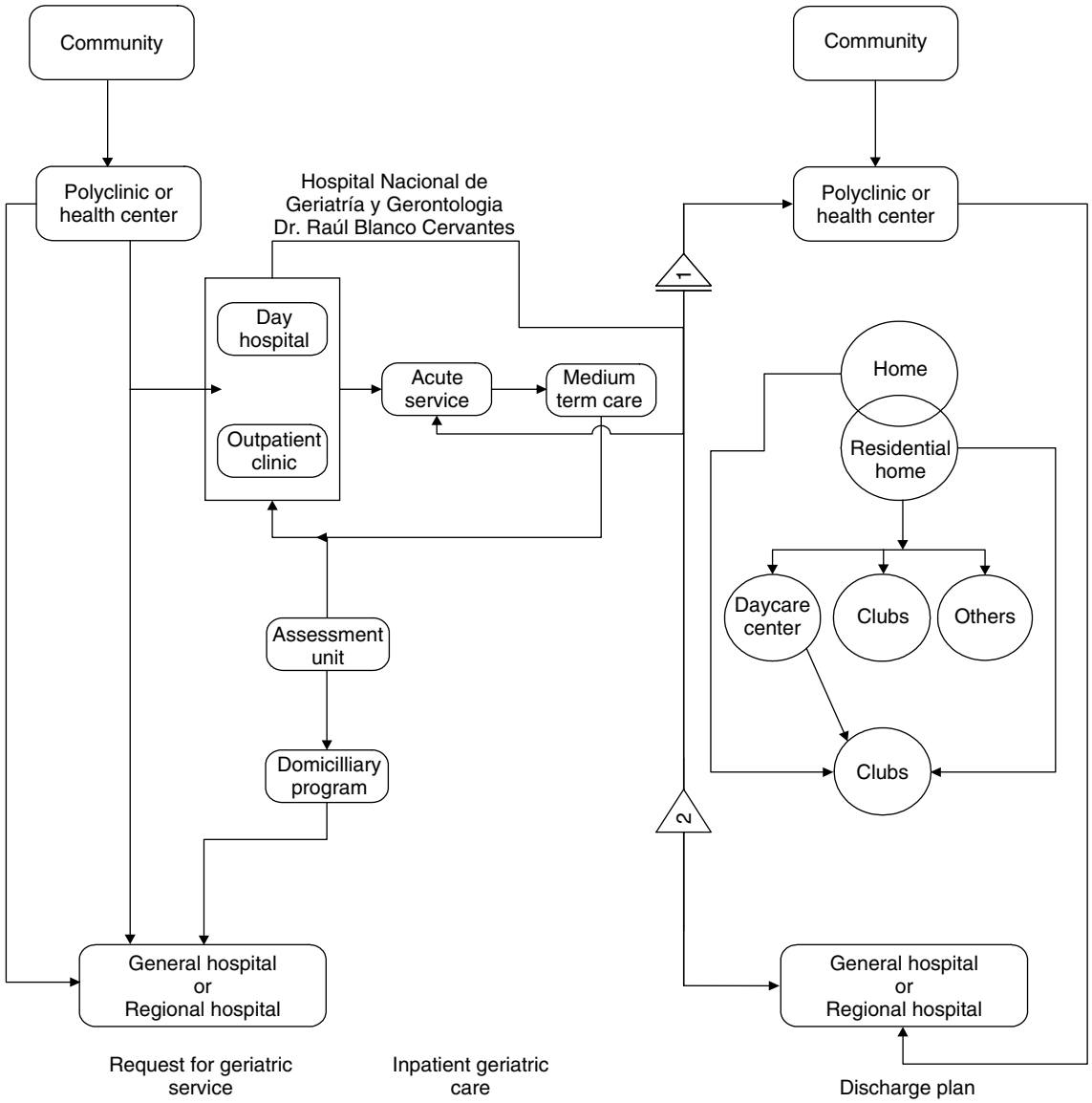

Figure 2 Scheme of graduated care of the elderly in Costa Rica

COMMUNITY INITIATIVES

Day-care Centers

Day-care centers are increasing in all areas of the country on the initiative of local communities with the support of public agencies and private institutions. The centers aim to provide care and resocialize disabled and disadvantaged older people into the community, especially those suffering from poverty, psychosocial problems, and family abandonment.

Day centers originate when residents take the initiative and form a local committee. The residents write a preliminary letter to public agencies and hold a meeting with interested individuals. They formulate a proposal for agency approval, develop a board of directors, and finalize plans for the center. They recruit volunteers to participate in programs and employ an administrator to coordinate the activities of the center. Some centers have as many volunteers as they have users of the facility.

Public agencies and private institutions support the development and maintenance of the center. They work with residents to construct the facility and employ the professional staff. They hold courses for volunteers on the problems of aging, recreational and cultural activities, social administration, and community organization. They hold courses for the elderly on the physical and psychological aspects of aging, group integration, and social interaction.

Day centers vary from one area to another, but there are some similarities among them. For example, one day-care center is located in a low-income area in a semiurban area outside San José. The facility includes a central room for social and recreational activities, a modern kitchen and

dining room, hot-water shower, medical consultation room, administrative offices, chapel, and a garden cultivated by members. The typical day includes praying, traditional songs, physical exercise, gardening, meals, refreshments, reading, writing, and other social and recreational activities.

Day centers provide a place to increase the interaction of isolated individuals.

They provide a community center with which to organize programs and provide services. They establish an institutional infrastructure on which to develop initiatives for the future.

Day centers are increasing in number but still serve only a fraction of the population. Staff members and community volunteers report that they tend to serve those who come into them, rather than extend initiatives into the community, that they serve women more than men, and that the elderly perceive themselves as passive recipients of services rather than active participants in society. These may be cultural characteristics of Costa Rican society, however, rather than particular results of the centers. It is difficult to anticipate the future functions of these centers, but they could provide an institutional infrastructure on which to further develop the national network.

Clubs for the Elderly

These community social clubs are voluntary associations of individuals who come together for social interaction around common interests. They offer opportunities for individuals to reduce isolation and foster active participation in the community.

Some clubs originate when older people take the initiative and form a group around their common interest. Others originate when public agencies or private institutions encourage local initiative and social development.

Social clubs vary in their scope and structure, but there are some similarities between them. Each club chooses a coordinator, other officers, and an organizing committee. Each committee consults with members, assesses areas of common interest, and formulates an annual plan and weekly meeting agendas. Each coordinator meets with other coordinators in groups to report on activities and contribute to the network.

In some of the communities, women play strong social roles, while men experience isolation and would benefit from club participation. These older women participate actively in the community, but do not necessarily view themselves as a distinct organizational unit, or view the clubs as vehicles for organizing in the community. There is little such consciousness in Costa Rican society, but this could change in the future.

OPPORTUNITIES AND OBSTACLES

Costa Rica is developing a national network in response to the challenges of an aging population. The National Council for the Elderly involves public agencies and private institutions in a process of formulating policies and coordinating programs in accordance with constitutional commitments, legislative enactments, and executive decrees emphasizing the rights of the elderly among all citizens.

Nongovernmental organizations representing health professionals, community caregivers, and older people themselves are advancing their interests in society.

Initiatives are increasing at provincial and local levels, including day centers and social clubs that involve individuals and groups in their communities.

NOTES

[1] Bridgetown, Buenos Aires, Havana, Mexico City, Montevideo, Santiago, and São Paulo.

[2] At present, the coordinator of the Council is Dr Fernando Morales-Martínez (2002–2006).

KEY POINTS

- Latin America and the Caribbean will have one critical decade to prepare the health workforce in the basics of chronic care and geriatric medicine.
- The teaching of geriatrics has to be included as an integral part of the training of general physicians.
- Geriatricians in the region need to be engaged in a constructive dialogue with public health leaders for the development of services adapted to the needs of older adults.
- Older adults in the region are aging prematurely, have more disabling conditions and more disability than their cohort in developed countries.
- The Latin American Academy of Geriatric Medicine (Cano *et al.*, 2005) has become the premier organization for strengthening the teaching of geriatrics in Latin America.
- Costa Rica has shown that a coordinated and comprehensive approach to policy development needs to go hand in hand with the training of Geriatric physicians.

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Management of the Dying Patient

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INTRODUCTION

Palliative care is the active total care of patients and their families by a multiprofessional team when the patient's disease is no longer responsive to curative treatment (World Health Organization, 1990). The focus is on quality of life, and care must address physical, emotional, social, and spiritual causes of distress.

Palliative care must begin early, to maintain quality of life for as long as possible. Any progressive disease process is continually evolving; new symptoms arise as the patient's physical condition worsens, so the patient needs constant reassessment and adjustment of all aspects of their management plan (Twycross, 1978). This continually changing situation means that palliative care is labor intensive both in terms of nursing and medical time (Twycross, 1978; Walsh and West, 1988).

The change in emphasis from cure to active palliation requires a change in attitude on the part of the carers (Finlay, 1976). In many instances, measures to control the disease may overlap with palliative care. The elderly patient often has coexisting pathologies which influence management (McQuay and Moore, 1984).

Growing awareness and acceptance of palliative care has allowed principles developed in the care of patients with advanced cancer to be applied to all patients with progressive life-threatening disease, irrespective of their diagnosis.

Patients who are terminally ill are often aware of their diagnosis and prognosis, but fear breaking the barrier of silence imposed by well-meaning family who believe the truth is devastating (Parkes, 1980). The patient can feel isolated and lonely, facing some "terrible, intangible, imminent death". All involved in the care of the patient need to understand the patient's and the family's perception of the disease process (Smith, 1993); for example, some patients think that everyone with cancer inevitably has pain, although only about 60% of patients with terminal cancer experience pain (Wilkes, 1984; Kane *et al.*, 1984). It is also important to know if the patient has had experience of similar disease in a close relative, since any horrifying experiences may compound the patient's own fears.

ASSESSMENT OF THE PATIENT

Is the Patient Terminally Ill?

The patient can be viewed as terminally ill when he or she is likely to die within the foreseeable future (usually under one year) from a specific progressing disease. The patient who is actively dying and is within the last days of life occupies a small subgroup. Many of the principles applicable to patients with a longer prognosis are important, even at this late stage; ethical dilemmas over stopping active treatments may need very careful consideration at this time.

It is tempting, but dangerous, to attribute to the prime pathology everything that occurs to patients once they are known to have a potentially terminal illness (Rees *et al.*, 1987). Intercurrent infections are particularly common to patients who are partially immunocompromised. Other diseases, such as myocardial ischemia, diabetes, Parkinson's disease, and hypothyroidism, may also occur. Each condition needs assessment and appropriate treatment; patients should not be denied the benefit of good general medical management simply because they happen to have a severe illness such as metastatic carcinoma.

The Problem List

At first, a problem list should evolve, which includes physical, emotional, social, and spiritual problems (see Table 1). The various components of each should be itemized: the patient may have several pains (Baines, 1989) and each pain should be separately recorded, for example, back pain, headache, myalgic pains, and abdominal colic. To maintain

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 ISBN: 0-470-09055-3

Table 1 Example problem list from a patient with lung cancer

Physical
Pain in chest – rib metastasis
Pain L2/3 – lumbar vertebral metastases
Oral candida
Nausea – possible hypercalcemia
Dehydration
Constipation
Weakness
Anorexia
Emotional
Wife died 18 months ago, still grieving
Wife had breast cancer and similar back pain
Social
Lives alone, not coping with meals
No carers
Daughter over 100 miles away
Spiritual
"God's tested me too far"
Awareness
Knows "cancer"; expects to live "several years"
Believes stopping smoking has slowed disease

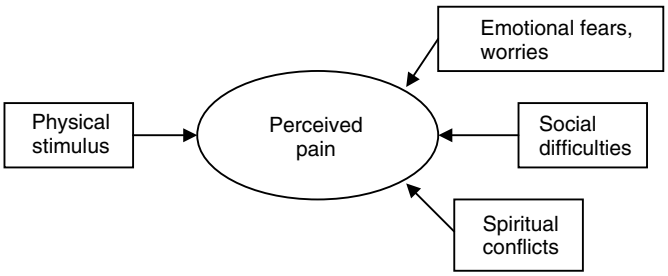

Figure 1 The components of pain

a holistic view, the patient's fears, disappointments, family tensions and conflicts, aims, and goals should be recorded. For example, if the patient feels that the diagnosis was delayed or missed initially, or feels that treatment was inappropriate, that information should also form part of the basic problem list.

Effective control of the physical aspect of a symptom cannot be achieved without attention to the social, emotional, and spiritual components of that symptom (Saunders, 1978) (see Figure 1).

ETHICAL CONSIDERATIONS

Many decisions in the management of the dying patient are less clear-cut than in those with a reasonable prognosis or chance of recovery. The four ethical principles of autonomy, beneficence, nonmaleficence, and justice create a framework within which each clinical decision can be formulated and tested.

Autonomy, usually taken simply to mean "self-governance", requires respect of the patient as a person in the context of the family which may have its own distinct identity and code of beliefs. Respect of autonomy means patients must be given information to make informed choices within the framework of their own language, vocabulary, and understanding. Patients' wishes for their future care, their values and their concerns, and the validity of any "advanced directive" (living will) must be confirmed and also clearly documented.

Nonmaleficence means that patients must not be burdened either by useless or futile distressing information, or by investigations or treatment which will not enhance their life.

Beneficence dictates that the predicted benefit must always outweigh the predicted risk. It is worth remembering that psychological benefit can validly outweigh physical risk in a holistic approach. This can mean that a drug or intervention is used for its positive effect, but in the knowledge that it may have some other adverse effects.

Within the principle of justice, the patient should have the best possible care within the resources available, but also these resources must be fairly allocated for the community they serve to derive maximum benefit.

Decisions such as feeding by artificial means, use of intravenous antibiotics and fluids, and the withdrawal of active treatments fall into the gray zone where an ethical framework becomes particularly helpful.

In patients with advanced neurological disease, feeding is often a problem. The evidence suggests that the dying, despite low fluid intake, often do not have biochemical markers of dehydration (Ellershaw *et al.*, 1995). For the few who experience thirst, this can be relieved by good mouth care and subcutaneous fluids, even at home (McQuillan and Finlay, 1995). It is essential that each case is assessed individually (Craig, 1996); rigid policies over hydration are unethical (Dunphy *et al.*, 1995).

SYMPTOM ANALYSIS

The diagnostic skills required in every patient encounter need to be applied to each symptom the patient presents, to ascertain the cause of that symptom (Baines, 1989). The patient who is terminally ill almost always has several symptoms. It is unusual for the patient to only have one site of pain; there are usually multiple pains, each in different sites and each with a different cause. The compilation of the problem list for the patient frequently elicits between 5 and 10 problems at first interview, although sometimes even more may be found.

The patient's perception of his or her own symptoms will be altered and exacerbated by fear, depression, insomnia, and worry (Twycross and Lack, 1983). For every symptom the four components (physical, emotional, social, and spiritual) should be defined (Saunders, 1978).

Some patients are "sick with worry" or experience "total pain", which requires care and counseling as a major adjunct to drug therapy. Patients all need time to talk about their fears (Maguire and Faulkner, 1988a,b) in a relaxed and peaceful

environment; the professional's role is to sit and actively listen to the problems.

PAIN (*see* Chapter 78, Peripheral Neuropathy)

Pain is wherever the patient says it hurts. For each pain the site, duration, intensity, and probable cause should be noted (Thompson and Regnard, 1992). Table 2 lists causes of pain found in 500 admissions to a palliative care unit. Pain may be the first indicator of local recurrence of cancer, for example, pelvic pain from rectal or gynecological carcinomas. Radicular thoracic or cervical pain may precede leg weakness by hours or days in impending spinal cord compression. Pain is also a common feature of patients dying from illnesses other than cancer (Higginson, 1998). About 95% of pains are opioid sensitive; the remainder are usually neuropathic in origin, or there may be psychosocial issues exacerbating the pain (Woodruff, 2004).

The type of pain can be assessed and documented using the PQRST pnemonic (Twycross and Wilcock, 2001) (see Table 3). A diagram showing dermatomes can be very helpful to record the site of each pain (see Figure 2).

It is important to have a baseline assessment of each pain, so the response of the pain to analgesic interventions can be evaluated. Such reevaluation should occur every 24 hours until pain control is achieved. As a general rule, if no improvement in pain has been achieved within 48 hours, then specialist palliative medicine advice should be sought.

There are different rating scales for pain. All are subjective and nonlinear, but are a good working guide. Different patients find some easier than others, but useful ones are a 0–10 scale of 0 = "no pain" to 10 = "the worst pain imaginable", or a verbal rating scale "very severe/severe/moderate/mild/no pain" (Caraceni *et al.*, 2002).

Table 2 Causes of pains found in 500 admissions to a Marie Curie hospice unit

Tumor bulk
Visceral, caused by compression of adjacent cells
Bone: metastases with pathological fractures
Intrinsic and extrinsic esophageal tumor mass
Organ capsule stretching, particularly liver capsule pain
Pleuritic, from tumor nodules
Diaphragmatic, on inspiration, from diaphragmatic and liver metastases
Nerve compression
Radicular from spinal cord compression: thoracic, cervical
Headache from raised intracranial pressure
Rectal tenesmus
Skin metastases
Pains not caused directly by the cancer
Concomitant infection
Pleuritic chest pain
Mouth discomfort
Bladder spasms from cystitis
Infected pressure sores
Herpes zoster (shingles)
Oral herpes simplex
Aches associated with debility, but not directly attributable to neoplasm
Stiffness in a paralyzed limb
Arthritis
Neuropathic pain, postthoracotomy pain
Skin burning following radiotherapy
Causalgia
Angina
Reflux esophagitis
Peptic ulcer
Abdominal pain
Shoulder tip pain from perforation
Dyspepsia

Table 3 The PQRST characteristics of pain

P	Palliative factors	"What makes it better?"	Effect of medications, heat packs, and so on
	Provocative factors	"What makes it worse?"	Movement, eating, lying down, and so on
Q	Quality	"What exactly is it like?"	Burning, stabbing, dull ache, and so on
R	Radiation	"Where does it go to?"	
S	Severity	"How severe is it? How much does it affect your life?"	0–10 out of 10 mild/moderate/severe/very severe effects on sleep, mobility, and so on
T	Temporal factors	"Is it there all the time or does it come and go? Is it worse at any particular time of day or night?"	Time since onset; constant or intermittent; duration of episodes of pain; time of day

Source: Copyright Twycross R. Wilcox A, 2001. *Symptom Management in Advanced Cancer*, 3rd edn; Radcliffe Medical Press, Oxford. Reproduced with the permission of the copyright holder.

Planning Analgesic Therapy

A few patients have good analgesia with regular paracetamol which is a Group I analgesic (Table 4), or with a nonsteroidal anti-inflammatory drug (NSAID). These may help as coanalgesics, particularly with opioids for bone pain. Elderly patients with an additional risk factor for peptic ulceration (previous history of ulceration or also taking steroids) require gastroprotection (Hawkins and Hanks, 2000), with a proton pump inhibitor or misoprostol. Cox-2 inhibitors were widely prescribed instead of conventional NSAIDs, but they do not eliminate the risk of peptic ulceration (Twycross *et al.*, 2003) and concerns about their safety have arisen recently.

A patient's perception of pain will be dramatically altered by fear and emotional or spiritual conflicts. The patient troubled by unresolved worries will not benefit fully from opioids without additional appropriate counseling. The patient must understand how treatment is aimed at the pain and be given realistic expectations by the prescriber.

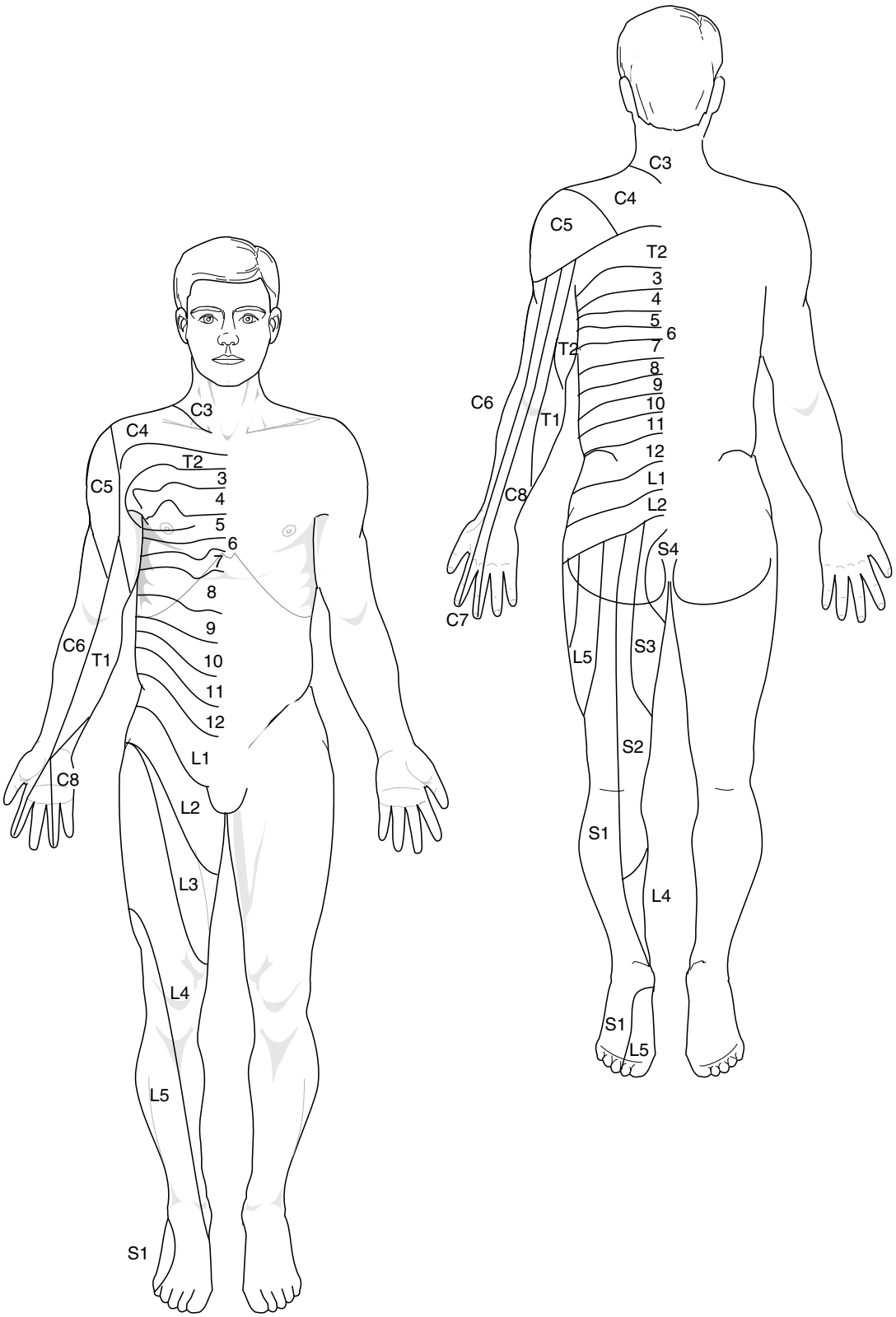

Figure 2 The use of a body chart allows quick and accurate documentation of the site and nature of a patient's pain. Dermatomes marked: C, cervical roots; T, thoracic roots; L, lumbar roots; S, sacral roots

Table 4 WHO classification of analgesics: the analgesic steps (World Health Organization, 1996)

Step 1	Step 2	Step 3
Nonopioid ± adjuvant	*Weak opioid* ± nonopioid ± adjuvant	*Strong opioid* ± nonopioid ± adjuvant
Paracetamol NSAIDs	Codeine Dihydrocodeine Dextropropoxyphene Tramadol	Morphine Diamorphine Oxycodone Hydromorphone Fentanyl Alfentanil Methadone Buprenorphine[a]

[a]Buprenorphine is a partial opioid agonist.

Starting Opioid Analgesia

Most patients with pain need a Group II (mild opioid) or Group III (strong opioid) drug. Co-codamol 30/500 is an effective analgesic given 6-hourly, containing paracetamol and codeine (a prodrug of morphine). However, some patients are poor cytochrome P450 2D6 metabolizers and for these patients, the analgesic effect of codeine is significantly impaired; this applies to 7% of Caucasians (Twycross *et al.*, 2003). Dihydrocodeine is very constipating and can cause dysphoria. Tramadol can be a useful mild opioid for some patients, but it is expensive in the United Kingdom (Joint Formulary Committee, 2005).

If pain is not completely controlled, a strong opioid should be started early rather than late. It is preferable to move to step 3 of the WHO analgesic ladder rather than use a variety of different weak opioids. Gaining control of the patient's pain promptly helps gain his or her confidence.

Morphine is the recommended first line Group III opioid, given orally if possible (Hanks, 2001). It is available as a solution (morphine hydrochloride or morphine sulphate) (Hillier, 1983) or in tablet form. The dose is titrated up in increments of 30–50% of the previous dose until pain control is achieved (Table 5) (Regnard and Davies, 1986). Opioids can be given to patients with cardiorespiratory disease (Abernethy *et al.*, 2003). An initial dose of 5- or 10-mg morphine solution 4-hourly is extremely safe. There is no maximal dose, but most pains are controlled by oral doses of 10–30 mg 4-hourly round the clock (Walsh and West, 1988).

Some patients can omit the 02.00 dose completely; some require a double dose at 22.00 to enable sleep through to 06.00. The patient can be maintained on slow release 12-hourly tablets or suspension (Twycross, 1978), by dose conversion from the normal release 4-hourly dose (Table 6).

Table 5 Incremental doses of oral morphine (Regnard and Davies, 1986)

5 mg → 10 mg → 15 mg → 20 mg → 30 mg → 45 mg → 60 mg → 90 mg → 120 mg, and so on at 30–50% increments

In very ill patients who are unable to swallow, or if vomiting prevents adequate absorption of oral medication, alternative routes of administration need to be used to maintain adequate pain relief. Several opioids are available for subcutaneous use in a syringe driver (Dover, 1987; Oliver, 1988); diamorphine is most commonly used in the United Kingdom as it is very soluble (high doses can be given in small volumes) (Twycross *et al.*, 2003). Compatibility data for various drugs given together by a syringe driver are available (Twycross *et al.*, 2003). Breakthrough additional opioid doses should be given subcutaneously as intramuscular injections are painful. Intravenous opioids should be avoided as tolerance appears to develop rapidly (Rogers *et al.*, 1985).

Side Effects of Opioids

About a third of patients develop transient nausea when commencing opioids; this responds to antiemetics acting at the chemoreceptor trigger zone, for example, haloperidol 1.5–5 mg at night, prochlorperazine 5 mg 8-hourly or levomepromazine 6 mg at night or 12-hourly (Twycross *et al.*, 2003, 1997).

Opioids are severely constipating. Unless the patient has true diarrhea before commencing opioids, a stimulant laxative with a softener must be given with the first dose and continued long term. Fecal softeners alone are insufficient. Senna liquid 10 ml (a stimulant) mixed with magnesium hydroxide 10 ml (a softener) given two or three times a day, or a combination laxative (e.g. co-danthramer) is usually effective at maintaining good bowel function. Polyethylene glycol 3500 (e.g. Movicol®) is also effective.

Some patients become drowsy or confused at very low doses of morphine; the elderly seem to be particularly at risk of this. For patients who do not tolerate morphine well, switching opioid may be helpful (Hanks, 2001). Oxycodone, available in solution or tablets in normal release and sustained release preparations, is a useful alternative to morphine. A parenteral preparation for subcutaneous use is also now available (Joint Formulary Committee, 2005).

Toxic morphine metabolites accumulate in renal failure. For patients with renal failure, fentanyl or alfentanil is preferable to morphine (Kirkham and Pugh, 1995), as these opioids are mainly metabolized to inactive compounds by the liver (Twycross *et al.*, 2003; Back, 2001). Fentanyl is not absorbed orally but can be given transdermally, subcutaneously, or transmucosally (Twycross *et al.*, 2003). It is available in transdermal patches which come in 25 μg hour^{-1} increments and need changing every 72 hours. Fentanyl is less constipating than morphine so laxatives may need to be adjusted. Occasionally, patients who have been on morphine for some time experience opioid withdrawal symptoms for about 24 hours when switching to fentanyl; these are controlled with doses of oral morphine. For patients who have variable, escalating, or unknown analgesic requirements, it is difficult to titrate transdermal fentanyl and it should not be used in these situations (Twycross *et al.*, 2003). For patients unable to take oral medications, a continuous subcutaneous

Table 6 Opioid dose regimes and approximate equivalent[a] morphine doses. (Adapted from Back, 2001 and Twycross *et al.*, 2003)

Drug		Examples	Example of dose regime[b]	24-hour total dose	Approximate equivalent[a] oral morphine 24-hour dose
Opioids given orally					
Codeine			60 mg 6-hourly	240 mg	24 mg
Tramadol			50 mg 6-hourly	200 mg	40 mg
Morphine sulphate	Normal release	Oramorph®	10 mg 4-hourly	60 mg	60 mg
Morphine sulphate	Slow release	MST Continus® Zomorph®	30 mg 12-hourly	60 mg	60 mg
Oxycodone	Normal release	Oxynorm®	5 mg 4-hourly	30 mg	45–60 mg
Oxycodone	Slow release	Oxycontin®	15 mg 12-hourly	30 mg	45–60 mg
Hydromorphone	Normal release	Palladone®	1.3 mg 4-hourly	7.8 mg	60 mg
Opioids given subcutaneously					
Morphine			5 mg 4-hourly	30 mg	60 mg
Diamorphine			5 mg 4-hourly	30 mg	60–90 mg
Oxycodone			5 mg 4-hourly	30 mg	60–90 mg
Opioids given by continuous subcutaneous infusion over 24 hours					
Morphine			20 mg over 24 hours	20 mg	40 mg
Diamorphine			20 mg over 24 hours	20 mg	40–60 mg
Oxycodone			20 mg over 24 hours	20 mg	40–60 mg
Fentanyl			400 μg over 24 hours	400 μg	60 mg
Alfentanil			2 mg over 24 hours	2 mg	60 mg
Opioid given transdermally (self-adhesive patch): change every 72 hours					
Fentanyl (patch)			25 μg hour^{-1}	600 μg	60–90 mg
Opioids given rectally (suppositories)					
Morphine hydrogel (nondissolving) suppositories m/r			50 mg once daily	50 mg	50 mg
Morphine (hydrochloride) suppositories			10 mg 4-hourly	60 mg	60 mg
Oxycodone (hydrochloride) suppositories			5 mg 4-hourly	30 mg	60 mg
Unsuitable opioids					
Pethidine		PO	50 mg 3-hourly	400 mg	50 mg
		IM	25 mg 3-hourly	200 mg	75 mg
Buprenorphine (partial opioid agonist)		SL	200 μg 8-hourly	600 μg	36 mg
		TD (patch)	35 μg hour^{-1}	800 μg	50 mg approx
Methadone		PO	Very variable pharmacokinetics; specialist supervision required		

m/r, modified release; PO, oral; IM, intramuscular; SL, sublingual; TD, transdermal.
[a]Equivalent doses are approximations only; doses must be carefully titrated for each individual patient. [b]Lower doses may be needed initially for frail patients or those who have not taken opioids before.

opioid infusion is easier to adjust. Fentanyl is available as oral transmucosal fentanyl citrate (OTFC) in "lozenges" which can be applied to the patient's oral mucosa to give additional doses of analgesia for breakthrough pain (Chandler, 1999). Many patients who are dying have a dry mouth and may be unable to use OTFC; sublingual fentanyl or alfentanil are other options for control of short-lived episodes of pain, but they should be prescribed only under specialist palliative medicine supervision.

Pain is a powerful respiratory stimulant. Significant respiratory depression does not occur at the dose the patient needs for analgesia. Patients should not be denied opioid analgesia for opioid-responsive pain. They can remain on opioids for many months. An increase in analgesic requirements indicates that the patient has more pain; it is not indicative of addiction (Portenoy, 1995).

Initial sedative effects wear off after two or three days. If the patient remains very drowsy, the opioid dose should be decreased and the patient reassessed, since the pain may be opioid resistant and the patient may be opioid toxic. Symptoms and signs of opioid toxicity include hallucinations, grimacing, hyperalgesia (the patient is extremely sensitive to painful stimuli, so may experience frequent breakthrough pain), allodynia (the patient appears to be in pain on being touched), pinpoint pupils, respiratory depression, and twitching or myoclonus. If untreated, seizures may follow (Woodruff, 2004).

Breakthrough Pain and Incident Pain

Breakthrough pains should be treated by a dose of morphine 50–100% of the 4-hourly morphine requirement and then the baseline dose increased accordingly; the pain must be regularly reassessed.

Patients who are taking opioids often also need Group I analgesics for other incidental pains, for example, headaches. They may benefit from coanalgesics such as NSAIDs, antidepressants, and steroids.

Others need a boost of analgesia for a specific activity causing incident pain, such as getting out of bed or dressing in the morning. A breakthrough dose given half an hour before moving can be helpful.

Difficult Pains

Bone Pain

Pain on movement is often poorly responsive to opioids alone. This includes bone pain, common in many malignancies, as well as joint pain (e.g. due to osteoarthritis).

Plain X-ray may not show metastases at an early stage; therefore, a combination of investigations may be required to localize a lesion. Where bone cortex is eroded, particularly mechanically important areas such as the neck of femur, the bone may be at risk of pathological fracture, and surgical pinning of the bone should be considered. Radiotherapy provides good analgesia in 80% of patients with pain from bone metastases, and should therefore always be considered (Woodruff, 2004). When multiple sclerotic bone metastases exist and the patient has a predicted prognosis of 6 weeks or more, strontium may be more effective and less debilitating than multiple doses of radiotherapy (Hoskin, 2004). Combinations of NSAIDs with opioids are a useful part of the management. Some bone pain, particularly due to metastatic breast cancer or myeloma, responds well to bisphosphonate infusion, even when the serum calcium is normal. Oral bisphosphonates do not seem to provide any analgesia. A trial of a bisphosphonates should be considered in difficult bone pain (Mannix *et al.*, 2000).

Some patients with advanced multiple metastases such as in myeloma can develop pathological bone fractures in sites where immobilization is impossible, such as the clavicle. A simple technique to provide analgesia can sometimes be effective: the fracture site is infiltrated with Depo-Medrone® (methylprednisolone acetate) 80 mg and bupivacaine hydrochloride 0.5%. This does not always require X-ray control and can provide adequate analgesia to allow the patient to be turned in the last days of life.

Neuropathic Pain

Neuropathic pains due to reversible damage from nerve compression or irreversible damage from neurodestruction (e.g. due to infiltration by tumor) or diabetic neuropathy are characterized by a burning or electric shock quality. They are often severe and are associated with altered sensation including allodynia or dysesthesia (Meyerson, 1990). Allodynia means the patient feels pain in response to a nonpainful stimulus; dysesthesia is an unpleasant abnormal sensation. Opioids can be helpful but are often needed in high doses and their use may be limited by side effects.

Neuropathic pain requires relief of any pressure on nerve fibers if possible. Tumor mass can be shrunk by radiotherapy and peritumor edema decreased by high-dose steroids (e.g. dexamethasone 8–16 mg day^{-1} in divided doses).

Low-dose amitriptyline (10–25 mg once or twice daily) appears to potentiate opioids through inhibition of serotonin reuptake and reduction in pain perception (Twycross *et al.*, 2003). Membrane-stabilizing anticonvulsants (e.g. carbamazepine) may help some patients, but tend to make the elderly very drowsy. Gabapentin is licensed for use in neuropathic pain, but again may be limited by drowsiness (Twycross *et al.*, 2003). It is safest to start tricyclic antidepressants or anticonvulsants at low doses and titrate up as tolerated by the patient.

Nerve blocks have a small place in the management of the terminally ill patient; the success rate of the block depends on the technique (Baines, 1981). Pain from pancreatic cancer can be dramatically relieved by celiac plexus block (Lipton, 1989), which may need to be repeated after a few months. Psoas compartment block may provide relief of hip pains. Epidural injection of steroids can improve pain from tumor infiltration at the spinal nerve root. Unfortunately, a few patients suffer deafferentation pain following neurolytic techniques. Therefore, in palliative care the drugs used tend to be temporary in action, such as bupivacaine with a depot steroid preparation.

Complex pain, such as sympathetically maintained pain, can be relieved by the appropriate nerve block (Cherny and Coley, 1994), although the place for nerve blocks in pain control is relatively small. Transcutaneous nerve stimulation provides a temporary partial blockade and often warrants a trial as it is so safe.

Ketamine was used as an anesthetic agent as it provides powerful analgesia (Fallon and Welsh, 1996), but it can cause severe dysphoria, hallucinations, a dramatic rise in blood pressure, and other side effects (Twycross *et al.*, 2003). It can be very effective in low-dose subcutaneous infusion in intractable neuropathic pain, when given with an antipsychotic or midazolam. It should only be used with palliative medicine supervision.

Similarly, methadone can provide good analgesia but its unpredictable half-life, which can be up to three days in some patients (Twycross *et al.*, 2003), makes it difficult to titrate in routine use.

CONSTIPATION

About half of all terminally ill patients are constipated, usually from a combination of anticholinergic drugs, opioids, poor fluid intake, and immobility associated with debility (Bruera *et al.*, 1994). High fiber preparations usually aggravate constipation as patients lack fluid, and they are unpalatable.

The use of magnesium hydroxide with senna, movicol, or co-danthramer for patients on opioids has been referred to. Lactulose is an effective stool softener in large doses (60–90 ml day^{-1}) with a mildly stimulant action (Regnard, 1988), but it can produce much flatus. In very severe

Table 7 Suitable laxatives

Osmotic laxatives	Stimulant laxatives	Fecal softeners	Rectally acting agents
Magnesium hydroxide	Senna	Docusate (capsules)	Bisacodyl suppositories (stimulant)
Polyethylene glycol 3500 (e.g. Movicol®)	Dantron (contained in co-danthramer)		Arachis oil (softener)
	Sodium picosulphate		Sodium citrate (e.g. Micralax Micro-enema®; osmotic)

constipation, higher doses of polyethylene glycol 3350 (e.g. Movicol® up to 8 sachets a day for up to 3 days) or sodium picosulphate (5 mg ml^{-1} up to three times a day) may be needed (Table 7) (Twycross *et al.*, 2003; Back, 2001). Occasionally, patients have fecal impaction which requires either high-dose Movicol® (Culbert *et al.*, 1998) or manual removal (a painful procedure which should only be done with adequate analgesia).

Bowel Obstruction

Ovarian and colon cancer often cause bowel obstruction at multiple sites, making surgery impossible (Baines *et al.*, 1985). Prevention is important: large doses of stool softener can maintain the stool as soft as toothpaste. Vomiting occurs in most patients with obstruction (Baines *et al.*, 1985), but does not become feculent until quite late; pain and distension are also often late signs. The diagnosis is clinical; abdominal X-rays seldom add anything to the picture in established obstruction and early films may show remarkably little.

When surgery is not possible, medical management of acute obstructive episodes requires antispasmodics such as hyoscine butylbromide for colic (Baines *et al.*, 1985), with an opioid for constant abdominal pain. An antiemetic acting at the vomiting center, for example, cyclizine, can control vomiting to some extent. Fecal softeners such as docusate should be given. A trial of corticosteroids may be tried although a systematic review on their effectiveness was not conclusive (Feuer and Broadley, 1999). Octreotide, generally only given under specialist supervision, may also be helpful to reduce the volume of intestinal secretions (Mercadente *et al.*, 1993).

The oral route cannot be used to give antiemetics, as gastric emptying is delayed and absorption is poor. Therefore, the subcutaneous route is preferable and a syringe driver is the drug delivery system of choice.

There is no evidence that a drip and suck regimen (with intravenous fluids and insertion of a nasogastric tube) is of help to these patients, and a nasogastric tube is irritating and nauseating. The obstructive episode should be managed to control symptoms even if sedation is an inevitable side effect. Unfortunately, acute obstruction with hard fecal matter in the bowel will resolve poorly so the mainstay of management is preventive palliation. A defunctioning colostomy can be distressing and difficult for the patient to come to terms with and should not be undertaken unless the patient's general condition indicates several months of active life and the patient fully understands the implications of surgery.

NAUSEA AND VOMITING

As for pain, the cause of the symptom must be determined. Vomiting may be the only sign of early bowel obstruction or hypercalcemia.

The stimulus to vomiting is triggered through different nuclei in the brainstem, and antiemetics differ with respect to efficacy at each site. The clinical circumstances can guide appropriate antiemetic therapy (Bentley and Boyd, 2001; Twycross and Back, 1998).

The chemoreceptor trigger zone, lying adjacent to the integrated vomiting center in the floor of the fourth ventricle, is stimulated by toxins, drugs, uremia, and hypercalcemia (Rousseau, 1995). Central dopamine antagonists at low dose (such as haloperidol 1.5–5 mg (Plotkin *et al.*, 1973) or levomepromazine 6 mg, once or twice daily (Twycross *et al.*, 1997)) are effective. They can be given orally or subcutaneously by syringe driver. Levomepromazine is slightly more sedative than haloperidol but can act as a mild coanalgesic with opioids; it is useful when other antiemetics fail. Buccal or rectal prochlorperazine are useful when the patient cannot swallow and a syringe driver is not available.

Cyclizine is an antihistamine that acts at the integrated vomiting center and is useful in combination with a central dopamine antagonist. It can be given as a continuous subcutaneous infusion by syringe driver (150 mg over 24 hours) but single injections tend to be painful and use in a syringe driver can cause painful inflammation at the syringe driver site.

Prokinetics such as metoclopramide or domperidone (available as tablets or suppositories) can be helpful in squashed stomach syndrome (Fallon and Hanks, 1994), for instance, when liver metastases cause extrinsic pressure on the stomach; they promote gastric emptying and duodenal peristalsis (Schulze-Delrieu *et al.*, 1981). Liver metastases can sometimes cause severe nausea which responds well to dexamethasone in low doses (2–4 mg day^{-1}). $5HT_3$ antagonists are effective short term for chemotherapy- and radiotherapy-induced vomiting but are constipating and very much more expensive than the other antiemetics suggested above (Twycross *et al.*, 2003).

Hypercalcemia can be treated with intravenous fluids and a bisphosphonate, with dramatic relief from vomiting and other symptoms.

BREATHLESSNESS

Breathlessness is an extremely distressing symptom and is often inadequately relieved. It is a common symptom in

end-stage cardiac and respiratory failure, as well as many cancers. It becomes more common as death approaches (Dudgeon *et al.*, 2001).

The common causes of breathlessness can usually be differentiated on history and medical examination.

Patients with acute cardiac failure may feel as though they are suffocating; they can respond promptly to intravenous furosemide, infusion of nitrates and parenteral diamorphine. Bronchospasm can be treated with nebulized bronchodilators; pneumonia causing breathlessness warrants antibiotics and physiotherapy. Pleural effusions can be drained relatively simply and painlessly. When bronchial occlusion by tumor is the main cause of breathlessness, it may be possible (dependent on the patient's condition) for an endobronchial stent to be inserted (Back, 2001).

Patients may benefit from treatment of symptomatic anemia. Oral iron is incorporated too slowly for it to be effective; its use requires the bone marrow to be functioning adequately and this may not be the case in anemia of chronic disease or in advanced malignancy. Transfusion of packed red cells is likely to yield most rapid symptomatic improvement. Erythropoietin may be an effective alternative in some patients, particularly in view of the limited supply of blood products (Mijovic, 2004). Transfusion is usually futile in the last few days of life.

Long-term oxygen therapy is beneficial to selected patients with chronic obstructive pulmonary disease (COPD), but oxygen alone is rarely adequate to control breathlessness in the dying patient (Shee, 1995).

Facial cooling (by a handheld or bedside fan, or a draught from an open window) can improve breathlessness. Having treated reversible causes, the sensation of breathlessness can be suppressed by opioids, sometimes at very low dose (Jennings *et al.*, 2001). In those already on opioids, the dose should be increased above that needed for analgesia to decrease the central drive to respiratory rate. The dose should be titrated as for pain control but in smaller increments, of 10–20%. For most patients, nebulized morphine is no better than nebulized saline for symptom relief (Jennings *et al.*, 2001).

Effective physiotherapy can teach patients to move efficiently and minimize breathlessness on exertion. Nurse-led breathlessness clinics have been shown to have a small but potentially significant effect in improving symptoms, using breathing control, relaxation, and activity-pacing techniques (Bredin *et al.*, 1999).

Breathlessness correlates better with psychological state than with objective measures of respiratory function (Ripamonti and Bruera, 1997); patients should be assessed for anxiety and depression and treated for these if appropriate.

Constipation should be avoided since the effort of defecating aggravates breathlessness.

The breathless patient who is unable to take oral medications in the last few days of life may respond well to parenteral opioids such as diamorphine 2.5–5 mg subcutaneously, with or without midazolam 2.5 mg subcutaneously. A syringe driver with diamorphine and low-dose midazolam may also be helpful.

FATIGUE

Fatigue is a very common and debilitating symptom of advanced disease, whether due to advanced malignancy or end-stage cardiac or respiratory failure. It is underreported and underrecorded (Kendall *et al.*, 2004), perhaps because patients and doctors feel that "nothing can be done".

Medical history, examination, and simple investigations should identify anemia, depression, and thyroid disease which can be treated. Several drugs (including sedatives, alcohol, β-blockers, many antidepressants, and antipsychotics) can cause excessive daytime somnolence or fatigue; antihypertensives may need to be rationalized dependent on the patient's cardiovascular and fluid status. Hypokalemia can cause muscle weakness and may respond to potassium supplements; if these are not effective, the patient may be deficient in magnesium (Twycross *et al.*, 2003).

Nonpharmacological management is important. Optimizing physical fitness, sleep hygiene, pacing activities, setting realistic and achievable goals can help the patient make the most of the time he or she has left.

CONFUSION

The elderly are particularly susceptible to acute confusion, possibly on a background of cognitive impairment due to dementia or cerebrovascular disease. Acute confusion is usually multifactorial; contributing factors include medications (anticholinergics, opioids, and benzodiazepines, amongst others), withdrawal from various drugs, urinary retention, constipation, hypoxia, uremia, urinary tract infections, and chest infections. Poor vision and hearing also predispose patients to acute confusional states (Caraceni and Grassi, 2003).

Hypercalcemia is an important cause of acute confusion which can respond dramatically to correction. It is often seen associated with tumors known to metastasize to bone, but may also be due to parathyroid-like hormone secretion by tumor (Ralston, 1994). Concomitant symptoms of anorexia, constipation, nausea, and dehydration may not be obvious since they are so common in patients who are terminally ill. Corrected serum calcium levels of over 3.5 mmol l^{-1} correspond to severe hypercalcemia (Heath, 1989; Iqbal *et al.*, 1988). Rehydration with intravenous 0.9% sodium chloride is the first line of treatment. If the hypercalcemia persists despite rehydration, intravenous bisphosphonates (e.g. pamidronate) can rapidly and effectively lower serum calcium levels (Kovacs *et al.*, 1995). Zoledronic acid can be tried if pamidronate is not effective (Twycross *et al.*, 2003). Steroids and oral bisphosphonates are of no benefit in patients with severe hypercalcemia. Treatment for hypercalcemia may need to be repeated after 3 or 4 weeks, but it should be recognized that hypercalcemia carries a poor prognosis and the patient with resistant hypercalcemia may require symptom control as they enter their terminal phase.

Confusion caused by cerebral metastases may temporarily respond well to high-dose dexamethasone (16 mg daily)

(Kirkham, 1988; Garde, 1965). If there is no response after 5 days, the steroid can be stopped abruptly.

The possibility of switching to an alternative opioid in patients who experience confusion on morphine has already been mentioned.

Low-dose antipsychotic medication such as haloperidol 0.5 mg (repeated after 30 minutes if not effective; higher doses in severe delirium with agitation) (Caraceni and Grassi, 2003) can help improve symptoms associated with confusion, such as hallucinations and paranoid thoughts.

Patients often have insight into their toxic confusional state, which is aggravated by fears. Patients should be nursed in a well-lit room with minimal background noise and be spoken to in clear simple terms to provide calming reassurance. Their experiences, whether real, hallucinatory, or paranoid, feel real and will be aggravated by a doctor or nurse seeming to be sceptical. It is more helpful to let the patient know that you understand that these disturbing experiences are happening and that you will try to do something about it.

DEPRESSION

The patient may undergo a process of grief, associated with awareness of the illness and loss of an independent lifestyle, compounded by fears and unresolved issues in life (Lichter, 1991). Grief has been described in terms of stages of anger, bitterness, bargaining, coming to terms, and reconciliation (Worden, 1983). In practice, these are not clear-cut, and people waiver in and out of conflicting emotional states (Stadeford, 1984). It is important to remember that the patient losing life's functions may be grieving deeply for his or her past and future.

The onset of deteriorating illness can reactivate grief from a previous bereavement. Awareness by all those looking after a patient will increase understanding of the patient's reaction to the current situation.

Depression is frequently missed but it is a treatable entity (Lloyd-Williams *et al.*, 2004). Antidepressants should be considered for those patients with early morning wakening, an anxiety state, feelings of excessive guilt or overwhelming pessimism about others (Regnard and Mannix, 1992). Other pointers such as weakness, tiredness, loss of appetite, or pessimism about self are often expected manifestations of the life-threatening disease process (Cody, 1990).

INFECTIONS

There is a tendency to feel that treatment should be avoided in patients who are deemed to be terminally ill. As a general rule, all treatments should be directed to making the patient more comfortable and not causing any distress.

Symptomatic cystitis should be treated empirically. Pneumonia causing pleuritic pain, cough, or other discomfort warrants antibiotics. Oral antibiotics can be taken relatively easily. Depending on patient choice and ease of venous access, intravenous antibiotics may also be used. Intramuscular injections are usually avoided because they are painful; they may be a last resort for a patient with septicemia (e.g. from a urinary tract infection) for whom oral antibiotics may be insufficient to relieve symptoms and venous access is impossible.

Patients with chronic illness causing immunocompromise are also susceptible to other types of infection. Herpetic infection may respond to antiviral agents. Fungal infections of the mouth and esophagus are common and very easily treated with imidazole antifungal agents such as fluconazole (Finlay, 1995); systemic fungal infections are extremely difficult to diagnose and carry a poor prognosis (Pizzo, 1993).

There seems little rationale in resuscitating a patient to allow him or her to die again only a short time later (Gillon, 1986). But it is unethical to withhold treatments which make a patient feel more comfortable during the last days of life, irrespective of whether they prolong life or not.

MOUTH CARE

Many patients have dryness of the mouth with debris over the teeth, gums, and tongue. Fresh pineapple sucked frequently is a useful debriding agent, although it can predispose to dental decay. Sodium bicarbonate is a useful mouthwash. Ill-fitting dentures should be relined to encourage comfortable eating. Dryness can be relieved by sucking crushed ice, particularly in the later stages of illness. Some patients derive benefit from artificial saliva and should be encouraged to take frequent sips (Trenter and Ceason, 1986).

Dryness is a frequent side effect of drugs, including opioids and anticholinergic medication.

Oral candidosis is found in over 80% of patients who are terminally ill, but does not appear to correlate directly with oral symptoms or signs (Finlay, 1986). Patients with candidosis involving the oropharynx or esophagus should receive systemic treatment with fluconazole for 3 to 4 days. Some strains of candida are now resistant to fluconazole; nystatin solution washed around the oral mucosa four times a day may be effective for these patients (Finlay, 1995).

DYSPHAGIA (*see* Chapter 73, Communication Disorders and Dysphagia)

Oral or esophageal candidosis should be treated if suspected. Imaging with contrast is only indicated for dysphagia not responding to antifungal treatment.

Neurological dysphagia can be helped by developing techniques whereby the head and neck are positioned to assist gravitational movement of food. These are usually idiosyncratic and take time to formulate with each individual

patient. A speech therapist can advise on swallowing as well as communication.

Patients with esophageal obstruction may benefit from insertion of an endoesophageal stent (Woodruff, 2004).

ANOREXIA

As patients become frailer, they often lose the desire to eat. Food has great significance in social as well as nutritional terms: mealtimes may be a focus of household routine, and preparing food can be an expression of love. Close family members may feel rejected by the patient who no longer feels like eating their favorite meal. Food may also be the focus for anxieties about the patient's deteriorating condition; relatives may worry that "he should eat something or he will starve to death". Anorexia-cachexia syndrome, seen in many patients with cancer and some with severe COPD or cardiac failure, is not due to starvation *per se* but altered metabolism mediated by inflammatory cytokines (Strasser and Bruera, 2002).

It is helpful to explore the underlying worries about the patient who seems to be fading away before their eyes. Patients should be encouraged to eat what they fancy (often small portions are more appetizing) at times to suit them. Tastes often change in patients with advanced cancer. Calorie and protein supplement drinks may be of benefit but the patient should not be forced to drink supplements he or she finds unpalatable.

Good mouth care is vital to optimize oral intake. Treat oral candidosis and ensure any dentures fit well. Nausea has been discussed and can be treated with antiemetics dependent on the cause; prokinetics can improve gastric stasis.

Steroids are often used to augment appetite. However, in controlled trials, placebo treatment often has an effect, and the benefit seen in patients on corticosteroids is often short-lived (Woodruff, 2004; Jayasekera and Stone, 2004). Long-term steroid therapy is commonly complicated by side effects.

PRESSURE SORES AND OTHER WOUNDS (*see* Chapter 136, Pressure Ulceration)

Patients with terminal illness may be at risk of pressure sores for several reasons: poor mobility, malnutrition including vitamin deficiency, fragile skin, edematous tissues, and reduced sensation. Prevention is better than cure; optimizing mobility, pressure relieving cushions or mattresses, and frequent monitoring of pressure areas can all be helpful.

Painful open wounds may respond to topical morphine or diamorphine in gel (1 mg in 1 ml) (Back and Finlay, 1995), without systemic side effects.

Offensive odor can be reduced by topical metronidazole (0.75% gel) (Finlay *et al.*, 1996); charcoal dressings may absorb some of the odor (Woodruff, 2004), provided they are kept dry (they should not be in contact with an oozing wound). Wounds which ooze blood (e.g. fungating breast cancers) can be controlled by local radiotherapy (Woodruff, 2004) or electron therapy with minimal side effects. Oral tranexamic acid or topical application of weak adrenaline solution may also reduce bleeding.

LYMPHEDEMA

Input from a specialist lymphedema service can dramatically improve painful, heavy swollen limbs due to lymphedema. Meticulous skin care including hygiene and keeping the area well moisturized can help prevent inflammatory episodes. Massage by trained personnel can help drain lymphedema and compression bandaging can help to prevent fluid from reaccumulating; gentle exercise of affected limbs helps maintain lymphatic drainage (British Lymphology Society, 2001).

ASCITES

Ascites are commonly seen in patients with advanced ovarian or gastrointestinal cancers, as well as in end-stage cardiac or hepatic failure. For patients with symptomatic ascites and evidence of fluid overload, a trial of diuretics is indicated (Sharma and Walsh, 1995; Morris, 1984); protein-rich exudates may require paracentesis. Occasionally, patients benefit from insertion of a peritoneovenous shunt, if their general condition and prognosis allow it (Janu *et al.*, 1984). Guidelines for paracentesis in a palliative care setting have been developed (Stephenson and Gilbert, 2002).

HICCUP

The cause of hiccups may guide management; an H_2 blocker for dyspepsia or steroids for a subphrenic liver metastasis may help. Reduction of gastric distension (e.g. using metoclopramide as a prokinetic) may help. The acute attack may be stopped by direct pharyngeal stimulation; hiccups can also respond to nifedipine (Mukhopadhyay *et al.*, 1986; Lipps *et al.*, 1990) or baclofen (Bhalotra, 1990).

DISCUSSING THE DIAGNOSIS AND PROGNOSIS

It can be difficult to choose the correct time to inform the patient of an unfavorable prognosis (Buckman, 1984). The patient's family may exert enormous pressure that the patient should not be told, but lies to patients must be avoided (Gillon, 1985). Patients are aware that they are ill and not improving; imparting the truth should be done gently, answering the patient's questions honestly,

without denying hope (Lancet, 1983). While the hope of cure is unattainable, there is hope of good symptom control, of going home, of achieving other goals, for example, grandchildren's weddings and birthdays; the physician must also give the patient reassurance of a commitment to care. Before directly answering questions, it is useful to explore with the patient at length his or her concept of what is wrong (Maguire and Faulkner, 1988a,b; Maguire *et al.*, 1993), using open questions such as "what did you really think was happening?" or "how do you think things are going?" Knowing the patient is looking forward to some event can be vital; the truth of progressive disease can be imparted with the hope that this goal will be reached. However, it is important that goals set are realistic hopes, so that the patient can trust in the physician's honesty.

However much the family pressurize, the patient should never be actively lied to. It is the patient's right to know what is happening and to know that confidentiality will be observed. The truth can be explored gently and the family included to avoid a conspiracy of silence. Once lied to, a patient will never believe the physician again.

A previous bad experience of a friend or a relative dying in distressing circumstances will be crucially important since fear of pain, incontinence, or confusion is common in patients desperate to maintain their dignity and personal integrity to the end.

There are no set rules on how a patient should be told a bad prognosis but the physician should feel emotionally comfortable with the conversation he or she is having with the patient. When patients are aware of being kept "in the dark" for a time, fears become accentuated; "the truth must be so awful that nobody has dared to talk to me about it". The more frightened a patient is, the less likely he or she is to talk about their fears (van Assendelft, 1986).

People have different concepts of words, for example, "tumor", "growth", "cancer", "malignancy", and so on. The patient's own "language" should be used as much as possible (McKillop *et al.*, 1988). After any information has been given, a follow-up conversation is important to discover what the patient has understood.

Much communication is done nonverbally; many cues are picked up by the patient unbeknown to the physician. The physician who avoids opportunities for the patient to ask questions indicates a refusal to answer questions. Creating the impression of having "all the time in the world" means the physician must shed the protective barrier of appearing busy, be prepared to sit down and tackle issues at the patient's own rate (Maguire, 1985). Other members of the team, for example, nursing staff, auxiliary nurses, social workers, domestics, and therapy staff, may seem to have more time and be more accessible key personnel to confide in; good communication within the team must be an essential part of planning for holistic patient care.

Predicting a prognosis is impossible (Christakis and Lamont, 2000). There is no accurate way of predicting life expectancy for a particular patient; time estimates are misleading (Maguire and Faulkner, 1988a,b). A specific time, for example, "three months" or "before Christmas", will be interpreted by patient and family as absolute fact and should be avoided. Some people view a fixed time prognosis as a death sentence. This can be avoided by explaining that the aim is to keep the patient "as well as possible for as long as possible" by adjusting treatment as necessary; problems cannot be specifically foreseen but realistic goals are achievable.

REQUESTS FOR EUTHANASIA

Occasionally, a patient will ask for something "to end it all". This is a sad request to hear, but must be dealt with calmly and sympathetically (Woodruff, 2004).

Some patients feel that they have become a burden on those close to them. Some think that physician-assisted suicide is the only way to end their physical, emotional, or spiritual distress. Others may be simply begging for help or attention. It is important to recognize that demoralized patients are more likely to ask for euthanasia (Kissane *et al.*, 2001), but respond well to excellent care (Chochinov, 1999; Chochinov *et al.*, 1995).

It is vital to look for the reasons underlying the request: look for poorly controlled physical symptoms, associated symptoms of depression, and for existential distress. Effective palliative care can reduce persistent requests for euthanasia to an absolute minimum – such requests are almost never seen to persist when specialist palliative care has been able to provide effective care for some time.

Research into why people ask for death (Chochinov *et al.*, 1995; Mak *et al.*, 2003; Filiberti *et al.*, 2001) has shown that key themes behind the request are as follows:

1. Fear – fear of a future worse than death; fear of becoming a burden.
2. Feeling of being a burden to family, loved ones, or society.
3. Anger and guilt and a sense of wanting control when the disease has taken control of their life.
4. Lack of an adequate environment of dignity-enhancing care (Chochinov, 2002).

Occasionally, patients are so distressed and exhausted that it is appropriate to offer sedation, usually for 24–48 hours. Such sedation using midazolam carefully titrated can then be lightened after one to two days, allowing the patient to reevaluate their position after rest and sleep.

AS DEATH APPROACHES

Not all physicians may feel confident or comfortable to recognize when death is approaching. When a patient's condition is deteriorating day by day, when they are unable to take more than sips of fluid, when they are too weak to

get out of bed, their prognosis is likely to be measured in days.

As the patient becomes progressively weaker, the onset of a semicomatose state is often seen. At this stage, all measures must be directed at maintaining comfort and dignity rather than prolonging the dying phase. Rigorous review of medication is required; many drugs can be omitted with benefit (Ellershaw, 2004). Medications which are needed for control of symptoms can be given as subcutaneous injections or as a continuous subcutaneous infusion by syringe driver (Dover, 1987; Oliver, 1988). Fluid intake is often poor, but for those with thirst it can usually be relieved with oral care. "Routine observations" of blood pressure, temperature and oxygen saturation, blood tests, and other investigations become irrelevant and meddlesome and can be stopped (Ellershaw, 2004).

Doctors and nurses should discuss the aims of care with the family or next of kin (provided the patient does not object), so that they are aware that treatment is aimed at comfort and that futile measures will not be taken to attempt resuscitation. It may be helpful to reassure the relatives that "we will allow death to occur naturally" as a positive step, rather than that "treatment will be withdrawn" with negative connotations.

Secretions accumulate within the bronchial tree and cause "death rattle" which can be very distressing to relatives. Explanation of the cause of the sound, and reassurance that it is more distressing for the onlookers than for the patient, may help to alleviate some distress. Early administration of subcutaneous hyoscine or glycopyrronium can minimize the production of secretions, and should be repeated every 4 to 6 hours (Finlay, 1984), or given as a subcutaneous infusion over 24 hours. Repositioning can also drain secretions from the bronchial tree.

Relatives must have a clear explanation of what is happening and be warned that the cyclical pattern of Cheyne-Stokes breathing may occur.

The opioids are remarkably safe drugs. Many fear that a subcutaneous dose of diamorphine may "kill" the patient; the person who is dying should not have analgesia withheld, and well-planned doses will not hasten the end. It is sad to see a patient die of exhaustion when they have been denied adequate analgesia. The use of a syringe driver to administer a continuous infusion of opioid and other drugs (Dover, 1987) may often be easier for both relatives and nurses who find the process of repeated injections traumatic. If repeated subcutaneous injections are used, leaving a small "butterfly" needle *in situ* subcutaneously means that each dose can be given painlessly.

Restlessness in a patient who is dying has many potential causes, including urinary retention, pain, uremia, fear, and unresolved spiritual conflict. When reversible causes have been addressed, the patient may benefit from a benzodiazepine (e.g. midazolam) given subcutaneously, possibly by syringe driver.

The patient who appears comatose can still hear and relatives should be encouraged to continue talking to the dying person (Lamerton, 1979) and to each other. This may be an important time for apologies, reconciliations, or to express love and caring. Sensitive handling of the family at this stage can do much to avoid bitterness and anger developing later in their grief. The family benefit from knowing how to maintain comfort. For the patient at home, mouth care and turning regularly as part of pressure area care can be important physical care which the family can give.

It is important to ascertain any particular wishes they have for religious ceremony or customs around death.

A care pathway, giving guidance in the last few days of life, has been developed to improve care of the dying (Ellershaw, 2004). It is being implemented in many units throughout the United Kingdom and can guide care whether patients are dying in hospital, nursing home, palliative care unit, or at home.

EMERGENCIES

Most deaths are gentle and gradual. Occasionally, a sudden irreversible catastrophic event occurs such as massive hemorrhage, hemoptysis, massive pulmonary embolism, or stridor.

Death will occur within minutes whatever is done; the patient can be rendered unconscious using intravenous midazolam or other sedative drugs to relieve his or her terror. This is not any form of euthanasia; resuscitation attempts are futile and distress relatives and staff.

Whenever possible, such situations should be predicted and discussed with staff and relatives, but it is the one instance where the patient may benefit from ignorance.

BEREAVEMENT

The process of grief may begin before bereavement.

After a person has died, the family or close friends may find comfort from talking to the professional carers again about the person they have lost and often have questions about the way a person died which need to be answered to enable them to come to terms with their own loss.

The spouse of the elderly dying person is often at risk of complicated grief (Preston, 1989). After a lifetime together, often with increasing interdependence during retirement, the loss may result in a chronic or inhibited bereaved state (Stadeford, 1984). The primary care team may be key in providing long-term support and counseling (Charlton and Dolman, 1995). The effect of death on the other members of the family, particularly grandchildren, must also be considered; children may need permission to express their loss (Heegaard, 1988) and participate in the mourning process in the family (Preston, 1989).

WHAT CAN HOSPICE CARE OFFER?

The hospice movement was founded over 30 years ago in Britain and has developed into the speciality of palliative

medicine. The philosophy of care is to provide a warm, emotionally safe environment in which the patient can receive treatment aimed at improving the quality of life.

Many patients who are terminally ill will never require the specialized services of an inpatient palliative care unit; their symptoms are easily controlled, they are psychologically at peace and have come to terms with their situation. However, it would be foolish, and even arrogant, for any one physician to feel that he or she is able to provide everything for a patient; hospice care should be used as an adjunct to the current medical team rather than a replacement. Facilities such as day care can provide occupational therapy, social company, and monitor symptom control while allowing the family time to attend to their own affairs (Anderson, 1987; Deans *et al.*, 1988). Home care support can complement, but not replace, the role of the primary care team for the patient cared for at home. A hospice does not have the noisy pressures of acute medical admissions (Soutar and Wilson, 1986), thereby providing a peaceful homely environment in which patient can be assessed in terms of their physical, emotional, social, and spiritual needs.

Just as other aspects require individual planning, so does spiritual input. Most people have individualistic beliefs and their own religious traditions must be respected by all concerned (Neuberger, 1994). The person nearing death has a greater need for spiritual counseling than for the ritualization of religion.

CONCLUSION

The patient approaching death has a right to expect some things from the attendant physician: a commitment to care, promoting quality rather than quantity of life, and helping to live actively and die with dignity.

KEY POINTS

- It may not be possible to cure a patient's progressive illness, but there is still much that can be done to enable as full and active a life as possible.
- Treatment should be tailored to suit the individual, within an ethical framework that allows fair allocation of resources.
- Look for the causes of symptoms; treat the reversible as well as giving symptomatic treatment.
- Consider all domains of distress: symptoms which are difficult to control may be compounded by fear or unresolved spiritual issues.
- If symptoms are not settling within 48 hours despite appropriate treatment, ask for help or advice from a palliative medicine specialist.

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Education in Geriatric Medicine in the United Kingdom

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INTRODUCTION

Geriatric medicine was first recognized as a speciality in the United Kingdom (UK) at the time of the introduction of the National Health Service (NHS) in 1948 (Evans, 1997; Barton and Mulley, 2003). Since that time, increasing numbers of specialists in geriatric medicine have been appointed, at first largely self-trained, but now having completed formal training programs, and usually having been first introduced to the subject as students. Education in geriatric medicine has developed alongside the clinical speciality.

MEDICAL EDUCATION

Medical education is conventionally divided into several phases. The first phase is the initial training leading to qualification as a doctor. In the United Kingdom, this is usually taken at undergraduate level but as some medical students are already graduates, the term used by the General Medical Council (GMC) – "basic medical education" – is preferable. Basic medical education is usually followed by a compulsory year as the most junior hospital doctor – "preregistration house officer". In the United Kingdom, in 2005, the house officer year will be replaced by a 2-year period of foundation training. This is followed by several more years of postgraduate or specialist training which combines supervised clinical experience and formal education and assessment. The remaining phase is "continuing professional development" and refers to the need for all doctors to continue educating themselves and updating their skills throughout their professional lifetimes; this will not be discussed further in this chapter.

HISTORY

Three phases in the development of basic medical education in geriatric medicine in the United Kingdom can be recognized. In the first 15 years of the speciality, education was largely informal and clinically based. The teachers were consultants in the speciality, they usually taught in their wards, and the teaching was based on the plethora of clinical signs found in their patients. Attendance at classes was often voluntary and specific time for geriatric medicine rarely appeared in curricula. Specialist training was also informal, largely based on experience gained in clinical practice, and sometimes took the form of a short attachment or "conversion course" for doctors already trained in general medicine or one of its specialities.

In 1965, the University of Glasgow appointed Professor (later Sir) W Ferguson Anderson to the first chair of geriatric medicine. Following this, chairs of geriatric medicine (sometimes with other titles) have been created in almost all universities with medical schools in the United Kingdom and in many other parts of the world. During the two decades following 1965, the academic discipline of geriatric medicine developed, and formal teaching courses were designed and published. Geriatric medicine became a required component of many medical school curricula, encouraged by the Recommendations on Basic Medical Education of the General Medical Council (General Medical Council, 1980) (Table 1). The state of education in geriatric medicine and gerontology at the end of these two decades was the subject of a comprehensive review published in 1985 (Stout, 1985).

The third phase was a revolution in medical education which started in the late 1980s culminating in the introduction of radically new medical curricula in the United Kingdom and many other countries. The exact role of geriatric medicine in these new curricula has not been described.

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Table 1 The first published recommendations on teaching gerontology and geriatric medicine in the United Kingdom

United Kingdom (General Medical Council (1980))
The student should receive instruction in the special problems of diagnosis and treatment of illness in the elderly and in maintaining mental and physical health in old age. He should be introduced to the range of domiciliary and institutional services available for the care of the elderly

However, some of the "new" concepts in the revised curricula have already been in place in educational programs in geriatric medicine, and the change from the old to the new did not prove as difficult in this subject as it was in some other longer established disciplines.

Unfortunately, we now appear to be entering a fourth phase where some of the progress that has been made in introducing academic geriatric medicine in the United Kingdom is under threat. The threat arises from new imperatives on universities for quality assessments in both teaching and research. These have led medical schools to reorganize into smaller numbers of large academic units, and the smaller specialist departments, particularly those which have a broad clinical base and whose research is more applied and practice orientated, are not seen as a priority. As a result, a number of departments of geriatric medicine have ceased to exist. A survey of medical schools undertaken by the British Geriatrics Society in 2004 (Crome *et al.*, 2004) revealed that a considerable number of UK medical schools no longer had an academic department of geriatric medicine, and of those that had, only about one half had a professor as head of department. This contrasts with the state of academic geriatric medicine in 1996 when all UK medical schools had academic appointments in geriatric medicine, all but one at professorial level, several had more than one professor, and some also had professors of geriatric psychiatry. Of particular concern is, the poor recruitment into academic geriatric medicine and the lack of applicants for senior academic posts, including chairs. This is not unique to geriatric medicine, and is an extreme example of problems in UK academic medicine (Academy of Medical Sciences, 2002). Geriatric medicine, being one of the newer entrants into academic medicine, is particularly vulnerable. It is ironic that this should be happening at a time when the need for education and research in aging and the care of older people has never been greater.

THE APPROACH TO MEDICAL EDUCATION

Over the last two decades, medical education in the United Kingdom has become much more professionalized and most medical schools now have a department of medical education, usually staffed by a combination of people with medical qualifications who have taken a particular interest in education, and people with qualifications in education or related disciplines. Medical education departments play a major role in the design of curricula and provide training in techniques of delivering education and its assessment. They also coordinate the curriculum and it is no longer the case that individual disciplines, often identified by academic departments, are allocated a period of time in the medical curriculum and use it as they wish.

A number of issues have driven change in medical education. These include the following:

- much of what is learnt during the undergraduate period, frequently in the last few weeks before examinations, is rapidly forgotten;
- even if it was all remembered, much of it rapidly becomes out of date and is little used during the professional careers of medical graduates;
- much of the information that medical graduates use in practising their profession is acquired in the years following graduation;
- curricula did not always reflect the requirement for postgraduate education for whatever speciality the graduate enters; thus the aim of producing a doctor who could go into independent practice immediately after graduation is unrealistic;
- over the years, new knowledge and new subjects have developed and these tended to be fitted into the curriculum with very little thought on whether anything should be taken out;
- medicine is now practised in multidisciplinary teams, both in hospital and in the community, and preparation for working in teams needs to be included within the curriculum;
- new educational methods have been developed;
- the importance of assessment, both for students and for teachers.

The overall outcome of basic medical education is to produce graduates who have the knowledge and competencies to undertake the preregistration house officer year, have the basic framework of knowledge and skills to allow them to progress through postgraduate medical education in their chosen speciality, have an enquiring and reflective outlook on medical practice so as to be in a position to evaluate and, where appropriate, introduce new developments, and have the professional attributes expected of medical practitioners.

The first task in designing the new curriculum was to define the core knowledge and skills which were required of every medical graduate. This required hard reflective thinking on the part of medical educators and the acceptance by many that this might mean that their own particular subject would be taught in less detail than was previously the case. About two-thirds of the total curricular time is needed for a core education. (A European Directive rules that basic medical training, which includes the preregistration year, must be at least 6 years in duration, or 5500 hours of theoretical and practical instruction given in a university or under the supervision of a university.) Students also need to study some subjects in depth to allow them to see the boundaries of knowledge, to be introduced to methods of evaluation, literature searching, gathering and analyzing new data, and to study subjects of their own choosing, perhaps as a help

to making career choices later. Thus, a series of student selected components (previously known as special study modules) have been introduced. The third feature of the new curriculum is integration. This includes vertical integration of the basic sciences with clinical subjects so that students learn at the same time, for example, the anatomy, physiology, and clinical examination of a system; and horizontal integration where overlapping subjects are taught together or in a coordinated fashion. Some components of the course should be taught on a multidisciplinary basis along with students of other health-care professions, including nursing and the allied health professions. New teaching methods have been introduced, including clinical skills centers in which students can learn clinical skills on lifelike models, and computer-aided and web-based teaching.

Integrated teaching is often system based using the anatomical and physiological systems of the body. Some medical schools in the United Kingdom use problem-based learning where the responsibility for their education is placed on the students who are presented with a clinical problem and then use their own initiative to acquire the appropriate knowledge of normal and abnormal structure and function. Problem-based learning is highly resource intensive, particularly in staff who act as facilitators rather than teachers, and not all medical schools have been able to introduce this method. Whichever method is used, the curriculum is student centered with the student carrying increasing responsibility for active learning rather than, as previously, being a passive recipient of what is delivered by teachers.

Assessment methods are now multiple and it is generally accepted that often several methods are necessary for assessing particular areas. While both the traditional essays and the multiple-choice question papers have a role in medical education, their role is specific and limited and it is inappropriate for them to be the only assessment methods. Continuous assessment by means of logbooks, portfolios, and records of achievement are used to test skills and attitudes. While knowledge and skills can be readily assessed, it is much more difficult to assess attitudes. Concern about doctors who have behaved inappropriately has focused attention on the attitudes of students, both on admission to the medical school and during the course, and increasing supervision of students through personal tutors and other similar schemes may identify the small number of students who have inappropriate attitudes.

University education, including medical education, is increasingly governed by bodies outside the universities. Since its foundation in 1858, the GMC has had responsibility for medical education in the United Kingdom. It has discharged this responsibility by publishing "Recommendations on Basic Medical Education" every decade and by inspecting the medical schools. The recommendations issued in 1993, under the title of "Tomorrow's Doctors" introduced radical change and set out the new educational principles mentioned above (General Medical Council, 1993). The GMC also introduced more rigorous inspections to ensure that medical schools complied with the recommendations. The latest edition of "Tomorrow's Doctors", issued in 2002 (General Medical Council, 2002), did not radically change the 1993 edition, but further emphasized the need to ensure that the standards of conduct for all medical practitioners set out in the GMCs document "Good Medical Practice" (General Medical Council, 2001) are infused throughout the curriculum. A number of GMC recommendations in "Tomorrow's Doctors" are relevant to the care of older people (Table 2). There are also recommendations on the principles of assessment and assessment procedures.

The Quality Assurance Agency (QAA) for higher education, which assesses teaching quality in higher education in the United Kingdom, has issued benchmark statements for each subject. These are a means for the academic community to describe the nature and characteristics of programs in specific subjects and represent general expectations about the standards for the award of qualifications at a given level. The benchmark statements are used by institutions in designing and evaluating programs, by external examiners, by the QAA when assessing the standards in universities, and by potential students and employers to help them understand programs of higher education. The benchmark statement for medicine (Quality Assurance Agency for Higher Education, 2002), although differing in style from "Tomorrow's Doctors", has essentially the same requirements. Some of educational outcomes are particularly relevant to the teaching of aging and the care of older people (Table 3). A further influential document, "The Scottish Doctor", produced by the Scottish Deans Medical Curriculum Group (2002), has a series of learning

Table 2 Recommendations on basic medical education relevant to the care of older people (General Medical Council, 2002)

1. Students must demonstrate respect for patients regardless of age (item 6c(ii))
2. Graduates must know about and understand the care of people with recurrent and chronic illnesses and people with mental and physical disabilities (item (16f))
3. Graduates must be aware of the importance of working as a team within a multiprofessional context (item (28f))
4. Graduates must understand the social and cultural environment in which medicine is practised in the United Kingdom and must understand human development and areas of psychology and sociology relevant to medicine including growing old (item (34))

Table 3 Benchmarks for medical education relevant to the care of older people (Quality Assurance Agency for Higher Education, 2002)

1. Graduates will demonstrate knowledge and understanding of
   (a) the different stages of the life cycle and how these affect normal structure and function (item 4.2(b))
   (b) impairment, disability, and handicap and the principles of rehabilitation (item 4.2(j))
   (c) epidemiological principles of demography and biological variability (item 4.2(o))
2. Core competencies: the graduate will be able to
   (a) undertake a relevant and systematic physical and mental examination in a sensitive manner appropriate for age. (item 6.2(1b))
3. Demonstration of competency:
   (a) Graduates should be capable of giving appropriate input into the multidisciplinary and multiprofessional teams involved in the management of patients in need of rehabilitation or palliative care, including the care of the dying (item 6.3(4))

outcomes, and the most extensive published description of assessment methods. These documents are all of great value in medical education and influential in curriculum development. In all cases, they look at the medical curriculum as a whole and do not mention specific disciplines or traditional university departments. Throughout all the documents, however, the principles of the care of older people appear and these allow the medical schools to ensure that education in aging and the care of older people is adequately represented in the curriculum.

It is essential that medical schools should have a lead for education in aging and the care of older people, whether as part of an academic department or in some other form, to ensure that the subject is adequately covered in the curriculum and that all doctors have basic knowledge of the subject. In addition to covering basic knowledge and skills, the course should enthuse students in the importance of the care of older people and encourage some to consider specializing in this branch of medicine.

BASIC MEDICAL EDUCATION

The Approach

The first task is to define a core curriculum – the essential knowledge, skills, and attitudes which all newly qualified medical practitioners must attain. This is expressed as outcomes. Because of its relatively recent introduction into medical education and the small amount of curricular time which is usually allocated to it, a core curriculum in geriatric medicine has already been defined (Stout, 1985).

The curriculum is "problem based", that is, learning is centered around clinical problems. Thus, when learning about the aging process, students might study the case history of an older person, or a life history, perhaps in written form or on video. In this way, the relevance of basic science to clinical practice can be demonstrated. The curriculum is "student centered" rather than "teacher driven". The emphasis is on learning rather than teaching and students are helped and guided to learn, with academic staff acting more as facilitators than teachers. Good clinical teachers are used to guiding students on how to learn from the patients they have seen.

Clinical teaching takes place in both the hospital and the community. Although teaching in the community is often considered to be the remit of general practice, other disciplines, such as psychiatry and geriatric medicine, extend beyond the hospital. The movement of teaching into the community is driven by two forces – the fact that much medical practice and the work of the majority of doctors takes place outside hospital, and changes in hospital practice, such as shortened lengths of stay, the increasing use of day procedures and the increasing specialization of hospital practice, which have changed the clinical profiles of hospitals in ways which make traditional clinical teaching difficult. Geriatric medicine with its hospital base and community outreach is well placed to lead new educational strategies combining hospital and community based clinical teaching. Multiprofessional education, with students of medicine, nursing, the allied health professions, and social work being taught together is also very appropriate for geriatric medicine.

CURRENT TEACHING OF GERIATRIC MEDICINE

Because of concern that the previous gains that had been achieved to ensure that aging and geriatric medicine were incorporated within the undergraduate curriculum were in danger of being lost, in 2004 the Education and Training Committee of the British Geriatrics Society undertook a survey of teaching geriatric medicine in UK medical schools. Questionnaires were sent to Deans or Heads of UK Medical Schools, members of the British Geriatrics Society Education and Training Committee, and Heads of Departments of Geriatric Medicine or their equivalent. Although the response was incomplete, the survey gave a useful snapshot of the place of geriatric medicine in UK medical curricula (Crome *et al.*, 2004). In all except one of the universities that responded, geriatric medicine is taught to all undergraduates. Human aging is also taught in many medical schools, most often as part of teaching in physiology, but also in social sciences and psychiatry. In most cases, the curriculum is organized and coordinated by a professor or senior lecturer in geriatrics although in some medical schools other academic staff or NHS consultants do this. Three-quarters of heads of departments felt that geriatric medicine should be taught as a separate subject although a few thought it could be linked to other subjects. Many also thought that nongeriatricians, including general physicians, general practitioners, psychiatrists, clinical pharmacologists, and therapists, could also teach geriatric medicine. Most felt that sufficient teaching time was allocated to the subject and that every student should be examined in geriatric medicine. In most cases, classical teaching methods of patient contact, lectures, and tutorials are used but about 50% of the medical schools that responded use problem-based tutorials. Geriatric medicine is taught in virtually all the clinical sites where it is practised. In about one-third of medical schools, undergraduates spend time in nursing home placements. One university was about to start a pilot program of multiprofessional education of medical and nursing students in geriatric medicine. There was a strong feeling that examinations should be clinically based, either during the course or at a final examination, and that geriatric medicine should be examined in association with other subjects. In most medical schools, geriatricians take part in the examination.

CURRICULUM DESIGN

Curriculum design must consider the educational outcomes, the educational program, assessment, and evaluation (Leinster, 2003a). Assessment differs from evaluation in that the

former is concerned with the performance of the students, while the latter is a measure of how the program meets its objectives.

Educational Outcomes

Outcomes are statements of what students should be able to do at the end of a course of study which they could not do initially; they imply the testing of the effectiveness of the teaching course in terms of the achievement of these outcomes (Irwin *et al.*, 1976). Thus, an outcome describes what students should be able to do in order to demonstrate that they have acquired a required level of competence. Outcomes allow those involved in the different aspects of the curriculum, planning, teaching, learning, assessment, and evaluation, to have a framework within which they can design the teaching program and methods of assessment. Both teacher and student can be aware of the aims of the course and they are able to judge progress against these aims.

Outcomes in medical education cover knowledge, skills, and attitudes. In the past, attention was mainly paid to acquisition of knowledge – now more attention is paid to skills and attitudes. The whole can be incorporated into the concept of competence – the combination of knowledge, skills, and attitudes that enables the individual to practice medicine.

There are a number of reasons why a statement of educational outcomes is desirable. First, failure to state precise teaching outcomes permits and promotes unclear thinking and lowers the quality of learning. Second, identification of outcomes is a prerequisite for setting evaluative criteria. Third, only when outcomes are behaviorally stated, is it possible to determine whether they are trivial or not. When constructing outcomes, it must be emphasized that only outcomes which are intended and measurable are worth stating. Unanticipated outcomes from the course which distort the achievement of stated objectives require to be identified and incorporated into the stated outcomes. Thus, a process of "hard inventive thinking" is necessary in the construction of these outcomes (Irwin *et al.*, 1976).

Outcomes for basic medical education that have been subjected to "hard inventive thinking" are those from Queen's University Belfast (Stout and Bamber, 1979) (Table 4). Other lists of outcomes have been published, most notably those which were agreed at a World Health Organisation workshop in Edinburgh in 1982 (World Health Organisation, 1982) (Table 5). Although these outcomes were drawn up by a group of people who had experience in teaching gerontology and geriatric medicine, they were not subjected to the rigorous analysis suggested by specialists in education. Nevertheless, they correspond quite closely to the Belfast outcomes. Other published outcomes have been reviewed elsewhere (Stout, 1985). Common topics in all the published outcomes include:

demography of aging;
the aging process;
the presentation of disease in old age;
management of illness in older people;
attitudes to old age.

Any educational program in geriatric medicine must cover at least these topics.

The Educational Program

The educational program should be student centered and problem based. Geriatric medicine is ideal for problem-based learning as the essence of geriatric practice is the identification and resolution of problems presented by patients. The nonspecific nature of the problems allows wide-ranging discussion and hence a broad educational experience. The "giants of geriatrics" identified by Isaacs (1992) – immobility, instability, incontinence, and intellectual impairment – cover a wide range of diagnostic and management possibilities and would provide the basic list of problems on which the program would be based. A detailed medical undergraduate curriculum in geriatric medicine has been published by the British Geriatrics Society (British Geriatrics Society, 2004).

Teachers

Ideally, teachers of geriatric medicine should be engaged in clinical practice in the medical care of older people. In this way, they will have the knowledge, skills, and attitudes to the health care of older people that will be an example to the students. However, it is not sufficient for teachers to

Table 4 Educational outcomes in geriatric medicine of Queen's University Belfast (Stout and Bamber, 1979)

A Knowledge
The student should understand
1. the epidemiology of aging and its implications
2. the normal aging process and its relationship to disease and disability in old age
3. the pattern and presentation of disease in old age
4. the interaction of physical, mental, and social factors in the production of disease and disability in old age
5. the purpose, facilities, and organization of hospital care of elderly patients
6. the role, availability, and organization of community services in the care of elderly people
7. the prevention of dependency in old age
8. ethical issues in the care of elderly people

B Skills
The student should have the following skills:
1. the assessment of disease and disability in older people
2. the principles of management of elderly patients
   (a) the value and limitation of investigation procedures
   (b) the appropriate use of drugs
   (c) rehabilitation
   (d) continuing care
   (e) terminal care
   (f) the value of the multidisciplinary health-care team
3. Communication with older people, both those who are healthy and those who have communication difficulties

C Attitudes
The student should have an attitude of optimism in the care of elderly people

Table 5 WHO learning outcomes in gerontology and geriatric medicine (World Health Organisation, 1982)

1. A humane and positive attitude toward old people and to demonstrate the satisfaction and fulfillment which comes from professional involvement with the elderly and their families
2. An understanding of demographic factors and social changes in the aging of societies
3. An understanding of age-related changes in the context of human development and an appreciation of the causes of disability in old age; prevention and management of disability should be understood within both community and institutional settings
4. An understanding of the special features of presentation of disease in old age and the problems of therapy. The problems associated with drug therapy in old age require special consideration
5. An understanding of the principles of rehabilitation and their application to the elderly, a major objective being the attainment and maintenance of optimum physical, social, and mental function for each individual
6. An understanding of the importance of working as a member of a multidisciplinary team, with full understanding and appreciation of the roles and skills of physicians, nurses, rehabilitation therapists, social workers, and other team members
7. An understanding of the importance of acquiring skill in communicating effectively with the elderly and those involved in their care. This should be done in such a way as to lead to fuller understanding of the importance of the family and the social network of care
8. An understanding of the importance of protecting the liberty of the individual, so that the elderly may retain maximum choice and control over their own lifestyles and the manner in which they face death
9. An understanding of services available to old people and their families, with special emphasis on community aspects, and to stress the essential interdependence of these services and the need for effective cooperation between them and families and other carers
10. An understanding of principles and responsibilities of continuing care for elderly patients with irremediable disabilities, and of terminal care of dying patients

be skilled in their clinical discipline – they must also be trained in modern educational methods. Staff development is an essential component of every medical school, and the aim should be that all teachers, whether they hold positions in universities or in the health service, should have undertaken a course in educational methods.

For the effective teaching of geriatric medicine, an academic discipline is ideal. This allows academic teachers time to develop programs and teaching skills. It also allows teaching to take place in a setting of research, the essence of university education. "Academic geriatric program leaders must be excellent clinicians, consummate generalists, superb teachers and outstanding, fully competitive researchers. Anything less risks second-class status for geriatrics" (Hazzard, 1994). Close cooperation with related academic disciplines is essential, particularly with general (internal) medicine, general practice, psychiatry, and public health medicine.

The Teaching Setting

Geriatric medicine is a practical clinical subject and is best taught in a clinical setting. This will be the hospital and community facilities for the care of older people, and will include visits to care homes and the homes of older patients, for example, during assessment visits. Teaching should not be confined to statutory services – voluntary and private sector facilities can give a different view of old age. There is a danger that the use of medical and nursing settings, the most convenient for curriculum planners to organize, may give students a view of old age that emphasizes ill-health, disability, and dependency. It is essential that students gain a balanced view of old age, and learn that for many people old age is a time of good health and independence It is possible to use families of patients and attenders at community facilities to illustrate healthy old age. This concept can be introduced early in the medical course. As care in the community is one of the educational objectives for geriatric medicine, teaching cannot be confined to the hospital. Students must have the opportunity to learn about domiciliary care of dependent older people by observing it in action. As at least half of the medical students will become general practitioners, the care of older people outside the hospital is particularly relevant.

Analysis of clinical problems, with the student using all resources available, including the library and members of the health-care team acting as a resource of expertise, is the preferred learning technique. Thus the teaching setting must have space for discussion and for learning, and access to information and expertise.

Learning Systems

Surprisingly, the British Geriatrics Society survey (Crome *et al.*, 2004) showed lectures as a common teaching method. There should be little place for formal lectures in teaching a practical clinical subject. If used at all, lectures should be few in number, and should act as signposts or "roadmaps", giving an overview of the subject, putting it in context. Lectures should never be used to impart large amounts of factual information.

Student-centered, problem-based directed self-learning is ideally suited to education in geriatric medicine. Study guides direct the students' learning by providing sample case histories, key questions to be answered, and advice on how to obtain information, for example, from studying patients, consulting written information, for which references are given, or experts. Study guides also include self-assessments to allow students to measure their progress. Study guides can be conveniently combined with log-diaries. In these, students are provided with a list of experiences to be encountered and procedures to be undertaken and they keep a record of what has been achieved. They would normally be countersigned by a teacher.

Study guides and log-diaries allow students to take control of their own education, while giving them confidence that they are covering the right topics and neither omitting important material nor learning unnecessary detail. Although study guides and log-diaries are usually in written form, they can be computerized, and students may base their education on programs on personal computers.

Study guides and log-diaries do not remove the need for teachers, but require a different type of teaching. Instead of the teacher delivering information, teachers facilitate learning, with regular meetings of small groups of students

reporting on their learning experiences, and being guided on future learning. Teachers function as catalysts and educational resources but do not necessarily control the teaching session. Changing from delivering information to facilitating learning is a major process and staff development is necessary before these teaching methods can be introduced.

The Content

Of the educational program in geriatric medicine is based on the outcomes described earlier in this chapter, modified according to time and facilities available and adapted to the needs of the entire medical curriculum. There is considerable scope for collaborative teaching in geriatric medicine. For example, the topic of rehabilitation may be covered in collaboration with specialists in rehabilitation medicine, rheumatology, orthopedic surgery, and psychiatry as well as in geriatric medicine. It is essential that there is coordination and central control of the curriculum so that important topics are neither inadvertently omitted nor duplicated in an unplanned way. Topics such as rehabilitation involve many disciplines and can be used for multidisciplinary learning as a preparation for working in a multidisciplinary team.

Evaluation

Evaluation of an educational program covers three aspects – the performance of the students in terms of the educational outcomes; the performance of the program in terms of the outcomes; the quality of the educational experience.

Assessment of Students

It may be regrettable but it is true that student learning is driven by assessments (Leinster, 2003b). Most students do not take seriously a program that does not have an assessment, and the students' expectations of the standard and content of the assessments has a major influence on their learning. Appropriate assessments are therefore an essential component of any educational program. The usual way of assessing educational outcomes is to test the students' knowledge and skills to appropriate standards (Leinster, 2004).

There is a wide variety of assessment methods available. The method chosen must be appropriate for the objective to be tested. Reproducibility and consistency in marking are other important attributes of any assessment method. When different attributes are to be tested, a combination of methods is often used. Traditional methods of assessment in medical education include written, both essay and multiple-choice papers, clinical and oral examinations. A written assessment of knowledge of geriatric medicine has been described (Lee *et al.*, 2004).

The objective structured clinical examination (OSCE) (Harden and Gleeson, 1979) combines clinical, oral, and written examinations in a test of clinical competence. All students sit the same examination. They move through a series of "stations", usually about 20, and spend about 5 minutes at each. At the stations, they may be asked to perform a procedure such as taking a clinical history, carrying out a clinical examination, or answering questions on treatment, photographs, medical images, or the results of laboratory investigations. Examiners are present at some stations and observe the students' performance, while students are left to write their answers at others. Simulated patients or plastic models can be used for testing clinical skills, as the OSCE is demanding on real patients. The OSCE requires careful preparation, the availability of suitable space and is intensive in its use of staff. However, large numbers of students can be examined in a relatively short time and the results are available almost immediately. It has the advantage of standardization and is relatively efficient in the use of examiners' time.

Separate assessments do not have to be held for each individual discipline in the medical curriculum, and there are both theoretical and practical reasons for combining assessments. By combining clinical subjects, the assessment can become more analogous to the clinical encounter where the doctor is faced with patients who are unclassified with respect to speciality and who may have multiple problems, physical, psychological, and social, involving many systems.

Assessment of the Educational Program

In the United Kingdom, the quality of university teaching is regularly assessed, both by the universities themselves and by external bodies. An important measure is the students' opinion of the course, assessed by questionnaire. It is important that students' opinions are sought on educational programs. Every part of the program will not be popular with every student. However, deficiencies which might otherwise remain undetected can be identified.

Attitudes

One of the educational outcomes is "to have an attitude of optimism in the care of older people". It is not possible to test this objective adequately in any form of assessment of student performance, and special surveys have to be undertaken. It has been shown in the past that many medical students, doctors, and other health professionals have negative attitudes toward old people. Well-designed educational programs in geriatric medicine may improve attitudes toward elderly people. Although a number of surveys of medical students' attitudes have been carried out, few have tested the influence of modern educational programs on attitudes.

The effect of teaching geriatric medicine on medical students' attitudes to older people was studied in Edinburgh (Deary *et al.*, 1993). Attitudes became more positive from first year to the clinical years, and improved further as a

result of the geriatric medicine course. Although women had slightly lower scores for negative attitudes, the extent of the changes across the groups did not differ between the sexes. Contrary to the reports of some previous studies, the attitudes of the Edinburgh medical students were not unduly negative. Similar positive effects of a geriatric medicine course on attitudes to old people were reported in the United States (Bernard *et al.*, 2003).

The available evidence suggests that current educational programs in geriatric medicine have positive effects on the attitudes of medical students to old age. It is essential that any innovative programs should be tested for their effects on attitudes.

SPECIALIST EDUCATION

Specialist education in geriatric medicine covers training in the discipline for those whose careers will be in other specialities, including general practice, and training for those who will practice geriatric medicine either exclusively or in combination with general (internal) medicine. Until relatively recently, training has largely consisted of gaining clinical experience in hospital departments practising high standards of care (hence the term "training" rather than "education"), but training is becoming more formal and curricula are being developed.

Educational outcomes, programs, and evaluation for specialist training in geriatric medicine have been described but have not been as carefully analyzed as those for basic medical education. Before entering higher training, the trainee will have completed the 2 foundation years immediately after graduation and spent 2 or more years as a Senior House Officer gaining experience in a variety of medical specialities, including geriatric medicine (Ives, 2003). In the United Kingdom, the responsibility for devising programs for higher medical training rests with the Joint Committee on Higher Medical Training (JCHMT) which has a series of Specialist Advisory Committees (SACs), one of which is for geriatric medicine. The JCHMTs curriculum for higher medical training for geriatric medicine (Joint Committee on Higher Medical Training, 2003) sets out the requirements for the 5-year training period in the speciality (Tables 6 and 7) against a specification of generic skills which are relevant to all medical specialities (Table 8). At the end of the training period, the trainee, who has achieved an appropriate level of knowledge, skills, and competence, will be awarded a Certificate of Specialist Training (CST), which is a prerequisite for appointment as a consultant in the NHS.

Table 6 Primary learning objectives for specialist training in geriatric medicine (Joint Committee on Higher Medical Training, 2003)

1. Perform a comprehensive assessment of an older person, including mood and cognition, gait, nutrition, and fitness for surgery in an inpatient, outpatient, day hospital, or community setting
2. Diagnose and manage acute illness in old age in an inpatient setting and community setting where appropriate
3. Diagnose and manage those with chronic disease and disability in an inpatient, outpatient, day hospital, and community setting
4. Provide rehabilitation with the multidisciplinary team to an older patient in an inpatient, outpatient, day hospital, and community setting
5. Plan the discharge of frail-older patients from hospital
6. Assess a patient's suitability for and provide appropriate care to those in long term (continuing care) in the NHS or community
7. Assess and manage older patients presenting with the common geriatric problems (syndromes) in an in- or outpatient setting (or where appropriate, in a community setting):
   Falls with or without fracture
   Delirium
   Incontinence
   Poor mobility
8. To demonstrate an appropriate level of competence in the following subspecialities:
   Palliative care
   Orthogeriatrics
   Old age psychiatry
   Specialist stroke care
9. To be familiar with basic research methodology, ethical principles of research, comprehensive scrutiny of medical literature and preferably to have personal experience of involvement in basic science or clinical (health services) research

Table 7 Core knowledge areas for specialist training in geriatric medicine (Joint Committee on Higher Medical Training, 2003)

Basic science and gerontology
Common geriatric problems (syndromes)
Presentations of other illness in older persons
Drug therapy
Rehabilitation in older persons
Discharge planning and ongoing care
Education
Research and audit
Ethical and legal issues
Management
Health promotion

Table 8 Generic skills for specialist training in all medical specialities (Joint Committee on Higher Medical Training, 2003)

- Good clinical care
- Communication skills
- Maintaining good medical practice
- Maintaining trust
- Working with colleagues
- Team working and leadership skills
- Teaching
- Research
- Clinical governance
- Structure and principles of management
- Information use and management
- Cross speciality skills

CONCLUSION

Geriatric medicine is an essential component of basic medical education. Educational programs must adapt to new educational philosophies, while other disciplines can learn from some of the innovations introduced by geriatric medicine. While basic medical education is well established, outcomes, programs, and evaluation of specialist training in the discipline require further study.

KEY POINTS

- Medical education has undergone radical change in recent years and department based teaching is no longer the norm.
- Education in aging and the care of older people is essential for all health and social care professionals.
- Geriatric medicine is an ideal subject for problem-based learning.
- Assessment methods must be chosen to test the desired educational outcomes.
- Academic geriatric medicine, combining education, clinical practice, research, and innovation must be strengthened.

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The Contribution of Family Doctors to the Primary Care of Older People: Lessons from the British Experience

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Based in part on the chapter 'The Contribution of Family Doctors' by Steven Iliffe, Joseph J. Gallo and William Reichel, which appeared in *Principles and Practice of Geriatric Medicine*, 3rd Edition.

INTRODUCTION

Population aging, escalating costs in pensions, health care, and long-term care has prompted the emergence of a new policy agenda for active aging and improved quality of life in old age in all industrialized countries. Family doctors are often seen as being well placed to implement some of the health-related elements of this new agenda, particularly around health promotion, disability reduction, and chronic disease management. Frequent contacts between older people and their family doctor, knowledge of the individual patients accumulated by their physicians over long periods of time, and the presumed skill of generalists in integrating biomedical, psychological, and social perspectives on illness and disability should, when combined, allow family doctors to function as community geriatricians. The role for the family physician and general practitioner is, therefore, potentially great.

However, actual experience of primary care for older people suggests that there are significant obstacles to systematic application of the new policy agenda, both in systems where general practitioners function as gatekeepers to specialist services (the Anglo-Scandinavian model) and in those where generalists and specialists compete in the community (the US and predominant European model). These obstacles include a broad range of attention across all age groups that can exclude older people, a largely reactive medical culture that favors the younger, less tolerant, and more articulate cohorts, high caseloads that militate against in-depth or complex assessments, and significant gaps in the knowledge and skills of practitioners that reduce the potential for multifaceted interventions. The actual role for family doctors in promoting healthier aging and the optimal division of labor between them and specialists in medicine for older people are both open questions.

In policy terms, this uncertainty is one example of a broader theme that preoccupies policy makers and health-care managers; should unmet need be met by creating new, dedicated, specialist outreach services, or by changing the practice and performance of existing disciplines? This article explores these issues, using the historic evolution of primary care for older people in the United Kingdom as an example. In my view, the British experience of encouraging primary care for older people has important lessons for family doctors everywhere, because both primary care and specialist medicine for older people are well-developed disciplines and function within a complex policy framework on aging.

In the United Kingdom, the government has made a commitment to improve services for older people through combating age discrimination, engaging with older people, better decision making for services for older people, better meeting of older peoples' needs, and promoting a strategic and joined up approach. A draft of policy initiatives not only set the tone for service reconfiguration but also specified objectives and timescales. The most important of these is the National Service Framework for Older People (NSFOP) (Department of Health, 2001a), an ambitious 10-year plan to transform health and social care services for an aging population (*see* **Chapter 161, Health and Care for Older People in the United Kingdom**). At the same time, a controversial and fundamentally flawed policy, the promotion

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of annual "checks" for those people aged 75 and over through general practice, has ended. This shift in policy also acknowledges the obstacles to developing primary care for older people and seeks ways to overcome them. As a contribution to this debate, I will suggest three related areas where efforts to change service delivery within communities may produce rapid gains – health maintenance and promotion in primary care, fostering a culture of case management amongst family doctors, and a new, multidisciplinary approach to medication review.

LEARNING FROM POLICY MISTAKES

A new contract for general practice in the United Kingdom, introduced in April 2004, has quietly deleted the contractual obligation to offer annual assessments of health to all people aged 75 and over, ending 13 years of ill-conceived policy based on thin science. The "75 and over checks" were introduced in 1990, without plausible evidence of health gain from such an approach and despite the objections of family doctors, and in practice were widely ignored. The UK government became the first to introduce a nationwide primary care–based screening program for older citizens, and has been followed by others in Europe, mesmerized by the rising demographic tide. There is much to be learned from this policy error, and as always the devil is in the details of conception and implementation.

Experimentation with population screening and assessment by different methods like postal questionnaires, specialist nurses, case-finding computer software, and dedicated clinics, and the search for "at-risk" groups were reflected in the debates that occurred both in the Royal College of General Practice and in the Health Visitors Association in the 1970s and 1980s. Although general practitioners dominated the reporting of the approaches to primary care for older people, health visitors pioneered much of the actual work on the ground, and the underlying ideas came as much from community nursing as from medicine (Taylor and Buckley, 1987).

These early studies explored the best ways to provide anticipatory care for older people, and acknowledged the iatrogenic risks of treating unimportant abnormalities and medicalizing old age. Brief, nonintrusive strategies for predicting functional problems during routine consultations were sought and tested in randomized controlled trials. The preoccupation of doctors with disease to the detriment of its social consequences, the failure to take into account the adaptive powers of older people, and the tendency to underestimate the burden borne by carers were all identified as major obstacles to progress in developing more effective primary care for older people. Medical and social problems overlapped in ways that were often puzzling to clinicians; screening led to an increase in referrals to other agencies but without clear evidence of benefit in many instances, and with variations in referral rates determined as much by the referrer as by the patient's problems. Finally, at-risk groups proved harder to identify than anticipated, for more pathological events occurred outside the expected at-risk groups than in them. The generation of general practitioners and nurses which did this work introduced important ideas about how aging in its organic, social, and psychological dimensions affected people's health, how essential multidisciplinary teamwork was to providing appropriate care for ill older people (Williams, 1995), and ultimately how networking with community-based agencies was a more useful model than referral to specialist care (Williams and Wallace, 1993).

Several such trials took place in the 1980s in the United Kingdom, Denmark, and the United States. Different trials used very different interventions and outcome measures, but there are some common features (Stuck *et al.*, 1993):

- a rise in morale amongst elderly people involved in screening programs;
- referrals to all agencies tended to increase, including to specialist medical care in some studies;
- the duration of in-patient stay fell in some studies, possibly through early intervention in disease processes;
- in-patient rates could increase through a greater use of respite care;
- reduction in mortality did occur in some trials, perhaps for the same reason that in-patient stays declined, but not in all;
- no trial up to 1990 demonstrated an improvement in older people's functional ability, and general practitioner workload only decreased in situations where alternative services were organized to bypass existing primary-care services.

In 1990, the UK government unilaterally changed the conditions of service for general practitioners, introducing a contractual obligation on members of primary health-care teams to offer annual assessments of health to patients aged 75 and over. These offers of assessment, which had to be made in writing, should be based on a home visit unless otherwise requested by the patient, and should include the following headings:

- *sensory function*
- *mobility*
- *mental condition*
- *physical condition including continence*
- *social environment*
- *medication use*

It was unclear what was intended when the contract for general practice was changed to include this obligation, but it was widely interpreted as a requirement to screen the 75 and over age group. As argued earlier, while there had been extensive research into the possible benefits of regular screening or assessment of older people, at the time of the introduction of the 75 and over checks there was still a lack of conclusive evidence that routine screening of whole populations was worthwhile. Nor was there a consensus on the best methods for such a screening approach, despite nearly 40 years of study (Harris, 1992). Many aspects of the elderly screening program built into the new GP contract

therefore lacked a scientific basis, and its implementation was similarly ill-conceived. Undoubtedly the lack of a plausible evidence base and the lack of guidance on how to carry out the 75 and over assessments added to their unpopularity with general practitioners and led to piecemeal and often unenthusiastic implementation of the program (Brown *et al.*, 1992). Where assessment tasks were undertaken at all, they were delegated to practice nurses and were given low priority by the local health service administration (Chew *et al.*, 1994), which (with a few exceptions) provided neither leadership nor training for the program, nor policed its implementation.

In response to the criticisms of this policy, the UK's Medical Research Council (MRC) funded a trial (Fletcher *et al.*, 2002) comparing universal versus targeted assessments, and management by primary-care teams versus a multidisciplinary geriatric assessment team, in order to strengthen the evidence base. The MRC trial, therefore, was launched in a situation where evidence and policy were divorced and risked becoming the intellectual underpinning for shaky policy foundations in which there was little evidence of balanced equipoise in scientific thinking. Critics of the emphasis placed on the randomized control trial (RCT) as an evaluation technique might have used this study as an example of an experimental method applied to the wrong question. The trial team escaped from this awkwardness by developing a complex design that tested an idea not yet enshrined in UK policy, comprehensive geriatric assessment, as well as evaluating different forms of brief assessment.

COMPREHENSIVE GERIATRIC ASSESSMENT

The evidence base for the United States approach to comprehensive geriatric assessment is richer than that for the screening approaches used in the United Kingdom (Stuck *et al.*, 1993). In summary (Stuck *et al.*, 2004), reductions in nursing home admissions appear to depend on multiple follow-up home visits. A recent meta-analysis of home-based visiting programs that offered health promotion and preventative care to older people suggested that it was associated with a reduction in mortality and admission to institutional care (Elkan *et al.*, 2001). Programs with several visits per year reduced admissions by about a third. This is probably related to the timely detection of new problems: repeated annual assessments detected on average two new medical and one new psychosocial problem per person per year. Programs offered to the younger old (from 65 to 74 years) reduced mortality by 24%, whereas in older study populations no mortality reduction was seen. Finally, programs based on multidimensional assessments prevent deterioration in functional status, which indicate that the reduction of nursing home use is not related to a shift of long-term care from institutions to the community, but to a genuine preservation of functional ability. However, it was uncertain which components of the home visiting activity were beneficial or which populations were most likely to benefit (Egger, 2001).

THE MRC TRIAL

The MRC Trial of the Assessment and Management of Older People in the Community randomized 109 general practices and investigated whether universal assessment was more effective than targeted assessment, and whether it mattered who subsequently cared for the patients in whom problems were identified – a geriatric or primary-care team. In the targeted arm, only persons who reported a prespecified range of problems were invited to have a detailed multidimensional assessment, whereas in the universal arm everyone was invited to undergo the detailed assessment. The specificity of the screening questionnaire was high, but the sensitivity was below 50% for all dimensions: at least half of the problems were missed at the screen. The results on mortality and hospital admissions were disappointing, with few differences after 3 years of follow-up. Universal assessment was associated with a 17% reduction in institutional admissions, but this failed to reach prespecified levels of statistical significance. There were small gains in quality of life, and specialist assessment seemed to offer little benefit over family doctor assessment, a gratifying result for primary care offset by the limited gains made by any form of assessment. The findings are compatible, therefore, with previous trials of preventive home visits in older persons (Stuck *et al.*, 2002a). The following seem reasonable conclusions to draw from this study, the largest trial of primary care-based geriatric assessment ever conducted: (1) a simple screening questionnaire does not identify a target group effectively (2) preventive multidimensional geriatric assessment does reduce the risk of nursing home admissions, (3) programs based on single assessments are less effective than those with repeated assessments and long-term follow-up and (4) the primary-care team can manage problems as well as the geriatric team.

Where does this leave primary care for older people? We now know that management follow-up after assessment matters, even if we do not know how to target those most likely to benefit. There is still a need for a shorter, practical, primary-care friendly tool that builds on existing information, focuses on unmet needs (Crome and Phillipson, 2000), and can be used to trigger a comprehensive assessment process. Readers can judge for themselves whether this was not known two decades ago, while family doctors can now think about how they can incorporate comprehensive assessment and management packages into their workload. Here the latest policy development in the United Kingdom may help them, if only by offering a framework for thinking and experimentation.

THE NATIONAL SERVICE FRAMEWORK FOR OLDER PEOPLE (NSFOP)

The NSFOP is the key policy guidance for health and social care services and outlines a 10-year program of

action. It advocates coordination of services to support independence and promote health, specialized services for key conditions, and a cultural change that fosters treatment of older people and their carers with respect, dignity, and fairness. Addressing ageism in public services is seen as an integral component of the modernization of health and social care services, and rooting out age discrimination is the first standard in the NSFOP. Through out the document "older people" are regarded as a heterogeneous group, with particular emphasis on the needs of ethnic elders, and it advocates that all services reflect the diversity of the population they serve, including the needs of carers.

The NSFOP addresses four themes with eight standards flowing through them. Amongst other functions, these standards address conditions particularly significant for older people, which are not covered in other National Service Frameworks: stroke, falls, and mental health problems associated with old age. The themes and standards are shown in BOX 1.

BOX 1

Theme 1: Respecting the Individual

Standard One: Rooting out Age Discrimination

National Health Services (NHSs) will be provided, regardless of age, on the basis of clinical need alone. Social care services will not use age in their eligibility criteria or policies, to restrict access to available services.

Standard Two: Person-centered Care

NHS and social care services should treat older people as individuals and enable them to make choices about their own care, achieved through: the single assessment process (SAP); integrated commissioning arrangements; integrated service provision; and including community equipment and continence services.

Theme 2: Intermediate Care

Standard Three: Intermediate Care

Older people will have access to a new range of intermediate care services at home or designated care settings, to promote their independence by providing NHS and LA services to prevent unnecessary hospital admission and rehabilitation services to enable early hospital discharge and prevent admission to long-term residential care.

Theme 3: Providing Evidenced-based Specialist Care

Standard Four: General Hospital Care

Older people's care in hospital is delivered through appropriate specialist care and by hospital staff who have the right set of skills to meet their needs.

Standard Five: Stroke

The NHS will take action to prevent strokes, working in partnership with other agencies where appropriate. People diagnosed with having had a stroke are managed by a specialist stroke service, and with their carers, participate in a multidisciplinary program of secondary prevention and rehabilitation.

Standard Six: Falls

The NHS, working in partnership with councils, acts to prevent falls and reduce resultant injuries in older people. Older people who have fallen receive treatment and rehabilitation and, with their carers, receive advice on prevention through a specialist falls service.

Standard Seven: Mental Health Services

Older people who have mental health problems can access integrated mental health services, provided by the NHS and councils to ensure effective diagnosis, treatment, and support for themselves and their carers.

Theme 4: Promoting an Active, Healthy Life

Standard Eight: the Promotion of Health and Active Life in Old Age

The health and well-being of older people is promoted through a coordinated program of action led by the NHS with support from councils. This standard is linked to the national public health agenda cited earlier.

The NSFOP creates opportunities for enhancing the quality of primary care for older people, and general practitioners and primary-care nurses with a specialist interest in aging and health may catalyze change at local level. In particular, the SAP, designed to ensure that older people receive *"appropriate, effective, and timely response to their health and social care needs in an integrated way"* (Brown *et al.*, 2003) calls for the introduction of a comprehensive assessment process. However, the lessons from previous policy and implementation in this arena raise two issues that still need

to be addressed. The first is how to target clinical attention on the often complex problems of comorbidity to maximum effect in an aging population that is not homogeneous but is as diverse as younger cohorts, without lapsing into a culture that delegates the tasks to insufficiently trained nurses who follow a check-list approach to health needs assessment.

The second issue is the problem of collaboration across professional and agency boundaries. Although the MRC trial suggests that generalists perform as well as specialists, long-term management of complex problems in older people will inevitably rely on good working relationships between disciplines and organizations. There are many challenges in implementing a public-service policy that advocates collaboration between sectors to address both broad quality of life issues as well as prevention of ill health. The complexities of health and social care partnership working at an organizational level are well documented (Balloch and Taylor, 2001), as are those at the service delivery level (Manthorpe and Iliffe, 2003), constituting a "*pessimistic tradition*" (Hudson, 2002) in inter-professional working. There is a risk that the well-intentioned plans of the NSFOP could remain aspirations for lack of careful thought about how to change services in a policy environment that tries to innovate at ever greater speed.

How can this be prevented? Expanding on arguments summarized elsewhere (Iliffe and Drennan, 2005), I propose that three areas of activity now deserve particular attention in primary care; a systematic evidence-based approach to promoting well-being in older people, the development of a case-management culture, and the organization of medication reviews using the expertise of doctors, local pharmacists, and primary-care nurses. Our knowledge in these three areas varies from a reasonably high level of certainty in the clinical domains of health maintenance and promotion to considerable uncertainty in both case management and medication review. Although these activities can be put to test in Britain in a way that may not yet be possible, across whole populations at least, in other countries, this next round of experimentation in primary care for older people can draw upon international experience and also inform it. In particular, we may be able to answer questions about how much of these tasks can be undertaken by generalists working in primary care, and how much will depend on specialist activity in the community.

HEALTH PROMOTION

The NSFOP explicitly demands for the first time that the NHS and local authorities in partnership agree on programs to promote health in the aging and to prevent disease in older people. These programs were expected to improve access for older people to "mainstream" health promotion services and also develop *"wider initiatives involving a multisectoral approach to promoting health, independence, and well-being in old age"*.

Policy makers, researchers, and practitioners have neglected health promotion and illness prevention with older people (Victor and House, 2000) and the evidence base for preventive services and anticipatory care for older people is small and inconclusive. While the evidence base is being extended, family doctors have little choice but to take a "best buy" approach to health promotion with older people, focusing on the most tractable clinical problems. Given the effort required for population screening and the relatively limited benefit gained, targeted case-finding and health promotion activities combined with techniques of case management may be an effective way forward, emphasizing the diagnostic role of the family doctor in case-finding, and the case-management role of the primary-care nurse. Case-finding is different from population screening because it relies on the encounters between older people and their family doctors to identify unmet needs. In turn, this requires the physician to routinely incorporate enquiries about health needs into consultations, just as blood pressure checks (for younger adults) are now part of routine practice. Information obtained routinely then needs to be incorporated into medical records, in a way that both prompts later review and stimulates the collection of a full profile of health-related behaviors, risks, and needs over time and in the course of sequential encounters. Advocates of whole population screening conclude that their approach has been shown to be beneficial, and they are right that the trials do demonstrate some positive (if modest) outcomes and some potential health service savings. The weakness of their argument is that the external validity of trials of complex interventions is relatively poor, since mainstream services do not perform over the long term in the same way as practitioners engaged in short-term and often highly reinforced research trials. Reengineering services toward screening whole populations of older people may not prove to be cost effective at all, while modification of routine practice, although difficult to achieve quickly, may be more durable and effective.

The case-finding approach needs to be limited in its scope – nobody can do everything – and the clinical domains discussed here are common, important, and tractable problems (Iliffe *et al.*, 2005) identified in the preparation of an evidence base for a European study of health risk assessment in older people (Stuck *et al.*, 2002b). Eighteen clinical domains where the evidence for beneficial intervention seems strong enough to warrant changing clinical practice are shown in Table 1. These 18 domains can be used to guide service development, structure continuing professional education, and frame audits of clinical activity. They are offered as a provisional program of clinical development, knowing that the evidence base for interventions with older populations is evolving and that questions about identifying those most likely to benefit remain unanswered.

CASE MANAGEMENT

Identifying cases and initiating health promotion and maintenance activities are unlikely to have sustained beneficial effects on health in later life if they are not followed by

Table 1 Health risk assessment, prevention, and health maintenance for patients aged 65 and over

Domains	Primary prevention
Hypertension case-finding	Yearly measurement
Hyperlipidemia case-finding	5-yearly screen/use Coronary Risk Prediction chart to quantify risk
Diabetes mellitus: early detection	3-yearly screen with fasting blood glucose (FBG)
Colon cancer screening	Annual screening by fecal occult blood test
Prostate cancer screening	Screening in asymptomatic men not recommended
Dental care review	Recommend annual dental check
Visual loss case-finding	Recommend yearly eye test
Hearing loss case-finding	Annual whisper test as minimum, or use of brief hearing function questionnaire
Exercise promotion	Recommend regular exercise for cardiovascular fitness, balance, muscle strengthening or stamina
Nutrition assessment	Basic dietary advice about high fiber/low fat diets
Physical function assessment	Periodic functional assessment for patients with comorbidity using simple instruments like Timed Up And Go
Pain management	Routine enquiry at each patient encounter
Regular medication use	Regular review for $\geq$3 medications
Injury prevention/falls	Annual falls risk assessment and referral for deeper assessment and intervention
Urinary incontinence; case-finding	Routine enquiry about symptoms
Depression/dementia; case-finding	Assess patients $\geq$75 years with symptoms using standardized instruments
Smoking cessation	Cessation counselling for all smokers
Alcohol overuse; case-finding	Routine enquiry about quantity and frequency of consumption

systematic management of the cases so identified. Case-management techniques can improve access to health and social care services (Pacala *et al.*, 1995), enhance quality of life (Marshall *et al.*, 1999), and reduce admission to institutions (Stuck *et al.*, 1995). This latter finding has attracted much attention, with the success in reducing hospital admissions for exacerbations of chronic disease through case management run by Kaiser Permanente in the United States prompting another round of experimentation in Britain. As a result, small partnership projects to promote health in older people using case-finding and case-management strategies have merged across the United Kingdom, while a national demonstration project in nine areas has examined how the American chronic disease management program for nursing-home residents at high risk of hospitalization (Kane *et al.*, 2003) can be translated to English primary-care settings. The national demonstration project hinges on the development of a new advanced primary-care nurse role involving coordination of proactive care for older people. Better monitoring and education of high-risk older people and engagement of existing general practitioner and community nursing services appear to reduce recurrent hospital admissions enough to make the UK government want to roll out the case-management method to all areas by 2008. These projects could identify the necessary components of case management in the United Kingdom setting and help promote the emergence of a case-management culture in primary care, without necessarily setting up a new specialist services that bypasses the slow rate of change in established primary care.

This is a potentially exciting and productive development in primary care, but will it become part of normal care in a well-established system? Can a method developed in the United States, which has poorly developed primary-care provision and little if any system of health care in the NHS sense, be imported to the United Kingdom? How will the existing roles of general practitioners, practice nurses, and other community nurses fit alongside the new roles of advanced primary-care nurses? Will case management actually work in the sense of identifying and supporting vulnerable older people? And are there more benefits to health-care providers through reduced hospital admission than there are to older people with multiple problems?

The precedents for a change in work culture of this magnitude, and in the provision of services to an older population, are ambiguous. General practitioners have rarely been involved in developing case-management approaches (Leedham and Wistow, 1992), and apart from community psychiatric nurses, the role of nurses in care management was peripheral in the 1990s (Bergen, 1994) except for a few primary-care nurses functioning as care managers with access to a budget for social care either as part of the district nursing, social work, or general practice team. On the other hand most general practitioners and primary-care nurses would probably argue that most of their practice is based on a case-management model, and there is evidence that district nurses and health visitors use many elements of case management in their daily practice. A recent survey of practice nurses reported that they were more likely to use all the elements of case management where they were involved in chronic disease management than in single tasks delegated by the general practitioner (Evans *et al.*, 2005).

The recipients of case management and the elements of the case manager's role change according to the organizational and funding context. In a range of different contexts, case-management schemes for older people have addressed health promotion and independence (Storfell *et al.*, 1997), the management of single diseases (Goodwin *et al.*, 2003), the management of multiple chronic medical conditions, residents of nursing homes (Kane and Huck, 2000), or on the management of both health and social care. The eligibility criteria for an older person to receive case management are determined by the purpose of case management. For example, health maintenance organizations (HMOs) in America are keen to lower costs to the individual and the organization through preventable hospital admissions (Dixon *et al.*, 2004). Reports of American nurse care management schemes, which use comparisons of health care utilization before and after the introduction of the scheme for small cohorts of high-risk enrollees to the HMO, demonstrated decreased costs through reduced utilization of emergency room facilities and duration

of patients' stay in the hospital and high levels of patient satisfaction (Quinn *et al.*, 1999). These findings are important for advocates of case management in primary care, but we need to be cautious because other evidence is less supportive. For example, a review of nine randomized control trials of case-management programs for any age group in primary care concluded that they improved some clinical outcomes, patient satisfaction, quality of life and functional status but did not reduce costs (Ferguson and Weinberger, 1998).

How case management is actually done also varies greatly. There appear to be two main models of the case manager's role: case managers holding budgets to finance care packages for the user (the brokerage model used by social services in the United Kingdom), and case managers providing services themselves and coordinating other agencies' service, as key workers. The different models variously employ nurses, nurse practitioners, social workers, or other health-care professionals as case managers, and also vary to the degree that the case managers work with doctors. Some models have regular structured reviews of the patients with primary-care doctors or specialist geriatric physicians (Quinn *et al.*, 1999); others have no specified relationship beyond the ability to refer to a primary-care doctor (Ritchie *et al.*, 2002). In some instances, case management has been incorporated as one element of a service redesign to integrate acute, primary, and long-term care (Johri *et al.*, 2003).

WHO BENEFITS MOST?

The evidence of impact is difficult to interpret and extrapolate to different health and social care systems, given the plethora of roles, aims, involvement of other professionals and differing types of services. Three randomized control studies in Italy, (Bernabei *et al.*, 1998) Canada, (Gagnon *et al.*, 1999) and the United States (Marshall *et al.*, 1999) provide more evidence about the impact of case-management approaches in different settings. The Canadian study reported no significant differences in quality of life, satisfaction with care, functional status, or hospital admissions between those receiving case management and those not, possibly because of the weak link between the nurse care manager and the patients' primary physician. The Italian and American studies reported that the intervention group receiving case management experienced less functional decline and were more independent for longer periods. The Italian study reported that hospital admission was lower in the intervention (case management) group than in the control and that use of family doctors was higher in the control group and overall costs were reduced in the intervention group. This study included an integrated model of care between primary and secondary care providers, with weekly multidisciplinary reviews of each patient's case. The American study reported that the use of the emergency department and hospital admission rates and health care costs were higher in the case-management group than the control group, possibly because the nurse and social work care manager were acting as advocates for older people.

While there is a growing body of knowledge internationally, it is still not clear which elements and services are most effective in which settings, and it is by no means certain that case management will reduce health service utilization and costs for the older population. Increased, coordinated use of case-management techniques between general practitioners and primary-care nurses could help address the interplay of comorbidity in a timely way, before older people become users of emergency services or start on a trajectory of repeated hospital admissions, but this does need to be demonstrated in well-designed studies. If case management is introduced widely in the absence of evidence from such studies, the error of the 75 and over checks may be repeated, potentially at higher economic cost to the health service. While this policy issue is being resolved, practitioners can use one component of case management virtually without extra resources, which is likely to be beneficial to patients and professionals alike; regular review of medication use in older people with multiple disorders.

MEDICATION REVIEW

The iatrogenic effects of prescribed medicines are a known factor in increased risk of hospital admission, and medication reviews are core components of case management. Medication management for older people is a major issue for the NHS, both in terms of the population health consequences and the resource utilization. Prescriptions in primary care for people aged over 60 account for about £4000 million of England's NHS budget annually (National Statistics Office, 2002), while the iatrogenic effects of prescribed medication are estimated to account for between 5 and 17% of all hospital admissions of people over 65 (Department of Health, 2001b). Multiple diseases, complicated medication regimes, transfer of prescribing between general practitioners and specialists, unreviewed repeat prescribing are all known risk factors for medication problems irrespective of the age of the patient. At the same time, it is recognized that there is underprescribing for older people for common conditions such as COPD, depression, and hypertension (Royal College of Physicians, 2000). Population studies reveal that about 50% of people prescribed medication for long-term conditions do not take the medicine as prescribed (Carter *et al.*, 2003). Current estimates based on return-to-pharmacy schemes for unused medicines indicate that each Primary Care Trust in the United Kingdom may be spending about £1 million per annum on prescribed medicines that are wasted (Department of Health, 2001b).

Shared decision making on medicines between professional and patient, known as *concordance*, has been advocated to address some of these issues. The target of annual medication review for all people over 75 advocated by the NSFOP, with more frequent reviews for people at risk of medicine related problems, is another solution (Department of Health, 2001a). Medication review activities can take one

of four forms (Task Force, 2003): (1) opportunistic, unstructured questions about medicines with patient, (2) technical review of a patient's prescriptions, (3) review of medicines with the patient's full medical records, and (4) face-to-face review of medicines and conditions with the patient.

However, the best approach to medication review for older people in general practice remains unclear. Older people are not a homogeneous group, and some studies indicate that not all older people would welcome the opportunity to formally review their medications with GPs or others (Knapp *et al.*, 2003; Zermansky *et al.*, 2001). Population and general practice studies report that between 20 and 42% of older people were not prescribed any medication while between 17 and 27% of patients over 75 were prescribed three or more medications. In contrast to hospital medicine, prescribing in general practice for older people is characterized by greater uncertainty about diagnoses, where people often present with multiple symptoms that are not easy to attribute and coexist with several known medical problems. Prescribing in these situations may be "realistic" in the sense it is aimed a symptom relief in the absence of diagnosis, or even at hypothesis-testing to reach a diagnosis, without being rational in the clinical-pharmacological sense (Cartwright and Smith, 1988).

The pattern of prescribing is likely to become more complicated as appropriately qualified nurses prescribe independently from a limited formulary of prescription-only medicines (Department of Health, 2002). This development is likely to contribute to the development and regulation of individual patient clinical management plans, and also permit a greater role for pharmacists in managing repeat prescription for people with chronic conditions. In the face of primary-care workforce and workload problems, the skills of pharmacists and nurses in primary care will be increasingly used in medication reviews with older people, potentially achieving therapeutic benefits with neutral cost implications (Krska *et al.*, 2001). However, this is an under-researched area, with little published literature on the effectiveness or cost consequences of nurse involvement in medication review for older people (Krska and Ross, 2002). Policy is clearly driving a greater role for pharmacists, practice nurses, district nurses, and nurse practitioners in medication reviews, alongside general practitioners. It is less clear what educational, organizational, and decisions support mechanisms are required for the different professional groups in situations where clinical risk judgments are complex or what the impact of review by different professional groups is on older people.

CONCLUSION

The proactive management of chronic diseases in adults is one the main challenges facing primary care, and health systems generally. In England and Wales, the NSFOP provides an impetus for primary care to address the health promotion and health care needs of older people with multiple pathologies and disabilities, and may be rekindling an enthusiasm for experimentation and innovation in primary care for older people. The great advantage of the national service framework is that it sets out not only objectives but also a research and development agenda, since there is much still unknown about how to enhance the quality of care for an aging population. Specialist and generalist disciplines can rebalance their division of labor, if transfer of skills into primary care can occur and hospital services become more effective in their management of late-life disorders. The lessons from the poor implementation of previous policies suggest that a cautious and selective approach building on existing skills while enhancing organizational capability is the best way to steer between policy imperatives and the evidence base. From my perspective there are three areas where focused activity in general practice could result in improved health care for older people: evidence-based health screening and health promotion, an increased culture of case management, and multidisciplinary strategies for medication review.

The 18 clinical domains that are described here as a core program for general practice-based care for older people constitute the easiest of the three areas of innovation. Clinical skills can be enhanced, educational skills can be built around the domains, and information systems modified to facilitate clinical thinking and the documentation of practice. Specialists in medicine and nursing for older people have obvious roles to play in promoting professional development in such domains, without necessarily having to provide services themselves, or at least not in the longer term. A transfer of skills from specialist to generalist domains is realistic, given the limited number of the clinical domains and their cultural familiarity to primary care, and may be facilitated by contractual changes for family doctors that resource and provide incentives for primary care for older people.

Case management is not so easy to introduce, partly because in general practice systematic review of patients with long-term problems is largely restricted to single domains like hypertension, diabetes, and asthma, and has yet to develop for complex patients with multiple pathologies and disabilities. Exploring this area needs time and energy, but can be given a positive impetus by specialist services where expertise already lies. The introduction of case management across the United Kingdom by 2008, possibly utilizing the expertise and personnel of US HMOs, will create a nationwide experiment in the application of case-management methods, worthy of carefully evaluation.

Medication review should be easy, and in the United Kingdom it is now part of the remuneration package for family doctors; it may prove more complex to implement than expected as pharmacists and nurses acquire new roles in evaluating medication use and become more engaged with clinical decision making. Again, specialists in medicine for older people can have an effect on primary-care development by promoting discussion about the problems of medication use with their colleagues in primary care, perhaps using critical incident methods to examine iatrogenesis as a factor

in hospital admission. Case management as a tool could begin around medication review and expand out into domains like functional ability and quality of life as practitioners become familiar with the approach.

Although we should not expect progress to be as rapid in these three areas as it has been in the development of condition-specific services for stroke and falls prevention, or even in service reconfigurations like intermediate care, lasting changes in primary care for older people appear possible, given long-term commitment.

KEY POINTS

- Experience from the poor implementation of the 75 and over checks suggests that cautious and selective approach to promoting primary care for older people, and building on existing skills while enhancing organizational capability, is more realistic than a sudden and dramatic leap forward.
- The existing evidence base suggests that health promotion for older people is realistic in 18 clinical domains.
- A transfer of skills from specialists to generalists is feasible, given the limited number of the clinical domains and their cultural familiarity to primary care, and may be facilitated by contractual changes for family doctors.
- The culture of case management is less well established in general practice, but current policies support its growth, which can begin around regular medication review.
- Multidisciplinary strategies for medication review, particularly in managing complex cases, will assist general practitioners by bringing relevant expertise to bear on complex problems of comorbidity and disability.
- Pharmacists and nurses will acquire new roles in evaluating medication use and become more engaged with clinical decision making, as part of this evolution.

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Carers and the Role of the Family

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Carers are among the unsung heroes of British life. . .Caring for carers is a vital element in caring for those who need care.

(Her Majesty's Government, 1999)

Carers must think of themselves first – because if they have to give up, there will be no carer.

(Aged and Community Care Division of the Australian Department of Health and Ageing, Undated)

Taking care of oneself is essential if the best care is to be provided to another person. Caregivers must learn how to balance their own needs with the needs of someone who needs care.

(US Department of Health and Human Services Administration on Aging, 2004)

INTRODUCTION

These opening statements encapsulate how better understanding of the role played by carers has become embedded into the political mainstream. In some ways, they represent the considerable progress that has been made since the UK Government's 1981 White Paper which lamented the declining numbers of single women describing them as the "*natural*" carers of older people (Department of Health and Social Security, 1981). In others, they indicate the way in which carers continue to be seen as a "resource" (Twigg and Atkin, 1994), and providing them with help is seen as the best way of ensuring that they will continue to care, a response typified in the observation that:

In a number of countries. . .carers are slowly becoming a central point in the strategic analysis of long-term care systems.

(Jacobzone, 1999, p20)

Nevertheless, despite the increasing recognition given to people providing unpaid care for a family member or friend, there are still reports that many carers continue to be unaware of their rights (Seddon and Robinson, 2001) or do not know whom to contact should they need help (Carers UK, 2005).

SCOPE

This chapter will give an overview of recent research looking at the role played by carers and other family members in the care of older people. It will draw on the evidence from the substantial literature on caring that has its theoretical basis in a number of disciplines, including medicine, nursing, psychology, sociology, and gerontology. These range from qualitative studies describing the experience of caregiving to large-scale surveys or complex intervention studies. It will reflect the fact that, while early literature was dominated by research undertaken in North America and the United Kingdom, there is now a growing number of studies from different parts of the world. However, as will emerge later in the chapter, while the literature on caring is extensive, its quality is uneven, and there continue to be areas where uncertainties remain about the best ways of providing support for carers.

The successful care of older people is dependent upon the ability of services to contribute in ways that either enhance pre-existing sources of support or establish changes in the way in which they operate (for example, when they have become inadequate to meet a person's needs). In order to provide clear and responsive solutions, professionals need a clear understanding of what help is provided in the family, by whom, and in what circumstances. This chapter will attempt to summarize these issues and to set the background of those older people who are seen by geriatric medical services in a wider context. It will also explore the interaction between family care and the utilization of health and social care services. This is where the links with the other chapters in

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this book will emerge most strongly. Finally, it will end by taking stock and raising issues about how support for family carers can be improved in the future.

DEFINITIONS OF CARING

The term "carer" or "caregiver" was first developed to describe the unpaid work that people, generally women, undertook while looking after relatives or friends needing support because of age, disability, or illness. These early studies were associated with feminists (Finch and Groves, 1983; Lewis and Meredith, 1988), although contemporary research undertaken independently by psychiatrists also highlighted the effects of providing care for family members (Bergmann *et al.*, 1978; Grad and Sainsbury, 1968). Conceptually, as Twigg and Atkin (1994) have pointed out, definitions of caring go beyond merely providing assistance with tasks such as shopping or bathing that people are unable to carry out independently by themselves. Caring takes place within pre-existing relationships (Finch, 1989; Qureshi and Walker, 1989) and there are likely to be strong ties of affection or obligation. Intensity is also an issue and it has become customary to distinguish between "heavily involved" carers – those providing care for 20 hours a week or more, and those who are less involved (Parker and Lawton, 1994). The failure of some researchers to incorporate these variations into their sampling and analytical frameworks has resulted in one of the most frequent criticisms within the caring literature, namely, the lack of differentiation between participants with differing relationships and with differing levels of caring responsibility (Schulz *et al.*, 1997). Furthermore, many people caring for family members or friends, particularly those who are older, do not define themselves as carers (Milne *et al.*, 2001) making it harder for policies aimed at supporting them to reach all those for whom they are intended.

Legal Frameworks

While the existence of legislative structures to support carers do not, in themselves, guarantee that carers will receive all the help that they need (Montgomery and Holzhausen, 2003–2004), it is also important to acknowledge the effects of the differing legal frameworks where family support is given and received. In the United Kingdom (UK), the Carers (Recognition and Services) Act (1995) gave carers the right to have their needs assessed. This was strengthened by the Carers (Equal Opportunities) Act (2004) which placed a duty on local authorities to tell carers about their rights and to consider carers' employment, education, or leisure commitments when carrying out carer assessments. Local authorities themselves were given powers to enlist the help of health, housing, and education authorities in providing support for carers. In Germany, the *Pflegeversicherung* (long-term care insurance) has given carers an annual right to respite care (Schunk, 1998) while, in Finland, carers are entitled to cash benefits in return for a contractual agreement to provide a certain amount of care (Martimo, 1998). These systems of support must also be considered within the context of the overall balance between state provision and family support. The extent to which families are held legally responsible for an older member's care varies throughout the European Union (Millar and Warman, 1996; Zechner, 2004).

Changes to the Way "Caring" is Conceptualized

More recently, some commentators, especially those associated with the disability movement (Morris, 1997) have challenged the assumptions underpinning the word "caring", criticizing its construction of people needing assistance in their daily lives as a "dependant" or "receiver of care". Researchers on caring (Forbat, 2005; Nolan *et al.*, 2001; Nolan *et al.*, 2003) have also advocated the need for new paradigms that reflect the realities of the reciprocities between carers and those for whom they provide support. Thus, while "caring" remains a useful shorthand word to describe the range of support that is given in the context of relationships of kinship or affinity, it remains a term that is not value free and is interpreted in a variety of ways.

WHO CARES FOR OLDER PEOPLE?

Reliable international estimates of the numbers of carers in the population are rare, but in 2001, a question on caring was included in the decennial UK census for the first time and the Office for National Statistics, the government department responsible for official statistics in the UK, reported that in England and Wales, around one in ten people (5.2 million) was caring for someone who was either "sick, disabled, or elderly" (sic). More than half of these carers were aged 50 and over. Around one in five cared for over 50 hours per week, at least two hours a week more than the maximum 48-hour week for people in paid employment laid down by the European Working Time Directive. Furthermore, in the majority of cases, family carers are the only people providing care; 80% older people rely on help from family and friends only (Pickard *et al.*, 2000).

In 1985, a question on caring was included for the first time in the *General Household Survey* (GHS), an annual survey covering a representative sample of private households in the United Kingdom (Green, 1988). Since then, it has been repeated at intervals, enabling researchers to build up information on caring in the United Kingdom over time. In 2000, the last time that the question was included, the largest group of carers (38%) comprised adult children caring for a parent. A further 14% were caring for a parent-in-law. While proportionally more people cared for other relatives (21%), friends or neighbors (21%), than spouses (18%), these figures conceal the importance of spousal care in supporting older people living in the community. Here, wives caring for husbands or husbands caring for wives accounted for

almost half of those caring for 20 hours a week (Maher and Green, 2002).

Carers' Age and Gender

The peak ages for caring occurs between the ages of 45 and 64, when almost a quarter of the people define themselves as having caring responsibilities, followed by those aged 65 and over, of whom 16% have caring responsibilities (Maher and Green, 2002). This highlights a consistent finding that the majority of older people are receiving care from another older person. There are now three times as many people in their 90s living in the United Kingdom than there were 30 years ago (Office for National Statistics, 2004). This means that carers, whether they are spouses or adult children, are increasingly likely to be in the older age-group themselves. Furthermore, older carers are much more likely to be caring for 20 or more hours a week and to be the sole carer of the person for whom they provide support (Arber and Ginn, 1991; Milne *et al.*, 2001; Parker and Lawton, 1994). As later sections will show, this has important consequences for identifying which carers are likely to experience difficulties in continuing with their caring role.

Contrary to many popular stereotypes, the overall proportions of men and women carers in the population are fairly similar (14 and 16% respectively) (Maher and Green, 2002). However, these overall figures mask important variations. The majority of men carers care for a spouse or partner living in the same household. Women are more equally divided between those caring for a husband or partner and those caring for a parent. Finally, women are more likely than men to be the sole or main carer (Maher and Green, 2002) and to be involved in giving personal care, such as helping with washing or dressing (Parker and Lawton, 1994).

The Impact of Social and Demographic Change (*see* Chapter 9, The Demography of Aging; Chapter 10, Social and Community Aspects of Aging)

While results from the GHS have been broadly consistent over the last decade (Maher and Green, 2002), less is known about the effects of demographic and social changes on the numbers of carers in the longer term. This is partly because many of the seminal studies from the late 1980s and early 1990s (Arber and Ginn, 1991; Parker and Lawton, 1994; Qureshi and Walker, 1989) have yet to be repeated. More importantly, there is still great uncertainty about how increases in the proportion of older people in the population (Office for National Statistics, 2004), changes in adult children's proximity to their parents (Shelton and Grundy, 2000), and women's increased participation in the labor market (Twomey, 2002) will influence family structures and kinship roles (Harper, 2003). However, one projection is that there will be an increase in the number of spouse carers but a decline in adult children providing care to parents living in the same household (coresident care) (Comas-Herrera *et al.*, 2003; Pickard *et al.*, 2000).

Another factor that has only recently been given attention in gerontological literature is the impact of the widespread international migration from the 1960s onwards (Harper and Levin, 2003). Older populations in North America, Australasia, and Europe have become increasingly ethnically diverse. Cultural competence, the ability of professionals to provide care that matches the needs and preferences of a diverse patient population, is seen as an important way of reducing health inequalities (Betancourt *et al.*, 2003). This is especially important for professionals working in settings such as cardiology, stroke, or diabetes, where they are likely to find comparatively high proportions of patients whose ethnicity is Black or South Asian (Riste *et al.*, 2001; Sica, 2004). While carers from a minority ethnic group may face issues similar to those experienced by their majority-culture counterparts, they are often additionally disadvantaged by professionals' stereotyped assumptions about the levels of support that they will have available from within their social networks (Adamson and Donovan, 2005; Katbamna *et al.*, 2004). This highlights the importance of approaches to older people and their families that are sensitive to differing cultural and ethnic backgrounds.

In order to understand how ethnicity influences caring, it is important to first appreciate the impact of caring itself.

THE IMPACT OF CARING UPON PEOPLE'S LIVES

Psychological Health

While it is difficult to demonstrate direct causal relationships between caring and psychological health, there is strong evidence that some carers are in poorer psychological health than their age- and gender-matched counterparts in the general population. A study using data from the first 10 waves of the British Household Panel Survey (BHPS), a nationally representative sample of more than 5000 private households in England, Scotland, and Wales, found that as measured by the 12-item General Health Questionnaire (GHQ) (Goldberg and Williams, 1988), a well validated screening measure for identifying psychological health problems such as anxiety and depression, between 15 and 17% of men and 20 and 25% of women without any caring responsibilities scored 3 or more on the GHQ-12. These scores are viewed as indicating that they were experiencing symptoms associated with psychological difficulties. By contrast, around 5% more men and women carers had scores that came within this range. More importantly, average scores were considerably higher among carers caring for a person in the same household and carers caring for more than 20 hours a week. This was especially true of coresident women carers or women caring for more than 20 hours per week of whom over a third appeared to be experiencing psychological distress (Hirst, 2003).

Buck *et al.* (1997) found that 39% of their sample of over 700 carers and former carers, identified using a random

stratified sample of people aged 65 and over in four parts of the United Kingdom, scored above the cut point for probable psychological illness on the GHQ-30 (Goldberg and Williams, 1988), in comparison with 31% in the general population (Cox *et al.*, 1993). They also identified that some carers who had ceased to care, continued to experience psychological difficulties, even though the person for whom they cared had moved into long-term care.

A third study (Livingston *et al.*, 1996) using a representative community sample of people aged 65 but using a different measure of psychological health, the shortened version of the Comprehensive Assessment and Referral Evaluation (Gurland *et al.*, 1984), suggested that being a carer was not in itself a risk factor for poor psychological health but that where carers lacked social support, they were at greater risk of experiencing depression.

Physical Health

As mentioned earlier, given that many carers are old themselves, they are likely to experience health problems in their own right. A study of dementia caregivers suggested that carers with long-term health conditions themselves were at risk of greater carer stress (Bruce *et al.*, 2005). Furthermore, there is some evidence that with improved health technology, many carers are undertaking tasks that in the past would have been undertaken by nurses or health-care assistants (Schulz and Martire, 2004) and that carers are providing more intensive care over longer periods (Hirst, 2002). Specific problems often cited by carers include the difficulties of assisting someone to dress if they have arthritis or back pain from lifting (Henwood, 1998; Levin *et al.*, 1994). Even where carers are receiving assistance from other family members or friends and services, they are still likely to be providing most assistance with activities of daily living (ADLs), such as washing, and instrumental activities of daily living (IADLs), such as shopping (Moriarty and Webb, 2000).

Social Support

Social isolation and loneliness are frequently reported by carers who may no longer have the time to meet up with family members and friends, or to pursue hobbies or other interests. Carers not only report feelings of loss and social isolation in their relationships with others, their relationship with the person for whom they care may also have altered. Others have argued that levels of *received* (or enacted) social support may not be as important as how carers *perceive* they are supported. Thus, if a carer does not feel supported, then he or she may express feelings of distress even if others are providing help. By contrast, good overall levels of perceived social support are associated with increased carer well-being (Chappell and Reid, 2002; Lynch, 1998).

However, although deficits in social support have long been associated with increased rates of depression, the extent to which the experience of caring, social support, and depression interact are more uncertain, mainly because of the way in which different studies have conceptualized and operationalized social support in different ways (Miller *et al.*, 2001). The lack of a confiding relationship has been associated with increased carer depression (Waite *et al.*, 2004). Unlike carers who are adult children (who may have supportive relationships with a husband, wife, or partner), spouse carers often have lower levels of social support and this may be why they tend to report poorer social support and higher levels of depression (Murray *et al.*, 1997). The impact of these changes may be reduced when the relationship between the carer and the person for whom they care has been good (Braithwaite, 2000).

Financial Aspects

Carers are also likely to be financially disadvantaged. Extra expenditure may be required to pay for equipment, services, heating, and clothing. In addition, carers may give up paid employment, forgo promotion prospects, or retire early. While women are still more likely to be affected more severely than men, particularly in terms of being able to build up savings and a pension in retirement (Ginn and Arber, 1996), this is an issue for both men and women (Carmichael and Charles, 2003). In addition to the actual costs that carers may incur through direct expenditure and loss of paid employment, economic evaluations are increasingly seeking to include some element of the opportunity costs of caring, in terms of identifying what carers might have done, had they not been caring or to include a calculation of replacement care costs representing the sums needed, had a carer not been available (Netten, 1996). This latter sum is considerable. One recent estimate suggests the average costs of so-called *informal care* at over £14 000 per year per recipient, almost three times as much as the costs of formal care from health and social care services.

Factors Relating to the Person Cared for

Carers find some aspects of caring more difficult to cope with, than others. In particular, feeling unable to deal with behavioral changes, such as wandering, night time disturbance, or aggression, are rated as especially hard to deal with (Chappell and Reid, 2002; Clark *et al.*, 2004; Draper *et al.*, 1995). Being unable to leave the person for whom they care alone has also been associated with poorer psychological health (Resource Implications Study of the Medical Research Council Cognitive Function and Ageing Study, 1999).

IDENTIFYING CARERS IN NEED OF SUPPORT

The research cited above suggests that it should be possible for health professionals to identify carers who are at greater

risk of experiencing greater difficulties in their caring role than others. In summary, these are likely to be

- coresident carers (Hirst, 2003);
- carers caring for more than 20 hours per week (Hirst, 2003);
- spouse carers, especially those lacking social support (Murray *et al.*, 1997) or those who have recently ceased to care (Buck *et al.*, 1997);
- carers coping with behavioral changes in the person for whom they care (Chappell and Reid, 2002);
- carers caring for an older person with depression or dementia (Murray *et al.*, 1997; Ory *et al.*, 1999).

This is not to imply that other carers will not require support, but it may help differentiate between the larger numbers of carers who may not need substantial help beyond acquiring information and practical support and those who would benefit from more sustained support.

Screening Measures for Carers

The interest in caregiver research has resulted in a considerable number of screening measures designed to capture carers' experiences. While measures such as Burden Interview (Zarit *et al.*, 1980) and the Relatives' Stress Scale (RSS) and Behavior and Mood Disturbance Scale (Greene *et al.*, 1982) were used extensively in early research, they have become less popular since we have acquired a broader conceptual understanding of caring. Measures that have been developed to screen carers (as opposed to those for whom they care) include the Carers' Assessment of Managing Index (CAMI), Carers' Assessment of Difficulties Index (CADI), and the Carers' Assessment of Satisfactions Index (CASI) (Nolan *et al.*, 1998), the Carers of Older People in Europe (COPE) (McKee *et al.*, 2003), and the Carers' Checklist (Hodgson *et al.*, 1998). These are among the few standardized measures to assess carers' needs that have been used in routine practice, as opposed to research settings (Moriarty, 2002).

WHAT HELP DO CARERS WANT FROM SERVICES?

The diversity to be found among carers themselves and in the sort of help that they provide means that there is no single service solution that will meet all their needs and preferences. Carers' cultural backgrounds may influence their ways of responding to caring. For example, US research suggests that carers from minority ethnic groups are more likely to use religion as a way of coping with caring variations and so professionals need to be aware of the different ways in which people deal with caring (Aranda and Knight, 1997; Connell and Gibson, 1997; Kuuppelomaki *et al.*, 2004). Furthermore, there are still uncertainties about the effectiveness of services to support carers. On the whole, intervention studies remain comparatively rarer in the United Kingdom than in the United States. In the United Kingdom, literature is better on studies looking at the process and at indicating what the carers' priorities in terms of services are – for example, a systematic review on supporting carers of people with cancer and those receiving palliative care concluded that we know more about the feasibility of interventions than their effectiveness (Harding and Higginson, 2003). Nevertheless, it is possible to identify a number of consistent messages. Not surprisingly, these broadly reflect the areas where carers may experience problems.

Information

The difficulty in accessing appropriate information and at the right time is a constant theme within carer research (Henwood, 1998). However, a Cochrane review of information provision for patients and carers following stroke concluded that few information giving strategies had been evaluated comprehensively (Forster *et al.*, 2005). Nevertheless, carers' accounts suggest that they value information that is delivered quickly and given in both verbal and written forms. This information may deal with information on prognosis, symptoms, and treatment (Low *et al.*, 1999; Mant *et al.*, 1998, Wachters-Kaufmann *et al.*, 2005), but carers also require information on other services, benefits, and legal issues, such as power of attorney (Moriarty and Webb, 2000). At the same time, it is important to realize the limitations of written information; not all carers use the information that they receive (Murphy *et al.*, 1995) and so it is important to review what they have received at a later date to see whether it has been useful.

Carer Education and Support

A number of studies have suggested that some carers benefit from programs aimed at helping them understand the problems faced by the person for whom they care and in developing strategies for coping with them. These include cognitive behavioral therapy (CBT) for carers of people with dementia (Marriott *et al.*, 2000), a psychoeducational program to help deal with behavioral problems (Ostwald *et al.*, 1999), and help with moving and handling techniques and simple nursing tasks for patients who have had a stroke (Kalra *et al.*, 2004). There is increasing interest in the use of information and communication technology (ICT) (Eisdorfer *et al.*, 2003), video (Hanson *et al.*, 1999), and telephone contact (Grant *et al.*, 2004) to supplement other support.

In addition to carers' groups designed as a way of delivering specific interventions, some carers appreciate attending general support groups (McFarland and Sanders, 2000). However, it has been suggested that people from managerial and professional backgrounds are overrepresented in their attendance (Wettstein *et al.*, 2004). It is not known whether this reflects their service preferences or whether they find it easier to make arrangements for substitute care and travel than other groups of carers.

Respite Services

Respite is the term used to describe a range of services giving carers a break, ranging from one or two hours in the home to overnight care in care homes or specialist units. A number of studies have looked at the impact of respite services, but the results present a mixed and sometimes contradictory picture (Arksey *et al.*, 2004). Partly, this is because the outcome measures used most often (changes in carers' psychological health and reductions in admissions to long-term care) may not be amenable to change from the provision of comparatively small amounts of help. Carers themselves rate respite services highly when they are felt to be of sufficient quality and meet the preferences of both themselves and the person for whom they care. Carers and service providers have different perspectives about what constitutes respite. This means that it is important that respite care is offered in a form that is meaningful to carers. In this sense, respite should be seen as an outcome, not a service (Chappell *et al.*, 2001).

Understanding the Needs of Carers at Different Times

It is becoming increasingly common to view caring as a trajectory, particularly when carers are caring for people with long or progressive conditions. (Wiles *et al.*, 1998). This means that the needs of carers will vary at different times. In addition to the support they need at the beginning of caring, carers also need continuing help; for example, many carers feel guilty when they experience negative feelings about caring but would be reluctant to admit this to the person for whom they care or to other family members and friends (Adamson and Donovan, 2005). Carers who have been bereaved or those caring for a person in long-term care may continue to experience feelings of distress (Buck *et al.*, 1997; Moriarty and Webb, 2000). Carers may also be reluctant to use services; in addition to the rationing of services by service providers, some carers are reluctant to use services in case they are denying them to others (Arksey, 2002).

DISCUSSION

Although there is now extensive literature on carers, much of it remains limited and there continues to be a need for more focused studies that are better able to demonstrate what sort of services help which sort of carers in which circumstances. It is noticeable that while there are many studies looking at carers' psychological health, few look at their quality of life (Low *et al.*, 1999). There are issues about the cross-national relevance from studies based upon service systems that may be very different. Furthermore, there is a need for new forms of evaluation (Qureshi, 2004) and forms of evaluation that take account of the outcomes that are important to carers, not just to service providers or researchers (Nicholas, 2003; Qureshi, 2003).

Nevertheless, as this chapter has shown, there are areas in which there is some degree of clarity. Many carers caring for older people are themselves old and are providing considerable amounts of assistance. Although the majority of carers will not experience difficulties with their caring role, a substantial number will and this is usually influenced by the amount of care that they provide and the emotional context in which it is given. Interventions increasingly use a combination of methods and may be based upon the use of new technologies. The amount and type of care that will be required to sustain older people in the future is uncertain. What is certain is that most family members continue to wish to play a part in its provision. The challenge for services is in responding to the diversity of caregiving arrangements and in providing help that is acceptable to both carers and to those for whom they care.

KEY POINTS

- Carers provide the majority of support to older people needing help with their daily lives. Many of these are spouses with health problems of their own.
- It is possible to identify carers at greater risk of needing support themselves.
- The sort of support that carers need will vary at different timepoints while they are giving care.
- Services need to be more focused upon the sort of help that carers themselves define as useful.

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Nursing Home Care

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INTRODUCTION

Nursing home facilities are more unique than similar. The care of elderly persons in institutionalized setting varies by country, region, societal, and cultural factors. Approaches to long-term care in various countries include chronic geriatric hospitals, short-stay rehabilitation centers, residential living centers, and institutionalized skilled nursing homes. The nomenclature of a facility varies across settings, including "nursing home" in the United States and "care home" in the United Kingdom. A "nursing home" in the United States may refer to a specialized center for persons on ventilators, with acquired immunodeficiency syndrome, or with dementia who need skilled nursing care. A "care home" in the United Kingdom generally refers to a home registered under the Care Standards Act providing personal and residential care for older people, and also includes homes that provide nursing care (nursing homes). Not only is the classification confusing, but the public, and often the professional, view of nursing homes involves a number of misperceptions.

Misperception: Most older adults will live for many years in a nursing home and eventually die there. Truth: Fewer than 5% of older adults in United States and fewer than 10% in United Kingdom reside in resident and nursing home settings.

Misperception: Once a person enters a nursing home, he or she stays there for good. Truth: Many older adults who enter a nursing home will recover and leave (short-stay residents), while fewer older adults will remain in a nursing home once admitted (long-stay residents).

Misperception: Nursing homes are warehouses for older persons with little or no stimulation: Truth: A good home provides a social environment that often is very comforting for older persons who may have been isolated in previous living environments.

Misperceptions: No one likes living in a nursing home. Truth: Many residents prefer the reassurance of medical care, socialization, and a safe environment, and find the experience positive.

Facility Demographics

In the United States, there are approximately 18 000 nursing homes with a bed capacity of 1.9 million. The number of residents in the current statistical period was 1.6 million, with a bed occupancy rate of 87% (National Center for Health Statistics, 1999). Ownership of most nursing homes in the United States is by for-profit entities, while only 7% are owned by governmental entities (Figure 1). In the United States, most nursing homes have between 50 and 199 beds (79%) and only 8% had more than 200 beds. The average size of nursing homes was 107 beds.

Fifty-six percent of nursing homes are affiliated with other nursing homes in a chain ownership. These facilities accounted for 56.9% of all beds, 56.5% of all residents, and 61% of all discharges. Most nursing homes (62%) are located in a metropolitan statistical area (Gabrel, 2000). The distribution of nursing homes is uneven, with the Midwest and South census regions having 34 and 32% of facilities and 32 and 33% of all beds, respectively.

The nursing home industry employs a large number of persons in various occupations. The number of employees by occupation is given in Figure 2. The rate of staffing does not appear to vary much by type of nursing home ownership. A major problem for patient care in nursing homes is the high staff turnover rate. A vacancy rate of 19% for nurses has been reported (American Nursing Association, 1991). Turnover rate for nursing assistant has been reported to be as high as 93% (Caudill and Patrick, 1991). These high vacancy rates disturb continuity and force continuous training of new personnel.

Nursing home care is expensive. The per diem rates for private-pay individuals and for Medicare and Medicaid reimbursement is shown in Table 1. In the United States, the primary source of payment for nursing home care is Medicaid, a means-tested governmental source (see Figure 3). There are regional variations in nursing home charges and reimbursement (see Figure 4). The national costs of nursing home care was $53 billion in 1990, and was the fastest

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Table 1 Average daily charge for private-pay residents by level of care of facility and for Medicare residents by selected nursing home characteristics: United States, 1997

	Level of care			Certification	
	Skilled	Intermediate	Residential	Medicare	Medicaid
Proprietary	$132.25	103.49	100.87	228.14	91.04
Voluntary nonprofit	147.47	118.01	80.91	201.45	116.49
Government and other	129.01	99.21	N/A	150.52	99.71

Source: Gabrel CS. An overview of nursing home facilities: Data from the 1997 National Nursing Home Survey. Advance data from vital and health statistics; no. 311. Hyattsville, Maryland: National Center for Health Statistics. 2000.

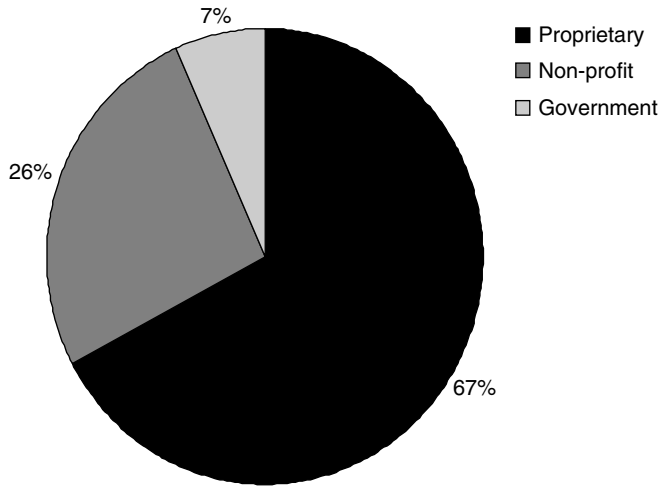

Figure 1 Percent distribution of nursing home facilities by ownership: United States, 1997. *Source*: Gabrel CS. An overview of nursing home facilities: Data from the 1997 National Nursing Home Survey. Advance data from vital and health statistics; no. 311. Hyattsville, Maryland: National Center for Health Statistics. 2000

growing component of major health-care expense in the national budget (Levit *et al.*, 1991). The projected cost for the year 2000 well exceeds $140 billion, and may exceed $700 billion by the year 2030 (Sonnenfeld *et al.*, 1991).

Nursing homes in other cultural settings differ considerably. For example, the Dutch experience demonstrates that among persons older than 65 years, approximately 20% had a short stay in an inpatient hospital department and 96% were discharged to their own home situation. Only 7% lived permanently in special institutions for chronic care, including residential care or nursing home care. Persons with physical disability or with progressive dementia, who have impaired activities of daily living (ADLs) and who need more complex continuing care beyond the range of home care services in a residential homes, are admitted to a nursing home. The number of nursing home beds is 3.6 per 1000 persons (in 2003), with a total of 330 nursing homes with approximately 26 000 beds designed primarily for persons with physical problems and 32 000 beds in psychogeriatric wards for persons with dementia. Nursing home care is covered by a mandatory national insurance system, the Exceptional Medical Expenses Act. In addition to the funds from this national insurance,

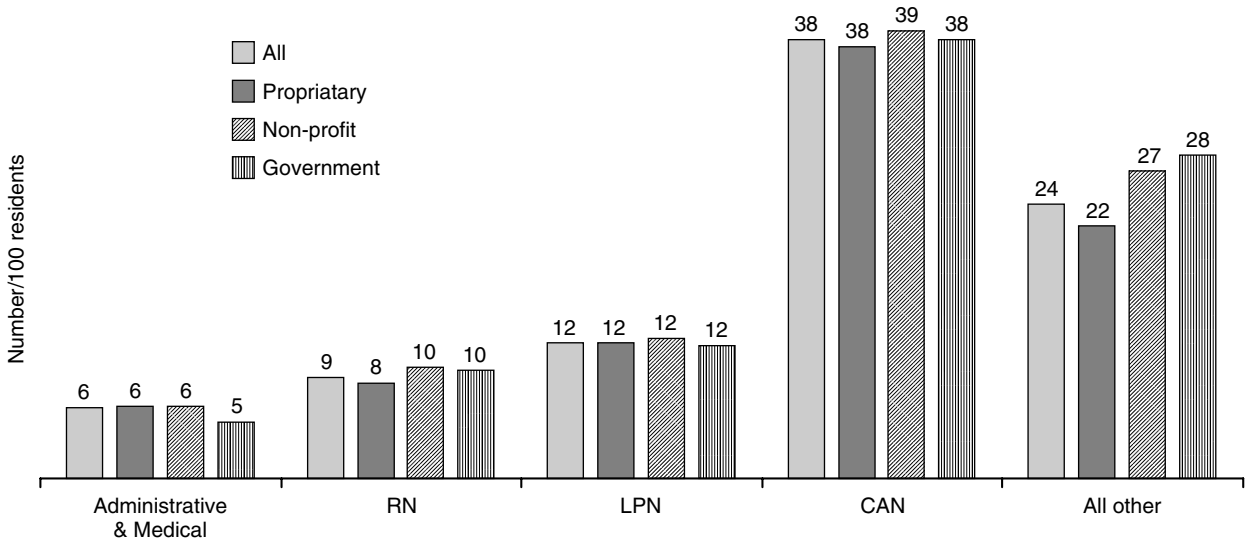

Figure 2 Number per 100 residents of full-time equivalent employees by occupational categories and selected nursing home characteristics: United States, 1997. Administrative & medical includes dentists, dental hygienists, physical therapists, speech pathologists and/or audiologists, dieticians or nutritionists, podiatrists, and social workers; N = registered nurse; LPN = licensed practical nurse; CNA = certified nursing assistant. *Source*: Gabrel CS. An overview of nursing home facilities: Data from the 1997 National Nursing Home Survey. Advance data from vital and health statistics; no. 311. Hyattsville, Maryland: National Center for Health Statistics. 2000

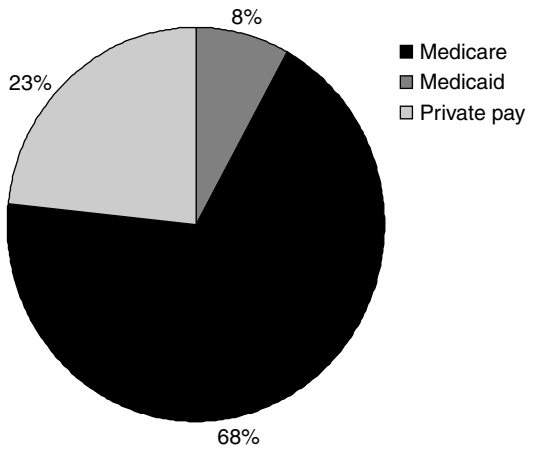

Figure 3 Nursing home payment *Source*: United States, 1997. *Source*: Gabrel CS. An overview of nursing home facilities: Data from the 1997 National Nursing Home Survey. Advance data from vital and health statistics; no. 311. Hyattsville, Maryland: National Center for Health Statistics. 2000

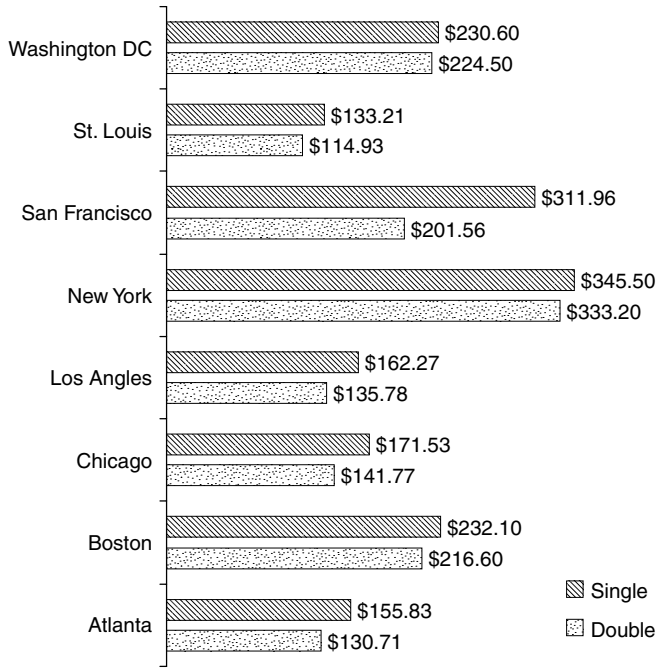

Figure 4 Average daily rate for a single-occupancy or double-occupancy nursing home accommodation: United States 2003. *Source*: The MetLife Market Survey of Nursing Home and Home Care Costs, August 2003

income- and household-dependent out-of-pocket payments are obligatory for persons admitted to nursing homes (Schols *et al.*, 2004).

In the United Kingdom, the number of patients in private or voluntary homes has risen from 18 200 in 1983 to 148 500 in 1994 (Black and Bowman, 1997). The number of institutional care beds for older persons has doubled to 563 000 between 1980 and 1995. National Health Service beds accounted for less than 10% of the total in 1995 compared with 23% in 1980, while private and voluntary (not for profit) residential and nursing homes increased to 76% (Kavanagh and Knapp, 1997).

Persons in the United Kingdom receiving long-term care provided in care homes are required to meet financial means testing. Those who have assets, including the value of their homes, above a limit (£18 500 in 2002) are required to pay the care home's fees in full. Those with assets below the limit make a copayment that is usually less than the full fee. For those with the lowest income and assets, this payment may be met from Income Support, the UK's means-tested welfare benefit. Almost all older people who own their home would be required to meet care home fees in full.

Means testing dates back to 1948 in the United Kingdom, and has changed little in the many years. However, the growing numbers of older persons and increasing home ownership has stressed the means test. Local public authorities are responsible for payment for long-term care for older persons who meet means test requirements, whether in a care home or in the person's own home. For care services delivered at home, the value of an older person's home is disregarded in determining how much he or she contributes. An older home owner is, therefore, likely to incur considerably more – and the public budget correspondingly less – of the cost of care in a residential setting than of equivalent cost care at home. The result is a financial incentive for public authorities to arrange for a home owner's care to be provided in an institution rather than in the person's own home. The financial incentive works in the opposite direction for older home owners themselves. Whether the likelihood of entry to a care home is increased or decreased by the level of an individual's economic resources would seem to depend on whether individual choice or the policy of the local public authority dominates (Hancock *et al.*, 2002).

Resident Demographics

In the United States, 43% of persons who were 65 years of age in 1990 will enter a nursing home in their lifetime. Of these, 55% will stay at least for 1 year, and 21% will stay for 5 years or longer (Kemper and Murtaugh, 1991). Nursing home use is strongly associated with age, even after adjusting for disability. This suggests that the future need for nursing home care will increase as the population increases in life expectancy. By the year 2030, the need for nursing home beds in the United States is projected to increase to 5 million (Zedlewski *et al.*, 1989; Doty, 1992).

Most nursing home admissions are for short-stay residents. About 2.5 million residents are discharged after an average length stay of 272 days. Long-stay residents remain in the nursing home for an average of 873 days.

Residents in nursing homes do not reflect the general population demographics. Ninety-one percent of nursing home residents are older than 65 years, but 46% are 85 years old or above. This raises the mean age for all current nursing home residents to 81 years (Figure 5). Most nursing home residents are women (72%), and these women are older

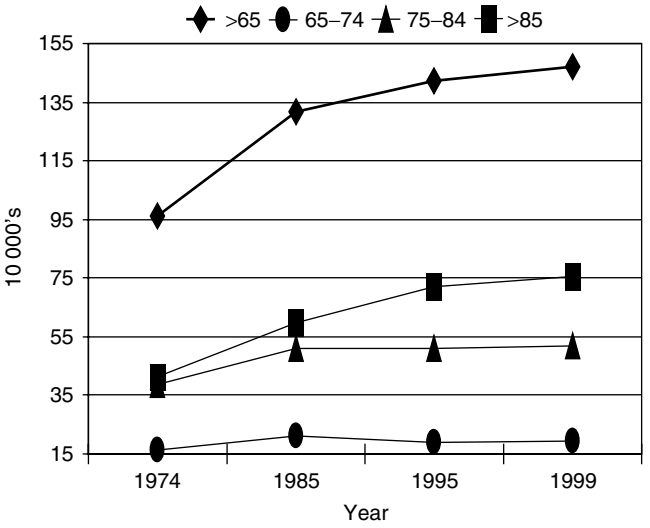

Figure 5 Nursing home residents 65 years of age and over: United States, 1973–1974, 1985, 1995, and 1999. *Source*: National Center for Health Statistics. Health, United States, 2004. With Chartbook on Trends in the Health of Americans. Hyattsville, Maryland: 2004

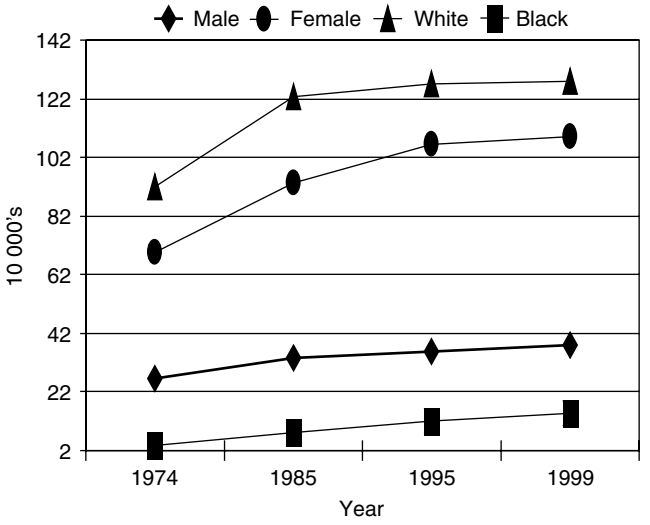

Figure 6 Nursing home residents 65 years of age and over: United States, by sex, and race 1973–1974, 1985, 1995, and 1999. *Source*: National Center for Health Statistics. Health, United States, 2004. With Chartbook on Trends in the Health of Americans. Hyattsville, Maryland: 2004

(mean age 83 years) compared to men (mean age 76 years). Racial demographics are only slightly different from the general population: 87% white and 12% black (Figure 6).

Nursing homes provide extensive services to residents. Almost all nursing homes reported providing nursing services (100%), medical services (97%), and personal care services that included ADLs (97%). Nonmedical services most frequently offered by nursing homes include nutrition (99%); social services including assistance to residents and their families in handling social, environmental, and emotional problems (98%); and physical therapy (97%). The least frequently offered services include hospice services (72%) and home health services (23%).

Nursing Home Regulation

In the United States, nursing homes are licensed by each state and require a certificate of need to operate. Each state regularly surveys nursing homes for compliance with state regulations. In addition, the Federal government contracts with each state to survey nursing homes for compliance with Federal regulations if the home receives payments from Medicare or Medicaid sources. Nearly all nursing homes (96%) had some form of certification in 1997. More than three-fourths of all facilities were certified by both Medicare and Medicaid. Only 4% of the 18 000 nursing homes were not certified.

Federal regulations are contained in two Congressional acts, the Omnibus Budget Reconciliation Act of 1987 (OBRA '87) and the Balanced Budget Act of 1997 (BBA '97). OBRA '87 had a major impact on general nursing care, including introduction of the Minimum Data Set (MDS), requirements for a medical director, and the reduction of physical and chemical restraints. Regulations based on BBA '97 initiate the Prospective Payment System and consolidated billing. These federal regulations have created standards of care in nursing facilities. The regulations resulting from OBRA '87 are divided into two parts. First, the law is stated. These statements are labeled by "F-tags" and a number. An "F-tag" is jargon for the actual law published in the Federal Register. Second, an interpretive guideline follows the regulation. The guidelines comprise the instructions used by surveyors to determine compliance with the law. Failure to comply with state or federal regulations can result in fines or in decertifying the facility from participation in federal programs. A comparison of federal quality-of-care indicators is published on the Internet and updated at intervals.

In the United Kingdom, nursing homes are required to report on their quality-of-care activities each year, and are also regularly visited by Health Care Inspectorate.

Medical Care

Care of residents in a nursing home is overseen by a physician. Each nursing home is required to have a physician Medical Director, who oversees the quality-of-care in the facility. Each resident is seen by their physician, who either visits them in the facility or arranges for clinic visits. The frequency of visits is dictated by medical necessity, but cannot be less frequent than once every 30 days for the initial 3 months following admissions, or less than once in every 60 days thereafter. Physician extenders or nurse practitioners may also see residents in a facility, but may not be used to meet this minimum standard.

The number of physicians who see residents in a facility is small. Only 1 in 10 primary care physicians provide care in a

nursing home. Seventy-seven percent of all physicians report spending no time in a nursing home. Only 15% of specialists spend any time in a nursing home. Among physicians who report seeing patients in a nursing home, a majority spent less than 2 hours per week with residents (Katz *et al.*, 1997). Contributing to this minimal involvement, over one-third of surveyed physicians report inadequate training in geriatric syndromes such as falls, incontinence, dementia, nutrition, and chronic pain (Darer *et al.*, 2004).

Medical care in nursing homes focuses on chronic disease and geriatric syndromes, owing to resident comorbid conditions. Functional impairment is the final common pathway of most chronic disease, especially in older persons with multiple advanced disorders (Thomas, 2002a). Nursing home residents in the United States are becoming older, increasingly female, and more functionally impaired (Figures 5–7).

An estimated 59% of adults with five or more ADLs impairments will be admitted to nursing homes (Guralnik *et al.*, 1994). In general, functional status declines with time. Older adults in nursing homes with substantial functional impairment show poorer function at the end of the 6 months than those with higher function (Buttar *et al.*, 2001), and a shorter life expectancy in the nursing home than institutionalized adults of the same age who are less impaired (Donaldson *et al.*, 1980). Functional status is the most sensitive clinical indicator with which to follow disease progression or response to therapy in the elderly. The MDS as well as standardized brief clinical instruments are used to assess functional status. Improvement in function rather than cure of disease is the major therapeutic goal of nursing home care.

Other chronic conditions affect the care of residents in long-term care facilities. Between 45 and 70% of the estimated 1.6 million nursing home residents fall annually (Thappa *et al.*, 1996). Of these, 30–40% will fall two or more times and 11% will sustain a serious injury as a result of the fall (Rubenstein *et al.*, 1994). Urinary incontinence affects approximately half of nursing home residents (Ouslander and Schnelle, 1995). Dementia of various types is present in over 60% of typical nursing home residents (Jakob *et al.*, 2002; Rovner *et al.*, 1990), many of whom exhibit behavioral disturbances (Thomas, 2002b). The prevalence of pressure ulcers is higher in long-term care settings (Thomas, 2001). In Medicare-certified nursing home beds, one-fourth of residents receive enteral feeding (Shaughnessy and Kramer, 1990; Haddad and Thomas, 2002). Weight loss and undernutrition frequently complicate the care of older adults (Thomas *et al.*, 2002). The prevalence of chronic conditions and interacting comorbid conditions increase the medical complexity of caring for nursing home residents. Several guidelines for the evaluation and management of common clinical problems in the nursing home have been published (Ouslander and Osterweil, 1994; Evans *et al.*, 1995). Table 2 provides some clinical characteristics of residents in nursing homes in the United States.

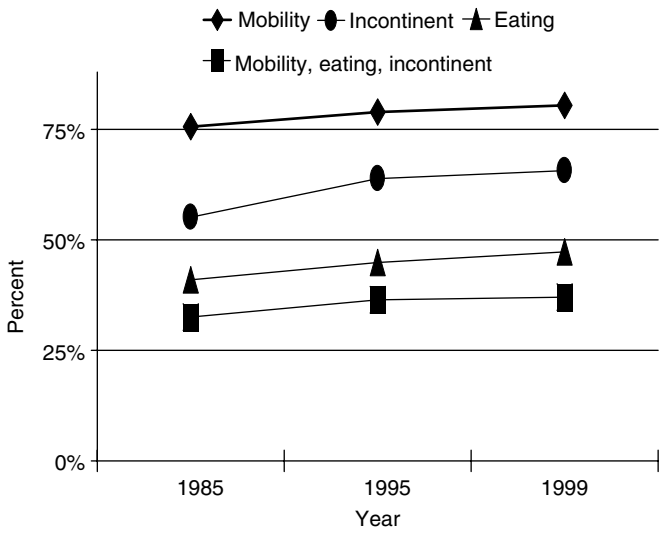

Figure 7 Nursing home residents 65 years of age and over: United States, by functional status 1985, 1995, and 1999. *Source*: National Center for Health Statistics. Health, United States, 2004. With Chartbook on Trends in the Health of Americans. Hyattsville, Maryland: 2004

Table 2 Some characteristics of residents in nursing homes in the United States in 2005

Condition	Residents (%)
Catheters	6.4
Contractures	30.5
Depression	45.5
Dementia	46.6
Urinary incontinence	55.8
Bowel incontinence	45.8
Behavioral symptoms	30.5
Pressure ulcers	7.3
Tube feedings	6.6
Significant weight loss	10.9
Influenza vaccinations	63.2
Pneumonococcal vaccinations	35.4
Fracture incidence	3.0
Dehydration	0.5
Moderate to severe pain	7.8
Nine or more medications	61.3
Urinary tract infection	9.5

COMPARISON OF NURSING HOMES IN DIFFERENT COUNTRIES

In 1997, *Age and Ageing* published a supplement comparing nursing homes in multiple different countries utilizing the data collected by the Resident Assessment Instrument (Fries *et al.*, 1997; Berg *et al.*, 1997; Ljunggren *et al.*, 1997; Sgadari *et al.*, 1997; Schroll *et al.*, 1997). Most of the data was collected in the early 1990s. These findings are summarized in Table 3. Some recent data collected using the Resident Assessment Instrument in the United States from 2005 is also included in the table. As can be seen, there is a large variability between countries.

Iceland and Denmark have over 50% of their nursing home population over 85 years of age, while in Italy and Japan, it is under 40%. Sweden and the United States have

Table 3 Comparisons between nursing homes across countries

Data collected	Denmark 1992–1993	Italy 1992–1994	Japan 1993	Sweden 1990–1993	Iceland 1994	France 1993	USA 1993	USA 2005
Age <65	4.2	4.5	4.6	3.8	1.8	10.2	6.5	–
65–84	45.7	56.1	60.3	52.6	46.6	45.5	53.9	–
85+	50.1	39.3	35.2	43.5	51.5	44.3	47.2	–
Length of stay								
≤30 days	2.6	–	0	22.8	0.7	3.8	20.9	–
>2 years	49.4	–	48.5	30.8	60.6	43.8	45.7	–
Cognitively intact	21.8	15.3	32.7	19.7	28.5	11.0	18.5	53.4
Low ADLs	49.0	55.0	42.0	–	38.0	–	48.0	–
Residents receiving rehabilitation	23.0	14.0	30.0	–	31.0	–	11.0	17.2
Restraints	2.2	16.6	4.5	15.2	8.5	17.1	16.5	7.6
Incontinence								
Urine	52.2	54.4	42.9	61.6	56.5	65.2	46.4	55.8
Bowel	22.4	45.3	30.6	39.5	23.0	55.5	29.5	45.8
Participate in activities	52.0	20.0	43.0	–	44.0	–	50.0	–
Nursing time per patient	–	–	84.4	133.7	–	–	118.3	–

over 20% of the nursing home population staying for less than 30 years, while none of the Japanese population stay for such a short time period. Except in Japan, under one-third of residents are cognitively intact. In the United States, this has changed remarkably in the 10 years since the survey, with now over half of the patients being cognitively intact. This almost certainly represents the shift from shorter length of stay in hospitals and more rapid discharge to nursing homes for rehabilitation. Of interest is that in the 1990s more residents in Japan and Iceland were receiving therapy than were residents in the United States, despite the fact that these two countries had the smallest number of residents staying for less than 30 days.

There was a low rate of physical restraint use in Denmark and Japan. The use of physical restraints has halved in the United States in the last decade. In Spain, 39.6% of residents were restrained. As all the evidence shows that restraints do more harm than good, it is extremely puzzling why nursing homes continue to use this abusive form of maltreatment. Of the five countries where social engagement was measured, only Italy had a very low level (20%). The other countries varied between 43 and 52%.

In the United States, it is now regulated that all residents have at least some form of social engagement every week.

Nursing time spent with each resident (patient) is highest in England and Wales at 155.5 minutes and lowest in Japan (84.4 minutes). In the United States, only 7.5% of the care was given by registered nurses compared to 53.2% in England and Wales. Registered nurses in Japan, Sweden, and Spain provided between 14 and 18.2% of the care.

Overall, these studies stress the differences between patient-mix and care in different countries. Asian nursing homes in Taiwan showed a moderate level of satisfaction with care, with a monotonous pace of life, inadequate privacy, and lost items being the major problems. The average Functional Index Measure (FIM) score was 49.2, which is similar to those seen in the United States in residential care facilities. 74.7% of patients had severe cognitive impairment. Physical restraint use was as high as 54%. Pressure ulcers varied from 5.3 to 12.1%. The prevalence of stool impaction was 29.4% (Yeh *et al.*, 2003). As the MDS is more widely used throughout the world, it will become possible to compare nursing homes throughout the world and to develop a gold standard for high-quality nursing homes.

Special Nursing Home Programs

Special Care (or Needs) Units have been developed in the United States to take care of persons with behavioral problems associated with dementia. These are usually locked units and have a higher staffing-to-resident ratio. Many also offer a higher level of recreational therapy. Some of these offer special programs such as pet or music therapy. Overall, studies have failed to show a major advantage of these units over general nursing home care.

Snoezelen is a multisensory therapy that provides easy-to-do activities in an enabling environment. It provides a high level of interaction. It is both stimulating and relaxing. While in some nursing homes staff have found it useful, high-quality-controlled studies of its efficacy do not exist.

The Eden Alternative is the introduction of a variety of animals to the nursing home as well as the provision of an environment where the residents can be involved in gardening. These environments can improve the home-like quality of the nursing home and encourage visits by young children. Again, however, quality studies improving efficacy do not exist.

The measurement of quality-of-care is fraught with difficulties. Fahey *et al.* (2003) compared the quality of medical care for elderly residents in nursing homes to elderly people living at home in the Bristol area. They found that in the nursing home only 74% of those persons with heart disease and 62% of those with diabetes mellitus had their blood pressure measured within the previous year.

Table 4 Example of facility quality measure/indicator report

Facility name _____ Run date _____
City/State _____ Report period _____
Provider number _____ Comparison group _____
Login/Internal ID _____ Report version number _____

Measure ID	Domain/Measure description	Facility				Comparison group		
		Num	Denom	Observed percent(%)	Adjusted percent(%)	State average(%)	National average(%)	State percentile
Chronic care measures								
	Accidents							
1.1	Incidence of new fractures	6	198	3.0	–	2.2	2.0	74
1.2	Prevalence of falls	33	215	15.3	–	15.2	13.0	55
	Behavior/emotional patterns							
2.1	Residents who have become more depressed or anxious	27	215	12.6	–	12.9	16.0	55
2.2	Prevalence of behavior symptoms affecting others: Overall	34	215	15.8	–	19.5	18.7	42
2.2-HI	Prevalence of behavior symptoms affecting others: High risk	26	115	22.6	–	23.5	21.8	51
2.2-LO	Prevalence of behavior symptoms affecting others: Low risk	8	93	8.6	–	8.2	8.0	63
2.3	Prevalence of symptoms of depression without antidepressant therapy	14	215	6.5	–	4.4	5.4	78
	Clinical management							
3.1	Use of 9 or more different medications	105	215	48.8	–	63.1	61.3	14
	Cognitive patterns							
4.1	Incidence of cognitive impairment	1	107	0.9	–	10.9	12.9	23
	Elimination/Incontinence							
5.1	Low-risk residents who lost control of their bowels or bladder	49	123	39.8	–	35.7	47.1	64
5.2	Residents who have/had a catheter inserted and left in their bladder	13	215	6.0	5.1	7.6	8.0	39
5.3	Prevalence of occasional or frequent bladder or bowel incontinence without a toileting plan	51	51	100.0	–	27.5	44.5	100[a]
5.4	Prevalence of fecal impaction	0	215	0.0	–	0.2	0.1	0
	Infection control							
6.1	Residents with a urinary tract infection	13	215	6.0	–	9.6	9.5	33
	Nutrition/Eating							
7.1	Residents who lose too much weight	36	208	17.3	–	10.0	10.9	89
7.2	Prevalence of tube feeding	26	215	12.1	–	4.7	7.2	92[a]
7.3	Prevalence of dehydration	1	215	0.5	–	0.6	0.5	74
	Pain management							
8.1	Residents who have moderate to severe pain	15	215	7.0	5.5	8.6	7.8	45
	Physical functioning							
9.1	Residents whose need for help with daily activities has increased	26	193	13.5	–	16.1	18.3	47
9.2	Residents who spend most of their time in bed or in a chair	16	215	7.4	–	3.2	5.5	92[a]
9.3	Residents whose ability to move in and around their room got worse	9	158	5.7	6.2	15.1	17.1	18
9.4	Incidence of decline in ROM	4	214	1.9	–	7.1	8.6	18
	Psychotropic drug use							
10.1	Prevalence of antipsychotic use, in the absence of psychotic or related conditions: Overall	28	188	14.9	–	22.8	21.9	21

ROM, range of motion.
Dashes represent a value that could not be computed.
[a]Above or below national average.

In contrast, in the United States, it is the expectation that blood pressure is measured monthly and in persons in Bristol living at home the rate of measurement was 96%. Only 38% of residents in nursing homes had been prescribed a β-blocker following a myocardial infarction. Nursing home residents were less likely than people living at home to have received a pneumonococcal vaccination, though the rate of nursing home vaccination was similar.

In the United States, studies using the MDS have demonstrated that residents who are incontinent are unlikely to be on a documented scheduled toileting regimen (Schnelle *et al.*, 2003). Troyer (2004) found that Medicaid residents had a slightly higher death rate than privately funded residents. Much of this difference was associated with the resident and also the market they were in. Stevenson (2005) found that consumer complaints concerning nursing homes, when made to State Survey agencies, were associated with low nurse aide staffing levels and the number of deficiencies found on the state survey. Persons who receive potentially inappropriate medications in the nursing home have a much higher chance of subsequent hospitalization or death (Lau *et al.*, 2005). Finally, it should be recognized that general

practitioners who work in nursing homes will have a higher death rate in their patients than those who work only in the community, making it essential to establish a different standard for these practitioners (Mohammed *et al.*, 2004).

The big picture as given by the recounting above can be reduced to statistics for a single facility so that it can assess its quality and improve its care. Facilities in the United States can use their data as reported in the On-Line Survey Certification and Reporting (OSCAR) and the MDS Quality Indicator data to compare their facility to others in their region, state, and the nation (Table 4).

The best method to improve care is to put in place a Continuous Quality Improvement plan where data is collected and presented to the interdisciplinary team leaders and staff representatives monthly. When an unacceptable variation in the data is seen, a plan is put in place to determine the reason and to fix the problem. The same data is evaluated each month to allow the team to determine their success at fixing the problem. The differences between continuous quality improvement and old-fashioned quality assurance programs are delineated in Table 5. Areas in the nursing home that are highly amenable to continuous quality improvement programs are set out in Table 6. Examples of monitoring of data in the nursing home for prescribing and efficacy of therapies are given in Tables 7 and 8. The keys to Continuous Quality Improvement resulting in improved nursing home care are administrative buy in, team empowerment to fix the problem, and continuous collection and feedback of data.

Table 5 Comparison between quality assurance and continuous quality improvement

Quality assurance	Continuous quality improvement
Retrospective	Prospective/continuous
Lays blame	No blame
Administrator lead	Team lead
Opinion driven	Data driven
Problem focused	Customer focused
Snapshot	Continuous
Resistant to change	Seeks change

Table 6 Problems in the nursing home most amenable to quality improvement

Depression
Polypharmacy
Pressure ulcers
Undernutrition
Falls
Incontinence
Osteoporosis
Behavior problems
Lost items
Food quality
Customer satisfaction
Skin tears

Table 8 Measurement of quality in a skilled nursing facility utilizing the Functional Index Measure (FIM)

Level of function	Home	Discharge to hospital	Residential care facility
At home prior to event	106	82	106
On admission	77	55	53
At discharge	96	64	69

Table 9 The most frequent legal allegations of malpractice against nursing homes

1. Fall
2. Negligent care
3. Pressure ulcers
4. Lack of care
5. Abuse/assault
6. Dehydration/malnutrition
7. Elopement/wandering

Legal Issues in the Nursing Home

There has been a marked increase in lawsuits against nursing homes in the United States over the last 5 years. In many cases, these are frivolous and rely on the fact that the fear of large awards by a jury and the cost of litigation make the nursing home chains settle without going to court. The largest awards are made for elopement (average $860 000) and pressure ulcers (average $293 000). Table 9 lists the most frequent allegations against nursing homes.

Visualizing the Resident

Communication between all the members of the interdisciplinary team and the physician is often limited. The Geronte is a visual communication device originally developed in France. This single sheet provides a snap shot of the problems the resident has. Problem areas can be colored in by any staff member (Figure 8).

Table 7 Pharmacy quality assurance report for an academic skilled nursing facility

	Jan	Feb	Mar	Apr	May	Comparison group[a]
Routine meds(*n*)	9.2	9.4	9.4	9.3	9.7	9.8
PRN meds(*n*)	1.9	1.8	1.6	1.5	1.5	6.5
Antipsychotics(%)	11	7	5	6	4	12.2
Anxiolytics(%)	9	8	11	15	9	22.0
Sedative/hypnotics(%)	14	7	8	11	9	24.4

[a]Comparison group is to skilled nursing beds in the same city.

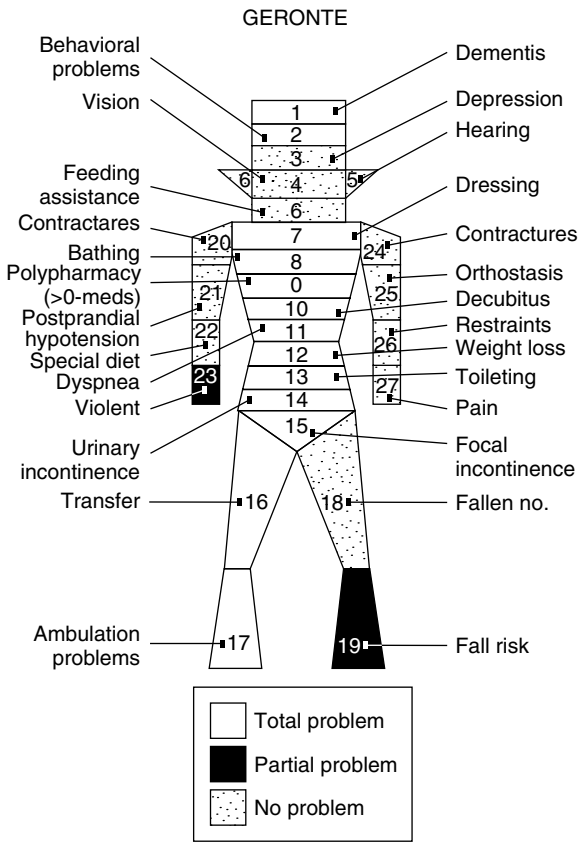

Figure 8 A visual communication device: the Geronte as used by LifeCare Centers of St. Louis and the Division of Geriatrics, Saint Louis University

KEY POINTS

- Nursing home facilities are more unique than similar.
- The Minimum Data Set provides a method to compare nursing homes worldwide.
- Nursing homes have short-stay residents who are predominantly there for rehabilitation and long-term residents who require custodial care.
- The introduction of special programs, for example, the Eden Alternative, increased involvement of physicians and Continuous Quality Improvement methods have improved quality of care in nursing homes.

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Clinical Audit of Health Care

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"The time has come for everyone in the NHS to take clinical audit very seriously"

Dame Deirdre Hine, Chair, Commission for Health Improvement
Sir Michael Rawlins, Chairman, National Institute for Clinical Excellence

Principles for best practice in clinical audit (NICE, 2002a)

DEFINITION

Clinical audit is a tool for improving the quality of care. A more detailed definition endorsed by the National Institute of Clinical Excellence (NICE) (NICE, 2002a) is as follows:

"a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. Aspects of the structure, process and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual, team or service level and further monitoring is used to confirm improvement in healthcare delivery."

The following chapter will expand on the components of this definition.

BACKGROUND

The concepts of measuring the outcome of clinical care are not new. Florence Nightingale recognized that some patients did better than others and worked out that ward hygiene mattered. But a combination of disinterest and sometimes outright resistance to criticism has prevented progress until quite recently. Ernest Codman, a surgeon in the eastern United States, suggested in 1917 that outcomes of surgery should be measured and went further to suggest that lay people could take part in the assessments. When his data pointed to colleagues functioning less well than others, he was excluded from the New England Medical Association. Professor Avedis Donabedian introduced the modern era of a more rigorous approach to improving quality in health care with his seminal works in the 1960s–1980s (Donabedian, 1966, 1988). He developed the concept of measuring structure (what is needed to provide a good service), process (what is done to provide a good service) and outcome (what is expected of a good service) as key elements to evaluating quality of care.

The 1980s saw the realization that health-care demands were in danger of exceeding the national capacity to supply. Resource management, including an important role for audit (Department of Health and Social Services. NHS Management Enquiry team, 1983), examined service function and costs. The Royal Colleges were promoting medical audit as part of good professional practice (Royal College of Physicians, 1989). As time passed, medical audit became clinical audit, recognizing that care is a multidisciplinary process, but audit remained a local activity with modest impact on the service. In the 1990s the National Health Service (NHS) commissioned a series of projects to devise clinical indicators of good practice. These were developed and published by the National Centre for Health Outcomes Development (NCHOD), for example, on urinary incontinence (Brocklehurst *et al.*, 1999) and fractured proximal femur (Fairbank *et al.*, 1999). Despite much endeavor, the outcomes of these activities were very limited and there was no coordination of them and no system for ensuring that action would follow if deficiencies were found.

In 1997, the new Government introduced a sea change in the role of quality management in the NHS with the White Papers *The new NHS; modern and dependable* (Department of Health, 1997) and *A first-class service: quality in the new NHS* (Department of Health, 1998). Quality of care was no longer to be the preserve of individual professionalism but became a matter of management responsibility. The Government sought to improve quality health care by:

- Continual improvement in the overall standards of clinical care

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Table 1 National developments to implement the quality agenda in health care

Setting standards
• National Institute of Clinical Excellence (NICE)
• National Service Frameworks (NSFs)
• National Clinical Governance Support Team (NCGST)
Delivering improvements in care
• Modernization Agency
• National Information Strategy
Monitoring standards
• Commission for Health Improvement (CHI)
• Performance Frameworks
• Patient Councils

- Reducing unacceptable variations in clinical practice
- The best use of resources so that patients receive the greatest benefit

These aims were to be achieved by:

- Setting, delivering, and monitoring quality standards
- Making quality of care a management responsibility rather than just a professional commitment.

To execute these changes the Government established bodies and programs as indicated in Table 1.

In an unrelated move the Department of Health also commissioned a series of National Sentinel Audits, of which audits for stroke (Rudd *et al.*, 1999) and evidence-based prescribing in older people (Batty *et al.*, 2004) were the most successful.

In the United Kingdom, a series of high profile incidents and consequent inquiries (Department of Health, 2001; Shipman, 2003) have made the concept of clinical governance, that is, effective regulation, a nationally important issue. Without a measurement of care quality, it is hard if not impossible to assess whether the nationally produced and evidence-based guidelines commissioned by NICE are being implemented. And nor can those charged with assessing or inspecting services reach objective conclusions without reliable and robust quality measures. Clinical audit is thus a national necessity and not an option.

HOW EFFECTIVE IS CLINICAL AUDIT?

With the national commitment to evidence-based medicine, guidelines, and audit, what is the evidence that audit can alter practice? In primary care, several clinical effectiveness programs have indicated significant changes in practice amongst general practitioners (Cranney *et al.*, 1999; Feder *et al.*, 1995). A systematic review of audit and feedback in improving immunization rates demonstrated a -4 to $+49\%$ improvement in rates and the conclusion that in clinical practice audit and feedback were well worthwhile (Bordley *et al.*, 2000). Lim and Harrison (1992) showed that audit improved care markedly at 1 month but by 6 months the effect had worn off completely. In a systematic review of 85 studies, Jamtvedt *et al.* have found that audit with feedback resulted in changes ranging from 9% decrease in compliance with prescribed practice to a 71% increase in compliance (Jamtvedt *et al.*, 2004). The factor that was most associated with improvement was baseline degree of noncompliance. They conclude that audit and feedback can be effective in improving professional practice; however, the effects are generally small to moderate. Johnston *et al.* reviewed the barriers and facilitating factors for effective clinical audit (Johnston *et al.*, 2000). They found that audit was a valuable tool for improving care. Barriers and facilitating factors that have been identified are shown in Table 2.

Table 2 Barriers and facilitating factors to the success of clinical audit

Facilitating factors
Practical mechanisms for making data collection easy
Modern medical record systems
Information technology linking routine data collection to audit
Dedicated staff
Protected time
Supportive organizational environment
Sound leadership
Monitoring of the effectiveness of the audit program
Barriers
Lack of resources
Lack of expertise in project design or analysis
Small sample size
Incomplete data collection
Lack of coordinated plan for audit
Organizational impediments.
Lack of implementation mechanism
Inadequate management buy-in.

The reviews indicate that, after 40 years of medical and clinical audit, the secrets of success in improving the quality of care are still elusive. Results from recent well constructed national audits – including the National Sentinel Audit of Stroke and the Myocardial Infarction National Audit Programme (MINAP) – which have addressed the issues raised in Table 2 – do indicate that improvements in service can be achieved (Rudd *et al.*, 2001; Birkhead *et al.*, 2004). There are several additional factors to those in Table 2 that have contributed to their success including very careful piloting to ensure that data collection is reliable and repeatable, that analysis includes appropriate interpretation from a multidisciplinary group, and that feedback is rapid, that is, while staff are still in the same posts. Conclusions must have credibility with those who have to implement them. The following sections discuss some of the factors necessary to achieve credible outputs.

THE AUDIT CYCLE

Critical phases of the audit cycle (Pruce and Aggarwal, 2000) are shown in Figure 1.

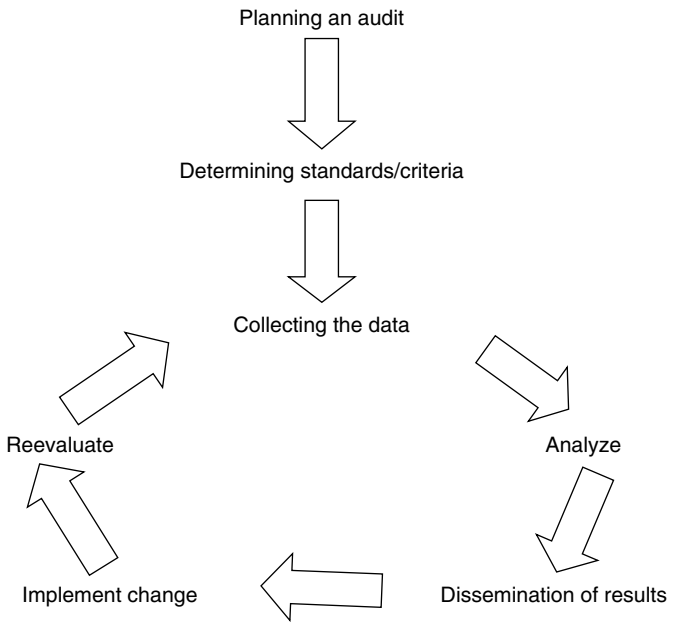

Figure 1 The audit cycle

PLANNING AN AUDIT

Identifying What is to be Reviewed

Any topic is suitable for audit. Pragmatically, it is sensible to focus on topics where there is a perceived inadequacy or variation in patient care or service provision. It is worth considering issues where there is a national priority to improve care, such as topics related to National Service Frameworks (NSFs) or the inspection criteria of the Healthcare Commission. Professionals with specialized areas of interest may wish to perform an audit of local practice. Results might be used as part of the clinical governance mechanism to explore aspects of care where there are concerns over the quality of care or where there have been significant numbers of complaints. A more powerful audit model is to perform the same audit in a number of sites and to use the combined data as a "benchmark" so that local performance can be assessed against the standards being achieved by one's peers elsewhere in the country.

Commitment to Audit

The recommendations of the Bristol Inquiry (Learning from Bristol: the Report of the Public Inquiry into Children's Heart Surgery at the Bristol Royal Infirmary 1984–1995) (Department of Health, 2001) emphasized the importance of clinical audit within the system of local monitoring of performance and the need for trusts to fully support such activity – including access to time, facilities, advice and expertise. These recommendations, welcomed by the government, echo the findings of systematic review, that clinical audit will only be successful if it is adequately resourced and it becomes part of routine practice. Commitment is not just a clinical matter. It is essential that health-care organizations as a whole seriously embrace these recommendations so that when results are available clinicians and managers are both willing to respond and jointly plan appropriate changes.

The planning phases need to look ahead to how the conclusions will be used. This ranges from the need to include variables that allow for useful interpretation of the results as well as quality consideration to ensure the results are valid and reliable. The huge potential of audit for improving care can only be realized if the outcomes of each study are accepted as valid by all parties and thus utilized as the basis for reviewing and adapting practice.

Skills for Carrying out Audit

The infrastructure required includes access to skilled personnel (with dedicated time for the project) to carry out the work and systems to facilitate audit. Expertise is required in establishing a sound methodology for the work (see the following text) including an understanding of such issues as the size of population required for study, identifying relevant data for collection, reliability and feasibility of data collection, data analysis, data presentation and implementation of change. A multidisciplinary team is required that can effectively plan, carry out and disseminate the results of audit work (Grant *et al.*, 2002). Even apparently simple tasks such as setting out a questionnaire are in practice quite difficult. Poorly phrased or ambiguous questions result in uninterpretable data. Therefore, most projects should be performed by nonclinical staff with experience and expertise both in the technical aspects and in project management. They need support from professional health-care workers to ensure the clinical acceptability and credibility and hence the validity of the study. If at all possible, there should be a wider steering group that is multidisciplinary and includes lay representation.

Modern audit has been made possible by the widespread availability of computing systems. They include software that can facilitate data collection, code and encrypt patient identifiable data and do sophisticated analysis – but they are not a substitute for the human skills and experience referred to in the preceding section.

Patient and User Input

Health services exist to serve the public and any assessment of care quality should include patient and users as full partners in the assessment process. Feedback from service users may shed a useful light on where services are inadequate, and also on the users' perspective of what is important as opposed to the views of management and professionals. Kelson (1999) has provided useful advice as to how user involvement can be achieved.

DETERMINING STANDARDS/CRITERIA

Explicit standards or criteria of best practice must be established against which to audit. While various definitions exist for a "criterion" and a "standard" in the context of audit, whichever term or definition is used, the important step is to establish a statement or statements of the level of practice against which health care is to be assessed.

There are two approaches (1) define a gold standard criterion and assess against that absolute target or (2) collect comparative data and assess relative performance against the benchmark created by what one's peers are doing. In theory, the gold standard is preferred but often the evidence needed to set that standard is lacking. Furthermore, gold standards can rarely command 100% compliance, for example, the top level aim for Chronic Obstructive Pulmonary Disease (COPD) might be 100% of patients have spirometry but the practical criterion might be set at 95% to allow for those who cannot do the procedure, who decline or who miss appointments. Similarly, the NSF target for thrombolysis is set at 75% meeting the "door to needle" target to allow for those who, for example, were not diagnosed until 12 hours after the infarct.

Evidence-based Standards

Where possible, such statements of best practice should be derived from evidence-based research. The methods used by such bodies as the Cochrane Collaboration (Cochrane, 2004), the Scottish Intercollegiate Guideline Network (SIGN) (SIGN, 2004) and the National Institute for Clinical Excellence (NICE, 2004a) all ensure a high degree of credibility in the recommendations derived. The process calls for careful attention to literature searching, critical appraisal and peer review. From such recommendations evidence-based audit standards/criteria can be determined.

Example: The NICE Clinical Guideline on "Chronic Obstructive Pulmonary Disease" (COPD) (NICE, 2004b) has as an evidence-based recommendation that "The presence of airflow obstruction should be confirmed by performing spirometry. All health professionals managing patients with COPD should have access to spirometry and be competent in the interpretation of the results".

The audit criterion proposed to complement the recommendation is:

"Percentage of patients with a diagnosis of COPD who have had spirometry performed."

Criteria may be derived from authoritative guidance such as the NSFs. For example, the NSF for Coronary Heart Disease has as a milestone:

"By April 2003 every practice should have clinical audit data no more than 12 months old available that describe: advice and treatment to maintain blood pressure below 140/85".

The NICE commissioned "Audit of the management of post-MI patients in primary care" (NICE, 2002b) included an audit review criterion:

Table 3 Benefits from using consensus techniques

Safety in numbers
Authority
Rationality
Controlled process
Scientific credibility

"The record shows (1) that the patient's blood pressure has been checked in the last 12 months and (2) that the latest reading is at or below 140/85 mmHg".

Consensus-based Standards

Where it is not possible to obtain evidence-based criteria/standards consensus techniques should be used (Murphy *et al.*, 1998). These will enable the best opinion of current health practice to be determined. The challenge in such a process is to ensure that there is no bias due to individual personalities or professions and to ensure that the views of all interested parties are included. Benefits of such approaches are shown in Table 3.

Approaches include the following:

Consensus panels: the use of panels who receive expert advice and representation and who then formulate a statement of best practice.

Nominal group techniques: relevant parties are brought together to discuss recommendations. Chairing has to be skilled to ensure that all view points are heard and to ensure that a full range of options are considered. Voting is in a blinded fashion so that personal views are expressed.

Delphi exercises: postal questionnaires are sent to a large range of individuals with a relevant interest. Statements of practice are proposed and voted on. Recommendations are refined and recirculated so that the recommendations move toward a consensus of the views of the group.

Selection of Gold Standard

In practical terms, health-care settings will need to determine what aspect of care they wish to audit. They will then need to seek the most appropriate standard(s) against which to audit that has the authority of being derived from one of the approaches above. Such standards may be derived from published guidelines, a NSF or a professional organization (Royal College of Physicians, 2004).

Types of Criteria/Standards Used

The Donabedian principle of measuring structure, process and outcome remains the basis for selecting the type of audit standards/criteria.

1. *Structure*: Measures of the facilities and resources available to a health-care setting will reflect the potential to provide high-quality care. It is difficult for staff to provide a high-quality service unless they have the resources to do it. Equally, it has to be recognized that high-class care is not guaranteed in premium facilities. Facilities have to be matched with staff who are provided with training and the expertise to carry out the appropriate care.

Example: For coronary heart disease, if a hospital does not have access to immediate coronary angiography it is not possible to provide the highest quality care for people with acute coronary syndromes.

Measures of "structure" can include facilities, staffing levels, skill mix, access to training, standard use of protocols, mechanisms for advice and information for patients and relatives.

Data relating to "structure" are the easiest of the audit measures to obtain. Such data form the basis of accreditation schemes and systems of this type are widely used internationally and in some parts of the United Kingdom as an indication of service quality.

2. *Process*: Audit criteria/standards of "process" explicitly define key aspects of care that should be provided if high-quality care is to be achieved. Aspects of process measured may include the history, examination, investigation, treatment, and follow-up care. The process may also include the involvement of carers. Processes of care need to be clearly defined to ensure reliable comparison between different sites and different data collection episodes.

Example: In stroke care, a swallow assessment is important as a process. The audit has to define what constitutes an appropriate swallow assessment and what detail within the records reliably reflect what was carried out.

Process data may be collected retrospectively by reviewing a selected number of cases. Such an approach has significant problems in ensuring that there is no selection bias in the notes that are retrieved. A planned retrospective audit such as the National Sentinel Audit of Stroke (assessing the care of 40 *consecutive* stroke patients in all hospitals in England, Wales and Northern Ireland) reduces the risk of bias. A more ideal, but organizationally more challenging approach, is to obtain prospective data with data collection part of routine practice as in the MINAP (Birkhead *et al.*, 2004).

In practice, measurement of process provides a useful reflection of whether care matches up with expected best practice. Data related to process can be more difficult to retrieve than measures of structure but tend to be easier to collect than outcome measures and have the added benefit that they are not dependent on case mix.

Structure, process and outcome are all interrelated. Data from the National Stroke audit has demonstrated that settings where good structures are in place presage better processes of care and lead to better outcomes. It is rarely apparent, however, at the outset, which will be the most sensitive measures. Increasing clinical audit experience will help provide an indication of the structures and processes that are important in determining high-quality care.

There are problems, however (Lilford *et al.*, 2004). If specific processes are identified as the markers for quality, departments and services wishing to be seen to provide high-quality care may concentrate purely on the selected process to the detriment of overall care.

3. *Outcome*: Ideally, the quality of health care should be evaluated by the outcomes it achieves.

Example: For urinary incontinence, does appropriate assessment and treatment of patients result in a reduction in the prevalence of incontinence? (Brocklehurst *et al.*, 1999)

Outcomes may be recorded as outcome "measures", for example, prevalence of a condition or death at 30 days or as an outcome "indicator", for example, percentage of asthma patients given a steroid inhaler on discharge. The latter is a process proxy that is linked to risk of readmission (Slack and Bucknall, 1997) but is not in itself an outcome.

Outcome "measures" can be difficult to utilize. Consideration needs to be given as to whether an outcome "measure" is a true measure or a surrogate measure. For the treatment of osteoporosis, reduced fracture rate is more important than increased bone density, although the latter is easier to measure. Terms must be clearly defined to permit comparative audit. For example, the number of people with incontinence (numerator) in a given population (the denominator) is difficult to determine. It is difficult to clearly define comparable denominator populations within which the prevalence of incontinence is to be measured. Case mix must be allowed for in comparing practice between settings. One setting may have a high proportion of older people in whom an increased level of morbidity, for example, incontinence, would be expected. Comparison with a setting containing a younger population would require case mix adjustment. A precise definition of incontinence will be required to allow comparative data collection. When the frequency of the outcome measure is very low, for example, death at 3 months after hip fracture – the large number of cases needed to be studied renders the outcome measure impractical.

Outcome "indicators" provide an alternative to outcome "measures" and have the potential advantage of being (1) measurable and (2) having face validity for those involved in treatment, that is, it is not surprising that giving out an effective therapy works. While it is important to determine whether outcome measures can be used, in practice it may be more pragmatic to use outcome indicators.

Whether "measures" or "indicators" are used, it is important to be clear from whose perspective the outcome is being considered; is it that of the professionals, the management, the patients, or the carers? For stroke, professionals may seek the best neurological recovery, the patient may seek the best functional recovery, and the management may seek the most cost-effective recovery, all of which will be measured in different ways.

For these various reasons, league tables relying on outcome measures have generated some bizarrely anomalous results and are mistrusted. One District General Hospital which was a beacon site for Stroke care had a very high stroke death rate (Hospital SMR was approximately 120)

but the district SMR was only 94. As a beacon site, the hospital was keeping all patients with transient ischemic attacks and mild strokes out of hospital or in intermediate care facilities – thus the hospital SMR was based upon a different population compared with other hospitals. If public scrutiny of outcome measures is to occur, great care will be required to adjust for the potential confounding factors (Lilford *et al.*, 2004).

COLLECTING THE DATA

Important considerations in collecting data are shown in Table 4.

Defining Terms

Consistency in data collection requires accurate definition of terms. In stroke audit, patients should be managed in a stroke unit. How is a stroke unit defined? Answers to audit questions may not be straightforward. Patients with stroke should have a CT scan, however, if moribund it may not be appropriate. In collecting data a "No but. . ." option will allow for such specific exclusions. The appropriate data to collect from notes may not be clear. If a blood pressure measurement is required during a hospital stay, is it the first recorded measure, the mean, or a measure at some specific time point that is required? How does the data collector deal with a comment such as "Blood pressure normal" rather than a specific measure.

It is essential that these issues are clearly addressed or there will be considerable variability in the audit data collected from different sites and between different auditors. Advice sheets or books addressing these issues are extremely helpful to audit teams and should, where possible, be backed up with recourse to the audit developer to clarify specific issues if necessary. The development of standardized or national data sets are also helpful as they establish key data to be collected and identify the problems that may arise in data collection.

Table 4 Considerations with regard to clinical audit data collection

Define terms	
Define population to be studied	Numerator
Define reference population	Denominator
Case mix adjustment	
Define sample size	
Define sampling strategy	
Define data source	
Define data analysis	
Confidentiality	
Data Protection	
Pilot	
• reliability	
• validity	
• acceptability	

Defining Populations

Outcome measures are often expressed as prevalence rates. Good health care for urinary incontinence should reduce the prevalence of incontinence. How is the population with urinary incontinence to be measured (the numerator)? Is this the population within a ward, a hospital, a general practice list, a Primary Care Trust? Is the prevalence to be determined per 1000 population, per number entering a service or on a GP list (the denominator)? In making comparisons with other health-care settings it will be important that both the numerator and denominator are comparable. Again, clear advice to the auditing team from the audit developer is essential.

Case Mix Adjustment

Comparisons between settings will require case mix adjustment. When planning a project, the ways in which data will be presented, and to whom, should suggest what objections are likely to be raised to the results. Usually, these will be because a particular confounding factor has not been considered. Adding the appropriate extra variables increases the work of the project but ensures that the results/comparisons are accepted as valid. For urinary incontinence when comparing between care in different nursing homes, it will be important to be aware of the physical dependency and cognitive function of people whose care is being assessed. Differences in the numbers of people with dementia and with relevant physical disability such as stroke, will have an important impact on the prevalence and management of continence. There are many potential factors to take into consideration in case mix adjustment. In practical terms, it is sensible to collect only case mix data that are relevant to the planned presentation and use of the data.

Sampling

The sample size must be determined to ensure that meaningful results are obtained. Numbers will vary according to the measure being audited. These are statistical considerations that will not be described in detail but intended to ensure that the results of a project are robust enough to justify changing care practice and are not simply chance findings. In the National Sentinel Audit of Stroke, 40 case notes are retrospectively reviewed. If analyzed alone, it would be hard to reach many conclusions but when compared with 8000 cases from other hospitals, the statistical power is greatly increased. For outcome measures, a power calculation is required depending on the degree of change expected. If the desire is to see whether the management of osteoporosis is satisfactory using fractured femur as an outcome measure, many thousands of cases will need to be studied. If the outcome measure is the appropriate prescribing of bisphosphonates to prevent osteoporosis, meaningful

results can be obtained with small numbers of subjects and can be achieved within hospital departments or general practices.

It may not be possible or practical to obtain all records and some method of randomization may be required. This may be achieved by collecting all cases over a limited period of time – or by the use of random numbers. Care must be taken to ensure that all randomly identified cases are obtained so that no systematic bias influences the findings. It may, for example, prove difficult to obtain notes when a person has died. Exclusion of such patients may have an important bearing on the evaluation of quality of care.

Data Source

Data are usually obtained from patient records. The difficulty in obtaining reliable data retrospectively from patient records is familiar to most health-care professionals. Unless there has been a predetermined data set incorporated into the records systems, there will be inherent difficulties in obtaining reliable data. The problem is more likely to arise with retrospective data collection. Processes and outcomes of care may occur without being recorded. The data required may not be readily accessible. Different departments and practices use different data record systems.

In order to increase the likelihood of reliable data collection, it is better to limit the numbers of items to be collected and to give careful consideration to what is most reliably available in the record systems to be reviewed.

For the future, standardized data collection systems in routine practice, for example, standardized admission clerking sheets, will simplify data collection. Furthermore, the goal should be to incorporate required audit data items into routine collection so that prospective real-time audit data collection becomes possible.

Consent and Confidentiality

Issues of consent and confidentiality are complex. The General Medical Council makes it very clear that patients have a right to have their medical data handled confidentially but also makes it clear that doctors must keep good records and should actively evaluate the services they deliver.

The Data Protection Act in the United Kingdom and parallel European legislation provide important safeguards to individuals to ensure that any data (paper or electronic) held on them is handled in a responsible manner that reflect their wishes. Local audit, that is, the evaluation of care quality within the clinician team is therefore part of direct medical care and does not require specific patient consent. Many patients have care from different parts of the health-care system, for example, diagnosis of a tumor in a district hospital followed by referral to a tertiary center for radiotherapy. Within cancer networks both secondary and tertiary units form part of the cancer team, such that when evaluating the effectiveness of care both parts are important. The concept of the "domain of care" is more useful than simply considering the institution. A guidance document (Information Commissioner, 2001) from the UK information commissioner has described the issues posed by the Data Protection Act and supports the above approach. It also identifies that the analysis of clinical care quality includes both clinical issues (process and outcome) and administrative issues (how the service was delivered). However, while it is permissible to collect data from the records of identified individuals, it is not permissible to identify those individuals in any of the resulting reports or analyses without the specific consent of that individual.

However, an important feature in the Data Protection Legislation is that patients receiving care should be made aware of how their data are to be used. It has not been routine practice in the United Kingdom to provide information leaflets for patients but it is likely to be so in future. If an individual wishes to "opt out" of allowing their data to be used, they have the right to be removed from the system.

Many audit studies would like to combine data from more than 1 unit and thus require local units to submit data to a central analysis system. This can only be done under three very specific conditions

- If the locally collected data are fully anonymized, that is, all identifiers such as name, date of birth, post code, are removed then the data may be transmitted to a center to be aggregated and analyzed.
- If some of the identifiers are retained within the data but encrypted or "pseudonymized" in such a way that no one in the central team can "read" the original, then the data are treated as "effectively anonymized". This may be useful if it is required at a later stage to link the data on an individual across more than one database – an activity that can be performed within the machines via the encrypted identifiers, and without needing central staff to break the code.
- If specific consent has been obtained from each patient to permit the transmission and use of their data.

Each local organization within the health service has an individual – the Caldicott guardian – responsible for monitoring how personal data are handled and shared and anyone setting up an audit that requires for data to be shared beyond the "clinical domain" should check with that local person to ensure that all necessary precautions have been taken.

Those collecting data must also consider other aspects of confidentiality such as the need to store data files in a secure filing cabinet or on a secure computer, and that data protection duties extend not only to the rights of the patient but also the rights of the clinicians delivering the services.

Pilot

It is essential to pilot an audit project. This will indicate whether the data required can be reliably obtained. It will

provide an opportunity for testing interrater reliability of data by asking more than one person to collect similar data. The acceptability of the audit can be assessed. Are the number of items to be collected reasonable, can they be readily found from the records, is there sufficient time to collect the required data, do the collection staff have the expertise to interpret the records in the notes? The validity of the audit can be checked to see whether the pilot results obtained represent a reasonable reflection of practice.

DISSEMINATION AND CHANGE

Clinical audit can only be justified if, when deficiencies are found, there is a mechanism for stimulating change to improve future care. But change is notoriously difficult within NHS systems. The size and complexity of NHS systems are a problem and so too is the lack of clear lines of responsibility. Much research has centered on the mechanisms that can facilitate alterations in clinical practice (Johnston *et al.*, 2000) and some key factors are outlined in Table 5. Unless these factors are addressed at the outset, it is unlikely that improvements in practice, and hence the benefit of audit, will be realized.

Commitment

The clinical team may accept the findings of an audit but be unable to improve care because they do not have the authority to alter the budget or personnel configuration appropriately. Change requires the active cooperation of both clinical team and management. Each audit project should therefore plan how to ensure that the results will have sufficient credibility (data reliability, numbers, case mix control) and that clinicians will embark on the discussions needed to create change. And the planning must also consider whether the right data are being collected that will convince local management that change is needed. Good planning should ensure that the audit topic is considered important and that the aims are shared by all parts of the organization before the data collection even begins.

Identifying the Cause of Problems

Where results of the audit diverge from accepted best practice, the reasons need to be investigated. A simple rule is "investigate before you castigate". It is important not to presume that the divergence is the "fault" of individuals or their morale could be unnecessarily sapped. Good staff may be handicapped by inadequate organization or poor facilities and resources available for service delivery. Or the problem may relate to poor or outdated clinical practice. Once a cause has been identified, an action plan can be drawn up to address the problems.

Table 5 Factors associated with facilitating practice change

Strong commitment to the project
• From management
• From clinicians
Identifying what the problems are
Using effective educational techniques

Educational Methods

Current evidence suggests that there is considerable variation in the effectiveness of differing educational methods. Most recent systematic reviews indicate that multifaceted intervention is not necessarily needed so long as one of the more successful targeted approaches is used. Details of the effectiveness of differing interventions are shown in Table 6.

Simple feedback of results may not be enough. In the National Sentinel Audit of Evidence Based Prescribing, change depended on the activities of local working groups. Within the overall project's 150 centers there was no overall improvement – but in one center there was significant change. This center adopted an active and multifaceted approach and showed what might have been more widely possible (Batty *et al.*, 2001). In contrast, the National Sentinel Audit of Stroke incorporated active regional feedback of data to multidisciplinary teams of clinicians and managers and demonstrated significant changes between audit cycles (Rudd *et al.*, 2001).

Sharing of Data

Access to audit data has become an increasingly important issue. "Medical" and "clinical" audit were both, in origin,

Table 6 Effectiveness of differing educational interventions on clinical practice

Effective
• Educational outreach visits (Thomson O'Brien *et al.*, 2004a)
• Reminders (manual or computerized)
• Multifaceted interventions (including two or more of the following: audit and feedback, reminders, local consensus processes, marketing)
• Local opinion leaders (Thomson O'Brien *et al.*, 2004b)
• Local consensus processes (inclusion of participating practitioners in discussions to ensure they agree that the chosen clinical problem is important and the approach to managing the problem appropriate)
• Patient-mediated intervention (any intervention aimed at changing the performance of health-care professionals for which specific information was sought from or given to patients)
Ineffective
• Educational material (distribution of recommendations for clinical care, including clinical practice guidelines and electronic publications)
• Didactic educational meetings, for example, lectures (Davis *et al.*, 1999).

Source: Adapted from Pruce D, Aggarwal R. National Clinical Audit – a handbook for good practice (Pruce and Aggarwal, 2000).

a professional process for improving the quality of care. With the advent of clinical governance derived from the NHS White Paper *The new NHS: modern and dependable* (Department of Health, 1997), audit has become very much part of the management process. Clinical data is increasingly required and used in monitoring the quality of services provided and the individual performance of clinicians. Audit data from multicenter projects are now made available at local Hospital and Primary Trust level, to strategic health authorities and nationally to the Department of Health and to regulators such as the Healthcare Commission. It may be better to consider multicenter audit not just as an assessment of local quality against a benchmark, but as a form of clinical performance management.

Information should also, whenever possible, be shared with the public. Results need to be presented in a manner that is understandable and will not include all the details of interest to clinicians. Such data may well in future be included in legal arguments over services and fitness to practice.

While this more open use of data is inevitable and will help drive the benefits of audit, it challenges those performing the audit process (managers and clinicians alike) to ensure that audit data are a true and fair reflection of the service and practice under review.

REAUDIT AND SUSTAINING IMPROVEMENT

Reaudit must be carried out to "close the loop" and assess whether changes in service have resulted in improvement and to ensure that improvements are maintained.

Ideally, with audit data incorporated within routine data collection, prospective monitoring of performance can be maintained. Where recurrent "snap shot" audits are required, it can be challenging for services to keep coming back to the audit of one particular subject.

In general practice, several clinical effectiveness programs have been developed which have achieved recurrent audit with sustained improvements in practice for example, the Primary Care Clinical Effectiveness (PRICCE) project (Bandolier, 2005). The essence of these programs has now been incorporated into the new general practice contract requiring general practitioners to achieve quality standards.

While the primary care experience is linked in part to financial benefits which would be difficult to replicate in the secondary care setting, the apparent success of these programs would suggest that a lesson could be learnt which might be applied to the secondary care system.

CONCLUSION

There is good evidence that clinical audit performed well can identify substandard care, can stimulate changes that improve care, and can confirm sustained improvement. Although the principles have been known for many years, audit has not been taken seriously by the professions and the health service has invested very little in quality of care assessments.

The advent of computing makes data collection relatively easy in every clinical setting and as electronic patient records are introduced in the next decade, so the opportunities will mushroom. Clinicians need to take the opportunities that now exist to contribute to well-designed and targeted clinical audit programs. Subjects should be chosen which are of priority importance locally and nationally and where there is evidence that current practice is suboptimal. Clinicians should get involved with the intention of seeking sustained improvements in the service they provide. All clinicians should seek to ensure that their job specification includes time for audit, and this should be seen as a duty and not an optional extra. Health-care management needs to be committed wholeheartedly to the process. The commitment must firstly be to providing the infrastructure in terms of well-established audit departments whose strategy is an integral part of the Trust strategy. There should be investment in systems for simplifying data recording and retrieval and there should be a commitment to routine audit data collection. Management also needs to demonstrate willingness to review and improve facilities, resources and staffing if such is required to improve services. Success breeds success. The realization that audit can induce change and improvement would strongly encourage commitment to the process.

KEY POINTS

- The time has come for everyone in the NHS to take clinical audit very seriously.
- Personnel, resources and information technology for audit must be built into organizational structures.
- Audit data collection must become part of routine clinical data collection.
- Managerial and clinical commitment to changes in practice to enhance care is a prerequisite for audit to be beneficial.
- Increasing public scrutiny of audit results places a responsibility on managers and clinicians to ensure the validity of data.

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Improving Quality of Care

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INTRODUCTION

Throughout most of history, medical care was delivered to an individual patient by an individual clinician. Public health services were rarely available and infection control practices were poorly understood. Institutional care was uncommon and reserved for those with means to afford the medical services. Over the last century, medical care has drastically changed through the development of antibiotics, immunizations, and new surgical techniques. The world's population is now growing rapidly, is aging, and requires more health services. Population-based medicine has become a priority as cost, volume, and efficiency have become critical issues in meeting the growing health-care demands of the medical consumer.

From providing services to meeting standards of practice, the health-care industry is under increasing pressure to provide the highest level of services to the greatest number of recipients. In an era of limited health-care dollars, practitioners often must do more with less, yet, medical advances and fear of litigation drive the cost of care upward. For these reasons, efficient, high-quality care is of increasing importance. Consumer groups, medical societies, and health-care organizations have been at the forefront in promoting quality in health care. With a collective voice, these groups have promoted change in the health-care system. Although slower than many other industries, the health-care establishment has recognized the importance of delivering quality goods and services.

With the advent of computers, the growth of the pharmaceutical industry, and advances in diagnostic technologies, the level of medical sophistication has risen dramatically. Clinicians and patients now have a multitude of therapeutic options that were unavailable only a few years ago. As with other industries, however, quantity of services does not automatically equate to quality of services. It is necessary to critically evaluate not only medical treatments and techniques but also the process by which medicine is delivered to the health-care consumer. Defining quality, measuring performance, and changing ineffective practices must now become routine activities as medicine moves toward more efficient and effective methods of health-care delivery.

THE HISTORY OF QUALITY

The History of Quality in Business

In 1906, the International Electrotechnical Commission (IEC) was established to provide uniformity to the electrotechnical field. (see Appendix 1 for organizational abbreviations) The IEC promoted quality, safety, performance, reproducibility, and environmental compatibility of materials and products. This was the first organization to develop international standards of business practice.

The International Federation of the National Standardizing Association (ISA) was another organization, focused on mechanical engineering, which set standards for industry and trade from 1926 to 1942. After ISA dissolved, a delegation of 25 countries convened to create a new organization to unify the standards of industry and production practices. In 1947, this organization, the International Organization for Standardization (ISO), was established in the United Kingdom to oversee the manufacturing and engineering trades.

The ISO is a federation of nongovernmental bodies now representing 148 countries across the world. The ISO has developed international standards by which trade, technology, and scientific activities can be measured. Companies may choose to be certified by the ISO-9000 quality management system. This certification ensures a minimum standard by which business processes, quality management, and safety are maintained International Organization for Standardization (2004). ISO certification is especially important for international and intercontinental business to ensure a uniform delivery of goods and services. The health-care industry is

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one of many fields that may be evaluated in the ISO method. Although used in some countries to evaluate medical practices, it is not widely accepted as a suitable model for the health-care system.

Around the same time, that ISO was created, Dr W. Edwards Deming, a physicist and statistician from the United States, developed a new process for quality improvement in business. Through this process, all members of a work unit were responsible for continuous monitoring and improvement of products along all steps of production. High frequency errors were identified, corrected, and the resulting outcome monitored for improved quality. Any step in the production process could and would be a continuous target for revision. In this method, focus was shifted from the specific error of an individual to the systemic faults that allowed an error to go unnoticed or proceed uncorrected. The workforce was thus empowered to identify problems and institute a plan of correction. Deming introduced this process, now known as *Continuous Quality Improvement* (CQI) and also referred to as *Total Quality Management* (TQM), in Japan where it quickly led to a revolution in the efficient manufacturing of high-quality goods.

Deming knew that successful management of a complex process or problem required the focused attention of a team of individuals. Although each member was uniquely skilled in a task, the team worked together in developing solutions. The TQM process is well suited for quality improvement in the complex health-care environment, but has not historically been embraced by the medical establishment. The narrow view that blame for errors be placed on a single individual and that physicians be allowed autonomous control over medical processes has hindered the acceptance of TQM. This view is changing as organizations realize that medical errors and inefficiencies are usually the result of systemic problems that require multifactorial solutions.

The Evolution of Quality in Health Care

One of the first efforts to standardize medical delivery occurred in 1917 with the "Minimum Standard for Hospitals" program set forth by Drs. Franklin Martin and John Bowman of the American College of Surgeons (ACS). A one-page, five-point set of criteria was crafted to assess the quality of hospitals (Shaw *et al.*, 2003) (see Table 1). In 1918, only 89 of 692 hospitals surveyed met the minimum criteria.

The ACS was responsible for hospital accreditation until 1952 when the Joint Commission on Accreditation of Hospitals (JCAH) was established to take on this responsibility. Led initially by Dr. Arthur W. Allen, the JCAH published standards for hospital accreditation in 1953. The JCAH initiatives were also incorporated outside the United States, with Canada offering its own accreditation through the Canadian Commission on Hospital Accreditation in that same year. Over the next two decades, the JCAH grew to include the review of long-term care facilities in 1966 and subsequently, mental health, dental, ambulatory care, and laboratory facilities. In 1987, JCAH was renamed the Joint Commission on Accreditation of Health care Organizations (JCAHO) to encompass the variety of services and activities offered Joint Commission on Accreditation of Health care Organizations (2004).

Table 1 "The Minimum Standard" – American college of surgeons 1917

1. That physicians and surgeons privileged to practice in the hospital be organized as a definite group or staff.
2. That membership upon the staff be restricted to physicians and surgeons who are
   (a) full graduates of medicine in good standing and legally licensed to practice
   (b) competent in their respective fields
   (c) worthy in character and in matters of professional ethics.
3. That the staff initiate and, with the approval of the governing board of the hospital, adopt rules, regulations, and policies governing the professional work of the hospital.
4. That accurate and complete records be written for all patients and filed in an accessible manner in the hospital.
5. That diagnostic and therapeutic facilities under competent supervision be available for the study, diagnosis, and treatment of patients.

JCAHO has been a world leader in health-care accreditation and a prototype for further development of organizations that monitor and measure the quality of health-care delivery. Over the past two decades, the interest and efforts in health-care quality have grown exponentially. A variety of national and international organizations have evolved to assist the heath-care industry in meeting new consumer and regulatory demands for high-quality services and programs.

Organizations Leading Health Care Quality Improvement

In the United States, the Agency for Health care Research and Quality (AHRQ), previously the Agency for Health Care Policy and Research (AHCRP), is a leader in health-care quality initiatives. Founded in 1989, this agency of the United States Department of Health and Human Services (DHHS) has a mission to improve the health-care quality, safety, efficiency, and effectiveness for all Americans. AHRQ awards millions of dollars in grants to further evidence-based–outcomes research related to health-care quality improvement. Federal legislation authorizes AHRQ to coordinate health partnerships, support research, and advance information and technology systems. Of the many projects that are overseen by AHRQ, the United States Preventive Services Task Force (USPSTF) and Consumer Assessment of Health Plans (CAHPS) are most prominent.

The USPSTF is a 15-member, private-sector panel of experts, first convened by the United States Public Health Service in 1984 to develop and assess evidence-based preventive service measures. The hallmark publication of this taskforce titled "Guide to Clinical Preventive Services" was published in 1989, with a second edition released in 1996 U. S. Preventive Services Task Force (2003). Although clinicians and health-care societies do not always agree upon the details, these guidelines are frequently cited as "best

evidence" and considered to represent the "standard of care" in preventive medicine services.

CAHPS is an organizational databank of health-care information used by consumers, employers, and health plans in evaluating heath-care systems and services. Surveys and reporting instruments are used to collect and present information on health-care providers such as Medicare and the Federal Employees Health Benefits Program. In the private sector, the National Committee for Quality Assurance (NCQA) reviews the quality of managed care health plans. Established in 1990, this nonprofit group also accredits the health-care organizations. The NCQA has recently partnered with AHRQ in support of the CAHPS program.

The Institute of Medicine (IOM) is another leader in the development of quality health care in America. This nonprofit organization was chartered in 1970 as a segment of the National Academy of Sciences. The mission of the IOM is to work outside the governmental framework in providing an independent, scientifically based analysis of the health-care system. "Quality of Care" was defined by the IOM in 1990 as, "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" (Richardson and Corrigan, 2002).

IOM formally launched the first of three phases of a quality initiative plan, beginning in 1996 with an intensive review of the state of health care in America. In a statement declaring "The urgent need to Improve Health Care Quality", the IOM began focusing on overuse, underuse, and misuse in medical care. During Phase Two, the Quality of Health Care in America Committee convened and has since published several reports, including "To Err is Human: Building a Safer Health System" and "Crossing the Quality Chasm: A New Health System for the twenty-first century".

More recently, the committee has lobbied for an error reporting system and legislation to protect those who report errors in an effort to promote quality improvement strategies. Twenty "Priority Areas for National Action" have also been established based on diseases or conditions that may be best managed using clinical practice guidelines.

The IOM has established six "Aims for Improvement" in health-system function. Health care should be (1) safe, (2) effective, (3) patient-centered, (4) timely, (5) efficient, and (6) equitable. The Committee has also identified "10 simple rules for (health-care system) redesign" which change the focus of health care from provider driven to consumer/system driven care.

In the United Kingdom, the National Health Service (NHS) has received annual reviews since the Commission for Health Improvement was established in 1999 by the national government. In April 2004, this organization was replaced by the Health-care Commission, which is charged with the task of reviewing and improving the quality of health care in the NHS and in the private sector. The Health-care Commission collects data on patient satisfaction and the health-care process on both a local and national level. This data is available for public inspection.

In Australia, evaluation and accreditation of medical practice takes place through the Australian Council for Health Care Standards (ACHS). Established in 1974, ACHS is an independent body comprising health-care leaders, governmental representatives, and consumers. ACHS accredits programs using a standardized model called the *Evaluation and Quality Improvement Program* (EQuIP). EQuIP sets standards in two broad categories: (1) patient-care services across the continuum of care and (2) the health-care infrastructure The Australian Council on Healthcare Standards (2002). ACHS also provides a Performance and Outcomes Service (POS) that measures the quality of patient care in health-care organizations. Using Clinical Indicators that quantitatively and objectively measure care, the POS compares individual performance to national aggregate data. Outlying data generates a "flag", which can alert the organization to quality control problems.

Australia is also home to The International Society for Quality in Health Care (ISQua). This nonprofit organization, representing 70 participating countries, provides services and information on health-care quality to medical providers and consumers. ISQua hosts an annual international summit to discuss performance indicators and promote a multidisciplinary approach to quality improvement programs. Participants include health policy leaders, researchers, health-care professionals, and consumer organizations. ISQua has established international standards for national health-care accreditation bodies, through their Agenda for Leadership in Programs for Health care Accreditation (ALPHA). The ISQua also supports the International Journal for Quality in Health Care, a peer-reviewed journal in its 15th year of publication.

Models for Evaluating Quality

The approach to quality in health care bears many similarities to quality improvement in the commercial sector by focusing on key issues of safety, effectiveness, consumer satisfaction, timely results, and efficiency. Within Europe, there is much diversity in the oversight and governmental mandates for quality of health-care practice. Most legislation surrounds the health system and hospital accreditation process, with less emphasis placed on individual clinical practices. On the basis of the established health care and payer system, each country may address quality control quite differently.

To better understand the most common methods of measuring health-care quality, a survey of European External Peer Review Techniques (ExPeRT) was initiated (Heaton, 2000). The results of this ExPeRT Project revealed four commonly used quality improvement models: health-care system accreditation, ISO certification (both discussed previously in this chapter), the European Foundation for Quality Management (EFQM) Excellence Model, and the Visitatie peer review method.

The EFQM was founded in 1988 by presidents of leading European companies and has used the "Excellence Model" for assessing the quality of an organization (Heaton, 2000).

The framework for this TQM approach includes nine criteria by which an organization is evaluated on "what it does" and "what it achieves". A Quality Award is presented after a process of self-assessment and internal review. Over 600 companies have been granted EFQM awards, and research indicates that the companies who employ these quality management principles demonstrate substantial financial and employee growth (Singhal and Hendricks, 2001).

The Visitatie model originated in The Netherlands and focuses on medical practice specifically, rather than on business practice broadly. Visitatie is a peer review process that uses practice and practitioner-derived guidelines to evaluate patient care. Emphasis is placed on individual and team performance, not organizational structure or outcomes. Unlike other methods, Visitatie does not result in a certification or accreditation award. Because the focus is on improving care through peer feedback, there is no "pass/fail" or punitive outcome. This model is becoming popular across Europe as a method for personal and peer review of medical care (Heaton, 2000).

Quality Improvement in Geriatrics

The elderly population is prone to adverse outcomes, especially when health-care delivery is fragmented. Research has demonstrated that adverse health events are more likely to occur in the elderly population and that the risk of adverse hospital events is twice as high for individuals over age 65 (Leap *et al.*, 1991; Miller *et al.*, 2001). Preventive medicine for seniors includes identifying patient safety issues that can lead to functional decline and poor-health outcomes. Identifying risk factors for decline and providing early intervention is effectively approached through a health care team-based TQM process.

Quality in health care has evolved from a reactive Quality Assurance (QA) model (Figure 1), to a proactive TQM model (Figure 2). Instead of focusing on compliance and adherence to external regulations or standards (QA model), TQM focuses on the continuous process of improving care relative to current internal practices. TQM involves not only change in practices on an individual level but also change in process on a larger scale that can benefit a broader population.

In the TQM team process, each discipline reports data collected on patient care since the previous team meeting, as well as areas of ongoing concern or newly identified issues. The team discusses markers (indicators) of quality and establishes targets to achieve by the next meeting. The team then develops a plan for achieving these targets. A method of measuring performance and collecting data is established. An individual or subcommittee is then assigned to carry out the quality improvement protocol and provide a progress report at the next meeting. If the goals are achieved, data continues to be tracked over time to identify trends in performance and to maintain the established goals. If previously established quality targets are not met, barriers or obstacles are explored.

Geriatricians are in a unique position to take a lead in the health-care quality improvement process. Interdisciplinary management and teamwork are at the core of geriatrics training and practice. Geriatricians are comfortable entrusting responsibility to team members and sharing in the problem-solving process. This is a requirement for the success of TQM programs. Geriatricians are also more likely than other physicians to have experienced the TQM process, as this is a routine activity in long-term care facilities. Through TQM, data on events such as falls and dehydration are tracked and shared with the staff at regular intervals. Trends are then discussed and solutions proposed when outlying results are identified.

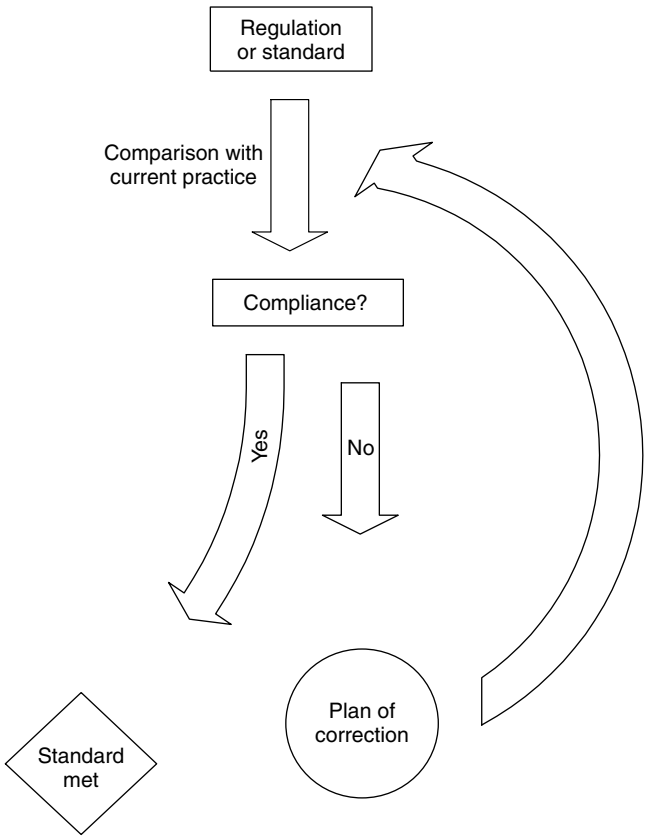

Figure 1 Quality assurance model

Quality Indicators

In the United States, markers for quality in nursing home care, termed "*Quality Indicators*" (*QIs*), have been developed and tracked by the federal government through the completion of the required Minimum Data Set (MDS) resident evaluation questionnaire (Center for Health Systems Research and Analysis 1999; Zimmerman *et al.*, 1995) (*see* Table 2). Sentinel event and prevalence rates for 24 outcomes such as dehydration, decubitus ulcers, and falls are obtained from data on the MDS. Facilities are compared with local and national data for these markers. Outlying rates on the markers are "flagged" which may prompt investigation or oversight by the state nursing home regulatory board.

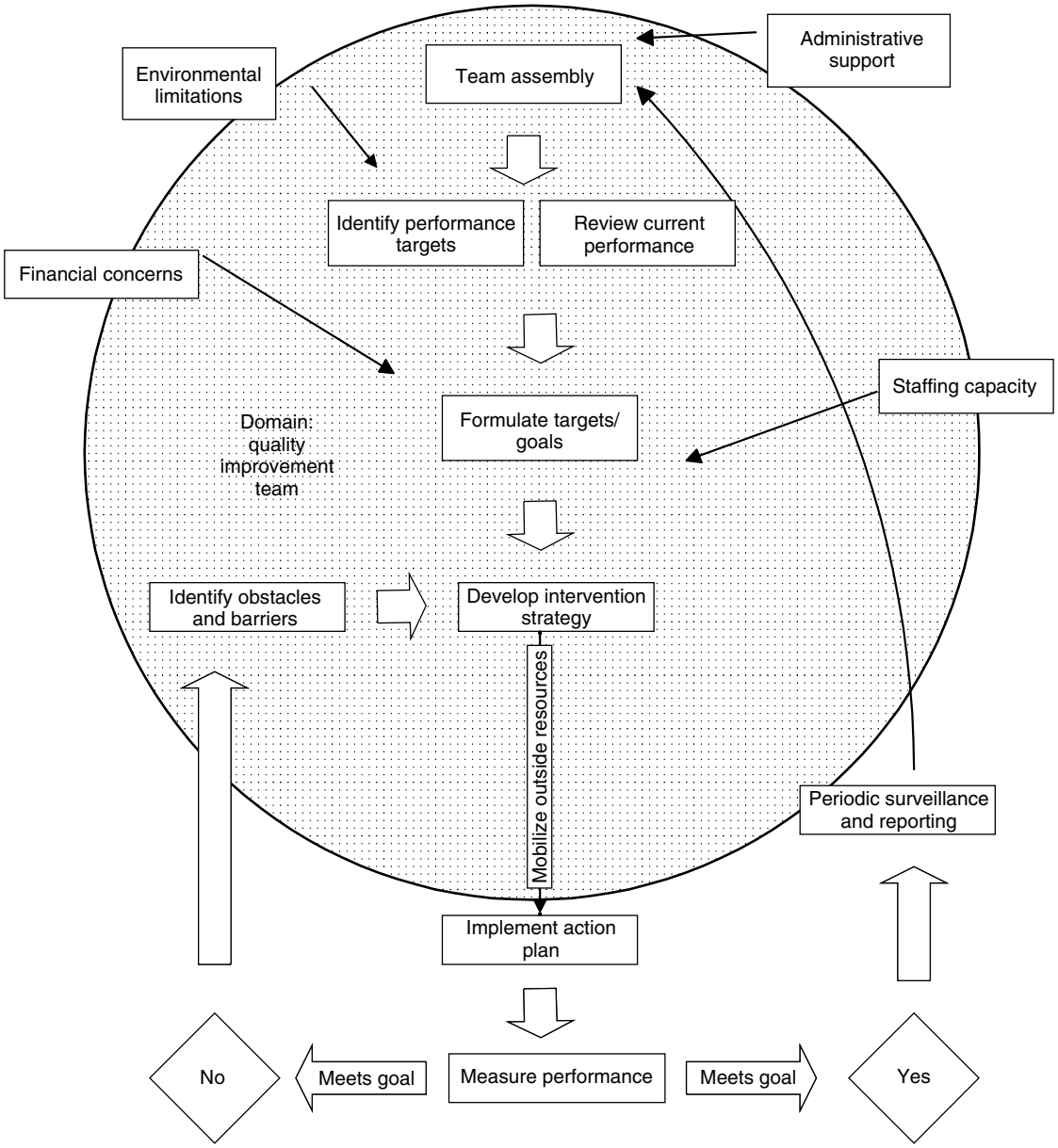

Figure 2 Total quality management (continuous quality improvement) model

The accuracy and utility of data extracted from the MDS has been debated, but quality indicators continue to serve as triggers for further assessment and care plan changes in the nursing home resident. Schnelle and colleagues have published a tremendous body of literature on the care process and health outcomes in nursing homes on the basis of information obtained from the MDS (Bates-Jensen *et al.*, 2004; Schnelle *et al.*, 2004; Cadogan *et al.*, 2004; Saliba and Schnelle, 2002). In some cases, the quality indicators are strongly associated with a positive or negative clinical outcome (Schnelle *et al.*, 2004; Cadogan *et al.*, 2004). In other cases, the indicators do not predict an event that might be expected on the basis of the provided data (Bates-Jensen *et al.*, 2004; Schnelle *et al.*, 2004).

The existing quality indicators do not adequately address quality of life and provision of daily care services. To address these issues, an expert panel of geriatricians convened and developed an additional set of quality indicators that complements the existing MDS-derived indicators. These measures may better track the quality of day-to-day care in nursing facilities (Saliba and Schnelle, 2002). The quality indicator domains include (1) preferences for daily life activities (2) frequency and form of activities of daily living (ADL) assistance (3) activity (4) assistive devices (5) goals of care and (6) communication. Although considered markers of quality care, many of these QIs are successfully achieved only in "the best nursing homes". Thus, although a target to strive for, these QIs may not be attainable for the average facility.

Table 2 Nursing home quality indicators

Domain	Quality indicator
Accidents	1. Incidence of new fractures
	2. Prevalence of falls
Behavior/Emotional patterns	3. Prevalence of behavioral symptoms affecting others
	4. Prevalence of symptoms of depression
	5. Prevalence of depression with no antidepressant therapy
Clinical management	6. Use of 9 or more different medications
Cognitive patterns	7. Incidence of cognitive impairment
Elimination/Incontinence	8. Prevalence of bladder or bowel incontinence
	9. Prevalence of occasional or frequent bladder or bowel incontinence without a toileting plan
	10. Prevalence of indwelling catheters
	11. Prevalence of fecal impaction
Infection control	12. Prevalence of urinary tract infections
Nutrition/Eating	13. Prevalence of weight loss
	14. Prevalence of tube feeding
	15. Prevalence of dehydration
Physical functioning	16. Prevalence of bedfast residents
	17. Incidence of decline in late-loss activities of daily living
	18. Incidence of decline in range of motion
Psychotropic drug use	19. Prevalence of antipsychotic use in the absence of psychotic or related conditions
	20. Prevalence of any antianxiety/hypnotic use
	21. Prevalence of hypnotic use more than two times in the last week
Quality of life	22. Prevalence of daily physical restraints
	23. Prevalence of little or no physical activity
Skin care	24. Prevalence of Stage 1 to 4 pressure ulcers

Geriatric Medicine Organizations Focus on Quality

Interest groups and specialty organizations such as the American Geriatrics Society (AGS), American Medical Directors Association (AMDA), British Geriatric Society (BGS), and Australian Society for Geriatric Medicine (ASGM) have taken a leadership role in bringing global quality improvement initiatives to the aging population. These organizations work within the health-care framework and governmental regulations unique to each country. Whereas national physician organizations focus efforts widely across the health-care system, these specialty groups address aging-specific health-care issues.

The ASGM has established a series of position papers that outline standards for geriatric care in Australia. One area of growing interest is in reduction of falls and fall-related injuries (Australian Society for Geriatric Medicine, 2004). Fall-related hospitalizations have increased to 0.8–1.4/year/100 adults aged 65–74, and accounted for 38.29 deaths/year/100 000 elders in 1996 (Australia Institute of Health and Welfare, 1997). With funding from the Australian Government Department of Health and Ageing, the Royal Australian College of Physicians (RACP) has developed a strategic plan, targeting general practitioners, to address the rate of falls and injuries.

The British Geriatrics Society has also published position papers on the care of elders in the United Kingdom including topics of palliative care, falls, and post-acute care of elders with hip fracture (British Geriatrics Society, 2004). One way the United Kingdom has addressed the quality of hospital care for seniors with orthopedic trauma is through the development and expansion of orthopedic rehabilitation units. These wards provide multidisciplinary care and partnership between geriatric medicine consultants and orthopedic surgery physicians. Although, individual studies have demonstrated some benefits in reducing length of stay and improved functional outcomes, a Cochrane Database analysis on the subject did not find conclusive evidence that coordinated multidisciplinary hip fracture care improved postsurgical outcomes (Incalzi *et al.*, 1993; Kennie *et al.*, 1988; Cameron *et al.*, 2003). In contrast, the United Kingdom NHS reported good evidence for pursuing collaborative approaches to geriatric care and has set a standard that, "All general hospitals which care for older people have identified an old age specialist multidisciplinary team with agreed interfaces throughout the hospital for the care of older people" (The Department of Health, 2004).

In the United States, medical organizations regularly lobby Congress on behalf of the geriatric medicine profession and elderly patients. The institution of a prescription drug benefit for Medicare health insurance beneficiaries is one example of the influence of health-care organizations and consumers on health-care policy and quality. The AMDA has been a tremendous advocate for quality, focusing primarily on the long-term care setting. AMDA has created clinical practice guidelines for nursing home care and has established a certification process for medical directors in these facilities. Within the medical community, AMDA has pressed for a change in approach to long-term care and is viewed as the leading organization in long-term care reform.

From a consumer perspective, the Leapfrog Group is an organization with great potential for influencing the quality of health-care plans and services. Founded by Fortune 500 executives, this group of over 150 companies aims to improve patient safety by lobbying for computerized physician ordering systems, appropriate patient referrals to subspecialty hospitals, and uniform critical care staffing in intensive care units. The Leapfrog Group represents 34 million health-care consumers and uses its health-care benefit purchasing power to influence the insurance industry in delivering health care that meets these quality standards (The Leapfrog Group for Patient Safety, 2004).

QUALITY IN THE NURSING HOME

When trying to improve quality of care, one must first characterize quality. Quality is the degree to which an

outcome measures up to the expected gold standard. In health-care delivery, a quality process or intervention is measured against a standard practice that is administered to an individual patient, in a given situation, with a particular problem. Deviations from the standard of care affect the quality of care. Patients and their families expect health services to meet or exceed the standard of care, but may not understand what constitutes a reasonable standard.

To maintain the highest quality of care, continuous system-wide observation, evaluation, and monitoring are needed. Health-care managers are responsible for establishing performance standards for their staff and ensuring that these standards are met. The employees should feel comfortable providing feedback to the supervisors when aspects of health-care delivery require improvement. Managers must work with facility administrators to negotiate the resources necessary to allow the staffing team to carry out daily duties in an effective manner. Many quality improvement teams use the term "continuous quality improvement" to describe this process because maintaining quality is an ongoing activity.

Identifying the Problem

Areas of concern are brought to the attention of the health-care manager through a variety of avenues. In the long-term care setting, a nursing home administrator collects and catalogs this information through direct or indirect contact with residents, their families, and the facility staff. Administrators should also expect feedback and performance reports from the medical director and attending physicians working within the facility. At times, areas of concern may also come from the community or neighborhood hospitals.

All areas of concern are important. Substandard performance must be identified and immediately corrected. Good communication between all members of the facility is essential to ensure a positive resolution to a perceived problem. In one illustrative example, a husband is concerned about the care of his elderly wife in the nursing home because when he visits early each morning she is still in bed. After talking to the husband, it is learned that the wife was always an early riser. For years, they have had coffee first thing in the morning together. Because she is not assisted out of bed in the early morning to have coffee with her husband, he feels that she is receiving poor nursing care. Once these care expectations were identified and a solution communicated to the nursing staff, the patient was able to again enjoy the special morning time with her husband. The husband's perception of the nursing care improved and positive interactions at the facility could then ensue. Through good communication and problem solving, both husband and wife are now satisfied with the quality of care they receive.

Identifying a problem shortly after it occurs and promptly initiating a plan of correction is paramount. Timeliness often affects outcome. First impressions are very important when a patient first enters a long-term care facility. Every effort must be made to ensure that the transitional period is a positive experience. Positive experiences might include having a greeter meet residents when they first enter the facility. The greeter may be another nursing home resident or a nurse to assist them with the admissions process. A knowledgeable staff member should be available to answer questions for new residents and their families. Having a room ready upon arrival is also important in making the resident feel welcome. After acclimating to the facility, it is important for the residents to have periodic meetings to discuss the plan of care. These meetings help maintain a good line of communication and empower the resident to be a participant in the health-care process.

The Nursing Home Administrator

The nursing home administrator is responsible for the overall care within a facility and must handle all areas of concern that arise. Problems should be examined and categorized to better understand the origin of the difficulty. This information can alert the administrator to potential problems or areas of concern that need to be addressed. Nursing home administrators should be visible and accessible to families and residents, as well as staff, when responding to facility concerns. Most concerns fall into one of three categories: nursing care, laundry/housekeeping, and food. When complaints increase, the facility administrator must investigate and take steps to correct the problem.

Nursing Care

There are many interrelated components that impact the care provided by facility nursing staff. One of the most important areas, besides ensuring skill proficiency in the nursing staff, is the organization and function of nursing "systems". Systems of nursing practice must be in place in order to deliver high-quality care. Two examples of these "systems" include the structure of the nursing staff and the function of the nursing staff. Critical components of these systems include staffing patterns, delegation of work assignments, supervision, and evaluation of performance. Educational programs for the nursing staff should also be provided on an ongoing basis. The nursing assistants as well as the licensed nurses need to learn and review basic skills as well as specialty techniques necessary for the care for their residents. Ensuring a smoothly running system requires responsibility, good communication, respect, and clearly defined expectations. Nurses and administrators must view their interactions as two-way streets in order to build and maintain well-functioning nursing systems within a facility.

To maintain high-quality care, nurses must be able to identify residents "at risk" for unwanted outcomes. This can be performed during weekly multidisciplinary "high risk" needs assessment meetings for problems such as skin breakdown, falls, and confusion. Because mental status may change quickly and without notice in older adults, medical status must be assessed frequently. Nursing managers should

periodically review high-risk individuals to help assure optimal care. Routine nurse manager oversight can address these and other potential problems before serious issues occur.

Laundry/Housekeeping

A second common area for concern in the provision of quality in long-term care facilities is its cleanliness. The administrator must convey to all of the staff that everyone be a participant in keeping the facility clean. All employees, from the director of nursing to the office assistant, should feel empowered to properly dispose of unattended waste or reduce clutter at the nursing stations. When trash and clutter are observed throughout the facility, the public perception is that care in other ways may also be substandard. Unpleasant odor is another factor that implies a lack of cleanliness. When the scent of urine or feces is present, even if transient, there may be a perception of poor patient care. Once a foul odor is identified, it must quickly be extinguished. Excessive rubbish and unpleasant odors imply to residents and families both a lack of concern and a lack of proper staffing in the facility.

Laundry, when done at the facility, is a service that frequently generates complaints. Laundry that is lost or not returned in a timely manner reduces patient dignity and increases care costs for residents and families. Lost clothing may be minimized by individually marking each item with a permanent marker or tape, or by placing a person's clothing in a special washing garment bag. Laundry problems may be best curtailed by encouraging residents to have clothing marked and by educating families on the laundering process. Some clothing does not withstand the rigor of industrial laundering and is best cleaned by the resident's family.

Food

It is difficult to please everyone when serving a large amount of food on a daily basis. A common complaint from nursing home residents is that their food is cold when it should be hot and that is not presented to them in a timely manner. Using a buffet-style dining system or a menu selection process can increase resident satisfaction. Allowing residents to participate in food choice improves interest in meals and adequate caloric consumption. Residents also need to participate in choosing the types of meals they receive. This can be done by interviewing the resident or by discussing meal plans at "Resident Council Meetings". Having an occasional "special" meal is also pleasurable and gratifying.

Quality Improvement Meetings

Members of the quality improvement team should include pharmacy, lab, attending physicians, the medical director, nursing, therapy, dietary, maintenance, activities, social service, medical records, and administration. Many long-term care facilities meet only on a quarterly basis to discuss various issues of quality care. This is not frequent enough. Monthly meetings help improve the communication of information and remind everyone of quality initiatives and areas for improvement.

Pharmacy should present the monthly number or percentage of residents on antipsychotics, anxiolytics, and antidepressants. By reassessing the continued need for psychotropic medication in nursing home residents, dosing and prescribing reduction frequently occurs. Pharmacy should also report the incident and type of medication errors and assist in developing methods to reduce errors. To minimize possible drug–drug interactions, a goal of nine medications or less per resident should be a target at the facility.

The laboratory service provider should report the number of microbial cultures performed during that month with those that were negative as well as positive. Organisms that are identified are reviewed along with antibiotic sensitivity patterns. Timeliness of the cultures reported to the facility and institution of appropriate antibiotics are reviewed. Trends in organisms, antimicrobial sensitivity, and clustering of infections should be assessed. Laboratory services should also investigate unnecessarily prolonged return of blood work reports and the effectiveness of data transmission to the nursing facility.

Each month, nursing should present the number of residents who developed decubitus ulcers, have indwelling foley catheters, and received physical restraints. To reduce the rate of injuries and falls, each facility should strive to be restraint-free (Capezuti *et al.*, 1998). The rate of facility-acquired decubitus and indwelling foley catheters, should be under five percent. If rates rise above five percent, action should be taken to justify or remedy this trend. Weight loss and excessive gain should be reported every month, including a probable cause and a plan of correction. Awareness is key and all disciplines can participate in weight loss prevention protocols.

Incident reports should be reviewed monthly. Investigation of resident incidents should include type, location where the incident took place, time of day (during which shift), weekend versus weekday, and degree of injury or impact. Trends or patterns in this data should be noted and a plan for incident reduction implemented. Employee incidents should also be evaluated. An increase in employee incidents and injuries is often directly related to employee dissatisfaction.

Patient census should be reviewed at each meeting along with admissions, transfers to and from the hospital, discharges to home/another facility, and deaths. When looking at nursing home admissions, one should also look at the source of their admission. Was the new admit from a hospital, and if so, which hospital? Are admissions trending up or down? What days and times are the hospital admissions arriving at the nursing home? Transfers to the hospital or emergency department should also be tracked. Was the transfer preventable? Are certain shifts or floors more likely to transfer residents out for urgent evaluation? This valuable information allows the nursing home administrator and

director of nursing to identify staffing or skill deficiencies within the facility.

When providing therapy to the long-term care resident, the therapist needs to keep a record of the functional level prior to therapy, the number of days in therapy, the functional level when therapy was discontinued, and disposition upon discharge. It has been demonstrated that extending therapy for a few more days often improves overall outcome. Therapy services can use this information as a marketing tool. The department may display, in a graphic format, the functional level of residents prior to illness, upon initiation of therapy, and upon discharge of therapy.

The quality improvement process that is discussed and monitored during team meetings should be documented in an organized and systematic manner using a standardized reporting process (Table 3). Topics relevant to patient-care quality (e.g. falls) are selected by the team. Indicators of quality (e.g. fall rate, injurious falls, number of fractures) are identified and a target rate for the facility is established (e.g. <5 percent of falls resulting in injury). Data on patient outcomes is collected within the facility and compared with the established indicator target. If current standards fail to meet the target, areas for improvement (e.g. reducing nighttime falls) are identified and a plan of action established (e.g. scheduled toileting at bedtime). During the follow-up phase, data on the indicators is again collected to determine if the intervention has resulted in successful achievement of the established goals.

QUALITY IN ACUTE-CARE PRACTICES

Hospital Accreditation

The internationally recognized JCAHO mission is to provide accreditation and performance review for the safety and quality of health-care facilities. Established over 50-years ago, this independent nonprofit organization reviews not only hospitals, but also a variety of health-care facilities such as nursing homes, home-care organizations, health-care networks, outpatient centers, and clinical laboratories. Accreditation is a marker of quality valued by the community and used to promote the excellence of an institution.

Accreditation takes place after undergoing an on-site survey by a team of medical and business professionals. All aspects of care are reviewed, including compliance with safety procedures, patient-care processes, and the work environment. Hospital accreditation is valid for three years. JCAHO uses standardized performance criteria that were developed with the expertise and guidance of health-care leaders in academic medicine, business, and governmental agencies.

In an ongoing effort to improve the accreditation process, JCAHO implemented the ORYX initiative in 1997. This project integrates performance and health outcome measure in the evaluation of patient safety and delivery of health-care services. Accredited organizations are required to collect data on health outcomes and submit this information to JCAHO as a part of the evaluation process.

In other parts of the world, the hospital evaluation process may take place through national regulatory organizations. In Europe, hospital accreditation was first introduced in Spain through the Catalan Hospital Accreditation Programme (CHAP) in 1981 Clinical Accountability, Service Planning, and Evaluation (CASPE) (2004). Due to financial setbacks, this program was not continuously active until 1991. In the United Kingdom, a sustained accreditation program has been in place since 1990. Results of a 2001 survey indicate that 11 European countries have formally implemented hospital accreditation programs and nine have programs under development (Shaw, 2002).

In the United Kingdom, two independent and nongovernmental agencies provide health facility accreditation services. The Health care Accreditation Programme (HAP) was first developed to oversee the National Health Service hospitals but has grown to include public and community health-care centers. The Health Quality Service (HQS) oversees the accreditation of both public and private-sector institutions. Accreditation reports are available for public inspection in the United Kingdom and a handful of other countries, but in general are not available to health-care consumers in Europe. Although the majority of accredited programs are hospital-based, evaluations of community and outpatient care centers are evolving in several European countries.

Both JCAHO and HQS offer international accreditation services. In 1999, JCAHO initiated an international program for accreditation. To address the international differences in health-care delivery, a 16-member task force developed "international consensus standards" for the Joint Commissions International. This task force represents the health-care concerns, values, and governments of countries on six continents. HQS offers consultation services to European countries that are developing quality and accreditation programs. Two organizations, the European Societies for Quality in Health Care and the International Society for Quality in Health Care have just begun efforts to unify health-care accreditation throughout Europe and worldwide.

The Hospital Environment

It has long been known by geriatricians that the hospital is a dangerous place for frail, elderly individuals who are at high risk for iatrogenic complications. If immobility, delirium, and nutrition are not addressed upon hospitalization, unwanted morbidity, and functional decline can rapidly occur (Inouye *et al.*, 1998a; Inouye *et al.*, 1998b). Altering the hospital environment to improve outcomes in the elderly has become a focus of research and a measure of quality in health care. *US News and World Report* magazine ranks United States hospitals and medical programs each year. Among a host of factors used to evaluate quality, hospital-based geriatric services are included in this calculation (O'Muircheartaigh *et al.*, 2004).

Table 3 Continuous quality improvement report

Topic_____ Dept._____

Report Date _____ _____Initial Report _____ Follow-up

I. Process Planning

Reason for selecting topic_____

Starting Date_____

Frequency of Monitoring_____

Sampling Population_____

Source of Information _____Records _____Survey

_____Observation _____Other

Method for Data Collection_____

II. Indicators and Data Presentation

Indicator	Goal (Frequency or %)	Data (Numerical)	Data (Percent)

Interpretation of Data and Comparison to Established Goals:

III. Analysis and Plan of Improvement

A. Areas for Improvement — Obstacles or Barriers

B. Action Plan

	Key Personnel	Initiation Date	Completion Date

IV. Follow-up and Re-evaluation

Indicator	Date to Re-evaluate	Key Personnel	Date for Follow-up Report

Report Prepared and Reviewed by:

Name Title Date

Over the past decade, several geriatric services have been developed with demonstrated benefit in reducing the risk of hospital-related morbidity and mortality. These programs have largely targeted the prevention of delirium and reduction in functional decline. Hospitals are increasingly aware that reducing adverse events in the elderly is important not only for maintaining a positive public reputation, but also in reducing health-care costs.

Acute Care for the Elderly (ACE) units have been shown to decrease discharge to nursing homes and to improve functional outcomes at hospital discharge (Landefeld *et al.*, 1995; Counsel *et al.*, 2000). The general principles of ACE units include an interdisciplinary care approach, tailoring the hospital environment to reduce iatrogenesis, maximizing functional status, daily geriatric assessments with an actively involved, specially trained nursing staff, and proactive discharge planning. The implementation of ACE units in hospitals is growing.

The Geriatric Evaluation and Management Unit (GEMU) is another multidisciplinary care model linked closely to the inpatient hospitalization setting. GEMUs provide subacute care and rehabilitation in a setting that bridges hospital to home. The goals of GEMU care include maximizing functional, social, and medical status through comprehensive geriatric assessment. Patients who would otherwise require nursing home placement receive dedicated medical and therapy services to regain lost independence. The GEMU model has demonstrated benefit in reducing rehospitalization, improving physical and cognitive functioning, reducing mortality, and increasing the likelihood of living at home after discharge (Stuck *et al.*, 1993). These outcomes are indicators of the quality and benefit of a multidisciplinary approach to care of the older adult.

QUALITY IN THE COMMUNITY SETTING

Home Care

Medical care in the home has shifted from the historical single-provider model of the early 1900s to a team-based service with the advent of home health-care organizations. This multidisciplinary approach has expanded the access and availability of health-care services to homebound individuals. Australia has taken home care to an even higher level of sophistication with the "Hospital in the Home" approach. This model provides hospital-like services to individuals at home who are acutely ill but unwilling to enter the hospital or for whom hospitalization is unlikely to provide any measurable health benefit. The quality of care for Hospital in the Home as measured by cost, patient satisfaction, and medical outcomes is at least equivalent to traditional hospital care (Board *et al.*, 2000; Caplan *et al.*, 1999).

Patient care in the home is of increasing complexity and acuity. For organizations to meet the quality care standards expected by consumers, home-care services must be broad in scope and efficient in delivery. The success of Hospital in the Home and growth of home care is in part due to the advancement of portable medical technologies. Mobile radiology and laboratory services have expanded the diagnostic capabilities of home-care providers. The availability of intravenous access services and infusion devices have allowed more frail and debilitated elders to receive necessary intravenous therapies without transfer to the hospital or nursing home setting. Portable electrocardiogram monitors and serum analysis systems, although not in widespread use, now allow providers a more efficient and expedited evaluation of the home-care patient.

To address the question of how home health services improve the quality of medical care, the AHRQ, through the Centers for Medicare and Medicaid Services (CMS) in the United States, has developed a Home Health Quality Initiative project. CMS currently provides financial reimbursement for more than half of the home-care expenditures for seniors Basic Statistics About Home Care (2000). A set of 11 quality measures was selected to evaluate home-care agency services. These measures were based on outcomes data from the Outcome and Assessment Information Set (OASIS) national standardized home-care database. Quality measures are functionally based, such as improvement in toileting or improvement in bathing, but also include the utilization of emergency or hospital services Centers for Medicare and Medicaid Services (2003). Using the reported outcomes on these quality measures, certified home-care agency evaluations can now be reviewed online by the medical consumer.

Home monitoring and telemedicine systems are of increasing interest in the care of chronically ill seniors. A variety of products that record patient information, transmit data to a monitoring center, or give patient reminders are now commercially available. Remote medical monitoring systems can intermittently or continuously monitor vital signs and disease symptoms using noninvasive and minimally intrusive sensors. These systems use Internet, radio, or phone-line transmission of medical information to a hardware- or software-based system that acquires, stores, and processes the data. Medical staff can examine the data in real time or at periodic intervals. Alert parameters can be programmed to immediately notify the provider, of abnormal findings. These systems are used almost exclusively in association with home health-care services. Initial studies suggest that for chronic disease management, electronic home-monitoring systems can reduce hospitalization rates, and length of stay, and improve disease control (Kornowski *et al.*, 1995; Mehra *et al.*, 2000; Maiolo *et al.*, 2003; Rogers *et al.*, 2001).

The most basic home-care technologies include personal alarm systems and emergency response telephones that make a voice connection between the patient and the response center. This "lifeline" monitoring system uses a self-activated call button that is often worn as a necklace or bracelet. More expansive and complex systems are being designed to monitor the home and activity of frail elders. The "smart home" technology utilizes sensors placed throughout the home to track "normal" daily activity and report potential emergencies by detecting deviations from typical activity patterns. These devices may improve the safety and security

of older adults living at home, but conjure up unsettling images of an Orwellian world where "Big Brother" is watching.

Database Analysis in the United States

Large, centralized health-care organizations, such as health maintenance organizations (HMO) and the Department of Veterans' Affairs Medical Centers (VAMC) in the United States, frequently use health database analysis to track costs, utilization of services, and patient-care outcomes. Data from these organizations is used for epidemiology studies and for population-based research on disease and health-care services. Although cost containment may be a driving force in the monitoring of health statistics, these organizations have the infrastructure to use health-care data for quality improvement purposes.

Because laboratory, radiology, and pharmacy services are usually provided within the organization, utilization statistics may be readily available to the clinical and administrative providers. Often this information is tracked electronically within the organization. Practice patterns can be monitored and feedback sent to clinicians or departments to improve the delivery of patient care. Appointment backlogs, vaccination rates, and cancer screening rates may be targeted by the organization. Goals for improving the delivery of health care can be set and trends measured after instituting a plan of improvement.

There is growing interest in a disease-based team approach to improve health outcomes. Common disorders that require regular monitoring or result in high use of urgent care services, such as diabetes and asthma, are often the target of these efforts. Using nationally developed practice guidelines or internally developed clinical care protocols, centralized health-care organizations have the infrastructure to implement care processes to improve health outcomes.

Although clinical practice guidelines are not universally agreed upon in every detail, they are generally considered to represent a reasonable and achievable standard of care supported by current evidence-based research. Thus, adherence to practice guidelines may serve as a marker for quality care within an organization or clinical patient base. Pharmacy and clinical laboratory databases are used to provide individual feedback to clinicians on decision-making behavior, compliance with national guidelines, and improvement in patient outcomes over time. The use of database monitoring to generate electronic reminders that prompt screening and disease management have demonstrated improvement in practitioner adherence to health-care standards (Bentz *et al.*, 2002; Kitahata *et al.*, 2003; Filippi *et al.*, 2003).

Although database analysis offers much statistical information, ongoing problems include limitation of content, relative inaccessibility to information, lack of automated data, and data mismatches (Fink, 1998; Mullooly *et al.*, 1999). This could be improved through new financial and technical support to HMOs interested in outcomes-based research.

Health Care Audit in the United Kingdom

In the United Kingdom, population-based review is conducted through a process called *clinical audit*. The National Health Service has used this method of quality improvement for over 15 years. Clinical audit is a "systematic, critical analysis of the quality of medical care including the procedures used for diagnosis and treatment, the use of resources, and the resulting outcome and quality of life for the patient". Department of Health (1989) Clinical audit has evolved from a clinician-targeted to a system-targeted review that evaluates the outcomes of a quality improvement process.

Clinical audit is an internal method whereby a clinical practice, such as the frequency of ophthalmologic evaluation in diabetic patients or rate of influenza vaccination, is measured using medical record review. Performance markers are compared with accepted standards, practice guidelines, or previously established audit goals. If performance falls below expectations, a plan for practice revision is established and implemented. Follow-up audit is conducted to assess the success in achieving the targeted practice goals.

Clinical audit is a dynamic process that requires attention to changes in population demographics, health resources, and advances in medical knowledge. Comparison of audit results between clinical sites or regions must account for this heterogeneity. The geriatric population itself is a heterogeneous group. For the elderly, important clinical outcomes are linked less to chronological age than to functional ability. A clinical audit outcome measure of cancer screening rates in a healthy 75-year-old population, for example, may be quite different from a chronically ill and debilitated 75-year-old cohort.

The success of a clinical audit requires a well-structured approach, appropriate time, and appropriate resources. Too frequently, a problem is identified through the clinical audit, but a plan of correction is not implemented or the outcome of the correction is never evaluated. This may be due to a lack of experience and time on the part of the auditors, who are often junior clinicians within the organization. Resources must be available if an organization plans to undergo a systematic review of a clinical issue with the intent to implement a meaningful change in clinical practice.

Large-scale clinical audits can require significant administrative support. Charts must be collected, data extracted, and statistical evaluation performed. A protocol for change in practice must be developed with the input and agreement of clinical practitioners. Piloting the proposed change may be necessary to troubleshoot unforeseen barriers before implementing the plan on a larger scale. After an appropriate duration of practice, the clinical issue must be reevaluated to determine if the new protocol has had an impact on the targeted outcome of the program.

It is important that a clinical audit be viewed as a quality improvement activity and not as a means to emphasize personal shortcomings or to generate punitive action. The audit should focus on areas in need of general improvement and methods to achieve practice goals of the group or within the organization (Dickenson and Sinclair, 1998).

Clinical audit itself is not research, although it may generate research questions. Because an audit reveals epidemiological and demographic information about a clinical practice, the results may lead to publication of health-care trends or results of a quality improvement process. In an era of increasing attention to patient confidentiality and ethical research practices, approval to conduct an audit may be required by an organization. This is especially true in the United States, where academic centers and many health-care organizations have institutional review boards to ensure the safety and confidentiality of patient information.

FUTURE INITIATIVES IN HEALTH-CARE QUALITY

With the advent of high technology, the perception of quality has expanded to encompass the use and accessibility of electronic and computer-based devices in health care. Medical diagnosis, treatment, and documentation have advanced in sophistication to a point where electronics is standard and necessary for patient-care practices. Health-care services, communication, and reimbursement are expedited with the use of high technology. Individuals and organizations without Internet access, electronic medical records (EMRs), or access to innovative diagnostic/therapeutic devices may be viewed as "behind the times". Health-care consumers have an increasing expectation, well-founded or not, that technology-based initiatives provide superior quality and better medical outcomes.

High Technology in Medical Education

The use of technology has fundamentally altered the format of medical education. Computers have changed the classroom environment and augmented the quality of medical presentations. Lectures now efficiently utilize multimedia resources with the ability to present complex content using sophisticated instructional formats. Internet-ready classrooms allow an educator to conduct a search of the literature and access clinical information in real time.

Online, as opposed to live, in-class lectures are available at some medical schools. In one study, students expended 50 minutes less time to complete an on-line lecture activity than the live lecture group, but demonstrated equal post-lecture knowledge (Spickard *et al.*, 2002). Many studies have failed to demonstrate the superiority of Internet-based or computer-assisted tutorials over the traditional lecture and textbook format (Buzzell *et al.*, 2002; Vichitvejpaisal *et al.*, 2001; Williams *et al.*, 2001; Seabra *et al.*, 2004). Thus, an "electronic professor" does not replace the need for live interaction with medical educators. Like any instructional tool, electronic and computer-based programs must be used in the right context, for the right group, and with the appropriate level of "real life" interaction.

Subjects with a high degree of visual-spatial complexity such as gross anatomy and histology have seen remarkable benefit from the growth of digital teaching tools. Three-dimensional views and electronically created images have assisted students in understanding anatomical and physiological relationships. Trainees are being exposed to new technologies from the classroom through the clinical years. Teaching tools that did not exist just a few years ago are readily being incorporated into the educational environment.

New methods of medical education using simulation models are of increasing interest in reducing the incidence of procedural complications. In some studies, surgeons who received virtual reality simulator training for laparoscopic procedures demonstrated significant improvement in skill performance over those without this training (Grantcharov *et al.*, 2004; Jordan *et al.*, 2000). Other research has failed to demonstrate a difference in procedure time and patient discomfort between medical residents trained using a virtual reality-based procedural simulator and traditional bedside teaching techniques (Gerson and Van Dam, 2003). As the use of technology in diagnosis and treatment expands, so will the use of technology-based teaching tools in hopes of improving the quality of medical training.

In an effort to improve the efficiency and safety of patient care, handheld Personal Digital Assistant (PDA) devices have become increasingly popular in medical practice and medical education. Some medical schools and residency programs are providing trainees with these devices preprogrammed with educational tools and reference databases. PDAs have demonstrated benefit in reducing adverse medical events and improving the accuracy of medical documentation. Data is most supportive in the reduction of medication errors and identification of medication side effects (Collins, 2004; Carroll *et al.*, 2004).

Because PDAs now have wireless and Internet access capability, the potential for remote-site electronic access to a central patient-care database is being explored at some institutions. This access can be especially useful for the geriatric medicine practitioner performing house calls, nursing home care, and rural community-based care. These sites traditionally have limited access to electronic resources. Several institutions within the United States, including the VAMC system, have employed technologies that allow practitioners to use portable devices for remote-access to patient information. Patient confidentiality has been addressed through the use of encryption programs that prevent unauthorized access by wireless users.

PDA programs can be used to track and store patient information. This is especially useful in the immediate and accurate retrieval of patient records during after hours, off site, and telephone consultation with patients and other medical providers. The applications to patient safety are of growing importance in the quality improvement process at all sites of care. The use of PDAs and other portable electronic equipment will continue to grow as the demand for immediate and accurate medical information increases.

Electronic Medical Records

Electronic documentation of patient information is also of increasing importance in the delivery of quality medical care.

The hospital setting currently makes greatest use of electronic records, given the volume of information that must be collected and shared among medical practitioners. Whether data is entered electronically by practitioners or accessed in a read-only format, the EMR facilitates communication and access to information. Electronic charting has been shown to reduce documentation time and to improve the accuracy of assigning diagnostic codes (Stengel *et al.*, 2004). The use of computer technology in patient management has repeatedly been associated with a reduction in the frequency of many types of medical errors (Bates and Gawande, 2003).

Many electronic record systems operate via an Internet-based access system that allows users to enter and access data through any Internet-ready computer. Other institutions use on-site computer systems that require users to access data through terminals or workstations networked for this purpose. This system limits access but is potentially a more secure means of maintaining patient confidentiality.

The VAMC in the United States exclusively uses an EMR. This Computerized Patient Record System (CPRS) is the largest EMR in the world. All medical orders, laboratory tests, medical progress notes, medications, and other data are entered and viewed electronically by all medical providers. The system can be accessed remotely by those providers located off of the main medical campus. Alerts, prompts, and predesigned order sets have reduced the occurrence of medical errors and improved the efficiency of medical care within the VAMC system. Those countries with national health-care systems or large health provider groups (such as the VAMC) may be at best advantage to use an all-electronic record system, given the need for a well-structured system to oversee the design and support this form of health information system.

Telemedicine

With the advancement of digital data transfer, the Internet, and wireless-based technologies, rapid relay of visual and audio transmissions have led to the development of telemedicine programs between remote geographic locations. Videoconferencing has extensive educational and clinical applications for the health-care systems. Training can be provided in real time using interactive video technology that allows remote classrooms sites to see, hear, and speak with the instructor. Telemedicine allows primary and specialty-care providers to interact with patients and clinicians in geographically isolated or underserved segments of the population.

In a Singapore hospital pilot project, geriatric specialists conducted telerounds with two off-site homes for the elderly (Pallawala and Lun, 2001). This project was considered a success and was viewed favorably by both patients and clinicians. Improving access to health-care resources is an area of ongoing interest in the quality improvement process. As the technology improves and hardware costs decline, telemedicine will become an increasingly popular means of providing a broader array of health-care services to a larger segment of the patient population.

CONCLUSION

"Quality of Care" has been defined as, "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge". Quality in health care has become a priority as cost, volume, and efficiency have become critical issues in meeting the growing health-care demands of the medical consumer. Over the past two decades, the interest in health-care quality improvement has grown dramatically. Consumer groups, medical societies, and health-care organizations have actively promoted quality in health care. These national and international associations work within the health-care framework and governmental regulations unique to each country to help meet consumer and regulatory demands for high-quality medical services.

Based on the established health care and payer system, each organization may address quality control quite differently. Health-care facility accreditation is a common means of marking quality and promoting the excellence of an institution. Other groups may choose certification using established standards such as the ISO-9000 process. At the level of the individual provider, performance may be assessed through audit or comparison of practices with established clinical guidelines.

The TQM process is well suited for the complex health-care environment. This method is used to critically evaluate not only medical treatments and techniques but also the process by which medicine is delivered to the health-care consumer. Quality improvement may then involve change in practice on an individual level and change in operation on a larger scale that benefits a broader population. Using quality indicators and outcome measures that quantitatively and objectively measure care, outlying data can be used to alert the organization to quality control problems.

Geriatricians are in a unique position to influence the health-care quality improvement process. Interdisciplinary care and TQM are already familiar practices for most medical practitioners. As medical directors, geriatricians have taken a leadership role in improving institutional and rehabilitation practices. The quality of care for the elderly has been enhanced through new initiatives such as ACE and GEMU models and home-care technologies. Using new technologies, electronic databases and Internet resources, care for the older population stands to broaden in scope and sophistication in coming years. Geriatricians will continue to be strong advocates for care practices that improve the process and outcomes of medical care for a growing and aging population.

KEY POINTS

- The process of standardizing health-care quality has evolved over the last 100 years.

- The Joint Commission on Accreditation of Health care Organizations (JCAHO) has accredited hospitals and health-care facilities for over 50 years.
- Continuous Quality Improvement, also known as *Total Quality Management*, is a team-based approach used to evaluate and institute system-wide changes.
- Database analysis and health-care audit are two methods of evaluating quality on a population-based scale.
- The use of computers and electronic communication systems have improved medical efficiency and reduced medical errors.

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Appendix 1: Health-care quality organizations

Abbreviation	Organization	Origin	Created
ACHS	Australian Council for Health Care Standards	Australia	1974
AGS	American Geriatrics Society	United States	1942
AHRQ	Agency for Health care Research and Quality	United States	1989
AMDA	American Medical Directors Association	United States	1978
ASGM	Australian Society for Geriatric Medicine (Previously Australian Association of Gerontology and Australian Geriatrics Society)	Australia	1960s
BGS	British Geriatric Society	United Kingdom	1947
CAHPS	Consumer Assessment of Health Plans	United States	1999
CHAP	Catalan Hospital Accreditation Programme	Spain	1981
CMS	Centers for Medicare and Medicaid Services (Previously Health Care Financing Administration: HCFA)	United States	2001 (HCFA 1977)
EFQM	European Foundation for Quality Management	Europe	1988
HAP	Health care Accreditation Programme	United Kingdom	1990
HC	Health care Commission	United Kingdom	2004
HQS	Health Quality Service (Previously Kings Fund Organisational Audit: KFOA	United Kingdom	1998 (KFOA 1989)
IEC	International Electrotechnical Commission	United States	1906
IOM	Institute of Medicine	United States	1970
ISA	International Federation of the National Standardizing Association	Europe	1926
ISO	International Organization for Standardization	United Kingdom	1947
ISQua	The International Society for Quality in Health Care	Australia	1985
JCAH	Joint Commission on Accreditation of Hospitals	United States	1951
JCAHO	Joint Commission on Accreditation of Health care Organizations	United States	1987
NCQA	National Committee for Quality Assurance	United States	1990
NHS	National Health Service	United Kingdom	1948
RACP	Royal Australian College of Physicians	Australia	1938
USPSTF	U. S. Preventive Services Task Force	United States	1984
VAMC	Department of Veterans Affairs Medical Centers (Previously Veterans Administration: VA)	United States	1989 (VA 1930)

Resident Assessment Instrument/ Minimum Data Set

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INTRODUCTION – COMPREHENSIVE GERIATRIC ASSESSMENT

Care of frail elderly individuals requires attention to a broad range of potentially interrelated problems. With advancing age, individuals are likely to have several chronic medical problems and conditions that need to be managed, and the need to take multiple prescriptions that have to be reviewed, and whose side effects need to be identified, monitored, and controlled. At the same time, appropriate care will also address issues of functionality – both physical and cognitive – to help maintain independence or assure that necessary assistance is available. In addition, an older person's well-being may be affected by the individual's social environment: whether she (the more likely gender) is isolated, able to get out (of her room in a nursing facility, of her home), and is able to interact reasonably successfully and often with others. Physical environment also plays a role in either helping frail elders maintain independence or placing them at risk, and must be evaluated. These are only some of the issues that may be part of a comprehensive geriatric assessment.

It would be impossible to address all of the potential issues that affect the health, functioning, and psychosocial well-being of a frail elder in a single assessment tool. One possible solution is to develop a tool that will permit the identification and codification, within a reasonable time frame, of sufficient information to allow a professional to identify problems or risk factors that serve as the basis for additional assessment and clinical interventions or care planning. This compromise is a "Minimum Data Set" (MDS). It is also important that the assessment items be standardized: rather than locally accumulated "baskets" of information, uniform information should be obtained using scientifically tested items. These items then begin to support a "language" for understanding and discussing long-term care.

While the driving force for developing an MDS is to support clinical decision-making around the care of an individual person at one point in time, it is easy to expand these notions to following individual's trajectories over time – how has the person come to this point in time? Are the problems we see now new or are they persistent manifestations of problems that have already been addressed? Knowing what a person was like, just prior to the onset of a hip fracture or stroke, can be critical in developing goals for recovery and clinical interventions. Thus, for a frail elder, an MDS can provide a structure for basic information that identifies the need for additional assessment that will ultimately generate the critical information needed to arrive at care decisions.

Beyond decision making for the individual, these same data have a spectrum of applications that greatly enrich the value of an MDS. These include monitoring quality, measuring outcomes, determining eligibility for services, setting payment levels based on acuity, evaluating programs, and developing policy.

In this chapter, we discuss one particular family of Minimum Data Sets, anchored on the United State's National Nursing-Home Resident Assessment Instrument (RAI), often referred to as the MDS. In particular, we address the design, development, and testing of the Nursing-Home MDS, other allied MDSs for other care sectors (such as home-care), applications of MDS data beyond care planning, implementation of these instruments in the United States and abroad, and finally, issues and future opportunities.

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DEVELOPMENT OF THE NATIONAL NURSING-HOME RESIDENT ASSESSMENT INSTRUMENT/MINIMUM DATA SET

A long series of documented abuses in nursing homes increasingly prevalent in the 1960–1970s began to focus attention on the deplorable status of nursing-home care. A series of legal actions in the late 1970s and early 1980s confirmed the responsibility of the US Government, as a principal payer, to assure the quality of such care. Thus, in 1982, Congress requested from the Institute of Medicine (IOM) a study of the existing regulations, and recommended changes that would strengthen the regulations and enhance the ability of nursing facilities to ensure satisfactory care for their residents (IOM, 1986). The IOM report suggested a series of reforms of the "Conditions of Participation," the standards or requirements that nursing homes must meet in order to be eligible for federal and state funds for care of Medicare and Medicaid beneficiaries. The reforms recommended by the IOM were comprehensive and included provisions addressing standards, the inspection process, and enforcement, and recommended increased aide training, minimum staffing by registered nurses, and assurance of quality of care, quality of life, and the rights of residents.

A 2-year study, including a series of hearings, led to the IOM report (1986), in which one of the central conclusions was that the development of a uniform, comprehensive resident assessment system was essential for improving the quality of care in the nation's nursing homes. The Committee viewed comprehensive functional assessment as the cornerstone of individualized care planning that would focus on helping each resident attain and maintain their maximum practicable functioning and well-being.

Spurred by the legal requirements of court cases and pressure from advocates, many of the IOM recommendations were passed into law as part of the Omnibus Budget Reconciliation Act of 1987 (OBRA '87). One mandate was that the Health Care Financing Administration (now the Centers for Medicare & Medicaid Services – CMS) fund the development and then the implementation in 1991 of the "National Nursing-Home Resident Assessment Instrument/Minimum Data Set."

The new instrument system was designed to support care planning. To accomplish this, it consists of several parts. The first is the Minimum Data Set (MDS), the assessment itself, containing the core items necessary for a comprehensive assessment of the residents of nursing homes. On the other hand, it also includes items that only supported care planning, no matter how urgent or attractive other items were. The domains covered are shown in Table 1. Items are also described in greater detail in an accompanying *RAI Training Manual* (Morris *et al.*, 1996).

The MDS also provides "triggers". These are individual items or combinations of MDS elements which identify residents for whom specific Resident Assessment Protocols (RAPs) – the second part of the system – should be completed. The triggers were developed to identify current problems or the potential for improved function, as well as predictors of who is likely to have a problem in the future; thus, they indicate those people who have or are at risk of developing a problem. There are 18 RAPs, each addressing a major problem in the care of nursing-home residents. Table 2 lists the nursing-home RAPs. These assessment protocols are not intended to automate care planning or to create "cookie cutter" care plans that look the same for all clients. Instead, they are intended to help the clinician focus on key issues identified during the assessment process, so that the provider and the client can explore whether and how to intervene and develop an individualized plan of care. Each RAP has a structured framework – guidelines – for conducting additional assessment. This additional assessment is intended to clarify the nature of the problem or risk factor, to identify underlying causes, such as diseases or side effects of a medication, and to explore the potential for treatment or management of the condition and the medical causes. This information is used by the facility, ideally a multi disciplinary team including the resident's physician, to develop an individualized plan of care to address the targeted problem.

The intent of the protocol is educational rather than prescriptive. Each RAP organizes the information from MDS items that can be used to inform the care planning process and identifies additional assessment items and background information that might be needed. Thus, RAPs provide a formal context in which information about residents, their strengths, preferences, and needs, can be linked to care plan options. The guidelines, in essence, also ask the care planners to consider whether one problem may masquerade as another: have you considered that loss of communication attributed to dementia might actually be caused in this patient by a loss of hearing? Could this be a side effect of a particular medication

Table 1 MDS 2.0 Domains

Identification and background information	Health conditions
Cognitive patterns	Oral/nutritional status
Communication/Hearing patterns	Oral/dental status
Vision patterns	Skin condition
Mood and behavior patterns	Activity pursuit patterns
Psychological well-being	Medications
Physical functioning and structural problems	Special treatments and procedures
Continence in last 14 days	Discharge potential and overall status
Disease diagnoses	Assessment information

Table 2 Resident assessment protocols (RAPs)

Delirium	Cognitive loss/dementia
Visual function	Communication
Activities of daily living function/rehabilitation	Urinary incontinence and indwelling catheter
Psychosocial well-being	Mood state
Behavioral symptoms	Activities
Falls	Nutritional status
Feeding tubes	Dehydration/fluid maintenance
Dental care	Pressure ulcers
Psychotropic drug use	Physical restraints

and have you considered a "drug holiday" or a change in therapeutic dose? While not telling the clinical staff what to do, the guidelines challenge and help the care planner think through the process of care for the individual elder. Overall, the RAPs are critical in that they help clinical staff understand how they can use the assessment data. Together, the MDS assessment, RAPs, and their triggers form the RAI system.

Several approaches were employed in the development of the MDS to improve the validity and reliability of the assessment process and resulting data. These included design decisions such as the following:

- To assess residents' performance and function rather than potential function. For example, rather than ask whether a resident could dress, the MDS asks how they dress, with an included possible response that the activity did not occur in the past seven days.
- To describe manifested conditions or behavior rather than interpretations of the condition or behavior. Thus, the MDS asks whether the resident had "sad, pained, or worried facial expressions" or "crying/tearfulness" rather than asking whether the resident was sad.
- To include full definitions of items and responses on the form. For example, rather than just have an item refer to "eating", it's better to indicate what is meant, directly on the form. The MDS assessment form includes the definitions and response categories that address what to do if the resident is fed by others, gets nutrition through a tube, or feeds himself, but does so while dropping food on his clothing and the table Thus, the MDS uses the definition – "How resident eats and drinks (regardless of skill). Includes intake of nourishment by other means (e.g., tube feeding, total parenteral nutrition)". Another example is diagnoses, where those recorded should be "only those diseases that have a relationship to current Activity of Daily Living status, cognitive status, mood and behavior status, medical treatments, nursing monitoring, or risk of death (do not list inactive diagnoses)".
- To include examples and exclusions that deal with common confusion about how to respond for an item. To return to the eating example, should a person be considered dependent in eating if they require someone to open a milk carton or carry their tray to a table? The MDS identifies such assistance as "set-up help" and has a special response code for this. Such information needs, however, to be part of the assessment system and clearly indicated on the form (instrument) or in training material.
- To include time delimiters. For example, an assessor might be confused about how to score the resident who was unable to dress herself on the day of the assessment (due to a flare-up of his arthritis) but dressed independently the rest of the week. The lack of such specification would make the information unreliable, so the MDS contains time frames that are carefully specified for each item.
- To cover many domains and focus on function. Any assessment of elders must go beyond medical conditions and diagnosis to physical and mental function, as well as psychosocial well-being and measures of involvement. Further, the MDS attempts to address not only individuals' weaknesses, but also their strengths and preferences. The "down side" is that an assessment instrument can get excessively long, and a balance between length and comprehensiveness has to be found: not every item, scale, or even domain can be included, for this would be unwieldy. While not small (with close to 400 items), the MDS was the smallest instrument that would balance these competing goals
- To use all possible sources of information. There are distinct advantages to self-reported assessments, not only because they can usually be accomplished with less cost but also because, more importantly, they capture subjective feelings and opinions of the subject. However, some information is not provided well by the elder, such as diagnoses or the use of health services. The elder cannot be trained in accurate assessment or may bias a response because of embarrassment, avoidance, or lack of knowledge or perspective. The best scenario, used in the MDS, is to combine the two methods, collecting information both directly from the elder and from all others knowledgeable about the elder, including family, health care professionals (e.g., physicians, nurses, social workers, therapists, and nurse aides) and nonprofessionals, such as a spouse, adult, child, or neighbor who helps the elder. Further, it uses information in the medical record and the clinician's own observations of the resident, and asks the clinician conducting the assessment to use all appropriate sources in making decisions. When the information gathered from these multiple sources is contradictory, the assessor should use his or her best judgment of which is the most appropriate.
- To use "items" rather than "questions". To gather information on a particular topic, the MDS describes the information needed rather than posing a specific question. There are several advantages to this approach. This provides assessors with the greatest flexibility and encourages them to use multiple sources of information, including their own observations. While items are ordered on the instrument, without a fixed "script", there is no fixed order in which information is gathered, making the assessment process simultaneously more efficient and more accurate.

The approach taken to the development of the RAI included highly systematic development of the conceptual framework, basic reliability testing of the instrument and training materials, extensive field testing, design of data flow systems, and detailed planning of the implementation. A wide range of clinicians and researchers was included at every stage of the process. The professionals came from a wide spectrum of clinical disciplines including nursing, social work, medicine, physiotherapy, occupational therapy, speech therapy, recreational activity, and nutrition. Also represented were consumers, resident advocates, providers, representatives of the nursing-home industry, and regulators and measurement specialists.

The RAI system was implemented in 1990–1991 throughout the United States, in all nursing facilities that participate in the Medicare or Medicaid programs – 98% of all nursing homes in the country. Facilities must use the MDS/RAI to assess all residents (regardless of who pays for their care) upon admission and to develop their plan of care. It is also used to assess residents annually after admission and upon any significant change in their health status. A reduced "Quarterly Assessment" is performed to monitor the effects of care and the need for modifications to the care plan. The MDS assessment itself takes approximately two hours to complete for a new admission, about three-quarters of that time for an annual reassessment, and half that time for the reduced quarterly assessments, all excluding the time to develop the care plans. The average nursing-home resident triggers on approximately eight of the RAPs around which care planning must be considered. A care plan intervention may not be implemented for all triggered RAPs for a variety of reasons. For example, the multidisciplinary care planning team may set priorities among the existing problems and address a few in order of importance. Alternatively, the clinicians may conclude that addressing one area, such as depression, may also resolve another, such as nutritional risk, if they conclude that the resident's leaving food uneaten is a sign of the depression. The federally mandated nursing-home survey system, as part of ensuring compliance with acceptable standards of care, audits MDS assessments and their use by facilities in care planning. Some states also audit MDS data if it is used for payment or eligibility determinations.

A revised RAI was implemented in 1996, and beginning June 1998, facilities were required to submit computerized assessments to CMS that developed a national archive for research and monitoring purposes.

The MDS has been tested multiple times for inter-rater reliability. The tests conducted throughout the country have included inter-rater reliability among trained nurse assessors in nursing homes, facility versus research staff, nursing homes that are large and small, and those run for profit and those that are voluntary. These tests have demonstrated high levels of item reliability (as measured by the kappa statistic) in the initial MDS (Hawes *et al.*, 1995) and even higher with the revised instrument (Morris *et al.*, 1997). The most recent evidence comes from an extensive study performed for CMS as part of a six-state study of quality indicators. A reliability study collected dual assessments of a total of 5758 residents in 209 facilities. In each instance, a research nurse independently assessed a resident who had recently been assessed by facility staff. The two assessments were quite close. For example, for the MDS items describing cognitive and physical functional and clinical areas, the average Kappa reliability obtained was 0.79, which was very close to the average of 0.84 which was obtained when similar cases were scored by two research nurses. In fact, only about 4% of facilities were found to have deficient reliability scores. The general conclusion was that the MDS is being completed with reasonable consistency in American nursing homes (Morris *et al.*, 2002).

Field testing has addressed not only item reliability but also how users assess the reasons for any misclassification, misunderstandings of items and instructions, and the "value" of individual items for the care planning process. Additionally, research has addressed the validity of items and scales; we shall discuss this work later.

The structure of the RAI system and its direct use in clinical care planning has enabled it to achieve many of its goals. Its introduction in the United States led to observable changes in the quality and outcome of care. The evaluation examined the care of a sample of 2000 nursing-home residents in 255 facilities in 10 states, at two points in time in 1990 and 1991 before the RAI implementation, with a comparable cohort of residents in those facilities at two points in time during 1993. This evaluation demonstrated several significant changes in process and outcome quality, including:

- an increase in the comprehensiveness and accuracy of the information available in residents' medical records (Hawes *et al.*, 1997);
- an increase in the comprehensiveness of care planning, with care plans in the post-RAI period addressing a greater percentage of residents' health problems, risk factors, and their potential for improved function (Hawes *et al.*, 1997);
- an improvement in a wide array of other care processes that affect residents' quality of care and quality of life, including increased involvement of families and residents in care planning, increased use of advance directives, increased use of behavior management programs, increased involvement in activities, and decreased use of problematic interventions, such as indwelling urinary catheters and physical restraints (Hawes *et al.*, 1997; Teno *et al.*, 1997);
- a significant reduction in decline among residents in such areas as physical functioning in Activities of Daily Living (ADLs), cognitive status, and urinary continence (Phillips *et al.*, 1997); and
- a significant reduction in the number of nursing-home residents who were hospitalized, with no increase in mortality (Mor *et al.*, 1997b).

Currently, there are two ongoing efforts to revise the RAI. The first, funded by CMS, will revise the RAI for use in the United States, including adding items that can address issues of quality of life and satisfaction (Kane *et al.*, 2003). There is a separate effort by the initial RAI designers, in concert with an international research consortium, to develop an integrated suite of assessment instruments for the broader field of long-term care. We describe this latter effort next.

OTHER MINIMUM DATA SETS FOR LONG-TERM CARE

The success of the RAI/MDS for nursing homes encouraged the development of parallel assessment systems for other long-term care sectors. The inter*RAI* group, a nonprofit

cross-national consortium of researchers including the developers of the original (nursing home) RAI, have developed a suite of instruments (interRAI, 2004), including:

- inter*RAI* LTCF – Long-term care facility (new version of the RAI)
- inter*RAI* HC – Home care
- inter*RAI* PC – Palliative care (institutional and community-based)
- inter*RAI* PAC – Post-acute care (institutional and community-based)
- inter*RAI* AL – Assisted living and residential care facilities
- inter*RAI* AC – Acute care – to address chronic care problems of individuals in hospitals with acute needs
- inter*RAI* MH – Mental health (psychiatric institutional care, short- and long-term)
- inter*RAI* CMH – Community mental health
- inter*RAI* CHA – Community health assessment (screener for lighter-care individuals in community settings)

Development is also proceeding on two additional instrument systems:

- inter*RAI* ID – Intellectual disability - persons with mental retardation and developmental disabilities
- inter*RAI* PWD – Persons with disability (younger individuals, usually under age 55, in both community and institutional settings)

Each instrument includes both an assessment – a Minimum Data Set – and applicable care planning guidelines (Clinical Assessment Protocols, like the RAPs for the RAI, discussed earlier). Each also has been tested for reliability and validity of items.

Although each instrument in the interRAI family of Minimum Data Sets has been developed for a particular population, they are designed to work together to form an integrated health information system (Hirdes *et al.*, 1999). In particular, all share a common language, that is, they refer to the same clinical concept in the same way across instruments. Using common measures enable clinicians and providers in different care settings to improve continuity of care, as well as to integrate care/support for each individual. Common language also allows families, advocates, and public payers to track the progress of program participants across settings and over time. Such information can yield important findings regarding what works to improve an individual's quality of life. On the other hand, specific items have been developed for each specific application. For example, the home-care instrument documents the individual's capability to perform more integrative activities (instrumental ADLs such as shopping, managing medications, housekeeping, etc.), environmental problems, and caregiver support; the palliative care instrument adds information on the individual's ability to address unfinished business and increased detail about pain control; the acute care instrument looks back to functional capability before the precipitating event of the stay, and so forth.

Table 3 Client assessment protocol (CAP) areas

Functional performance	Health problems/syndromes
ADL rehabilitation potential	Cardio-respiratory
Instrumental Activities of Daily Living (IADLs)	Dehydration
Health promotion	Falls
Institutional risk	Nutrition
Sensory performance	Oral health
Communication disorders	Pain
Visual function	Pressure ulcers
Mental health	Skin & foot conditions
Alcohol dependence & hazardous drinking	*Service oversight*
Cognition	Adherence
Behavior	Brittle support system
Depression and anxiety	Medication management
Elder abuse	Palliative care
Social function	Preventive health measures
Continence	Psychotropic drugs
Bladder management	Reduction in formal services
Urinary incontinence & indwelling catheter	Environmental assessment

As an example, the list of care planning areas addressed by home-care instrument (inter*RAI* HC) is shown in Table 3.

Thus, the suite of instruments provides a balance between common measures across the long-term care continuum and specialized measures for particular care environments. In 2005, the "harmonization" of all of the inter*RAI* instruments will be complete. This will assure that all items on multiple instruments have exactly the same wording and the same time frames, and will incorporate the experience of over a decade of their use to eliminate assessment items that have not worked and add new domains that need to be addressed. In the process, many of the instruments have been substantially shortened and divided into modules so that certain domains (e.g., mental health problems in home-care population) are only assessed in detail for individuals who meet specified triggering criteria.

APPLICATIONS OF MDS DATA

Although the sole primary function of the MDS is to support care planning, a variety of other applications of MDS data are valuable. Two – case-mix payment and quality measurement – have attracted the most interest, but other applications represent important capabilities that are available directly from secondary use of data already collected primarily for clinical purposes. The applications discussed here can apply to all of the instruments listed in the previous section, although not all have been developed for each instrument.

Scales and Profiles

The multitude of individual items in an MDS can make it difficult to describe major domains, such as depression or

cognitive impairment. There is great advantage to have a single measure (index or categories), which can have direct clinical utility in a summary report about an individual. However, such a measure can also be used in a profile of program participants to provide epidemiological insight into the status of a target population, in an outcome measure (for example, for measuring quality or program evaluation), or as a covariate in a research study. An additional advantage is that scale development represents a criterion validation of MDS items, by comparing them with known and trusted external measures.

For the nursing home and home-care MDS, the following represent some of the scales that have been developed and validated:

- *Activities of Daily Living Hierarchy*: The ADL Hierarchy Scale groups the various activities of daily living according to the stages of the disablement process. Early-loss ADLs (e.g., dressing) are assigned lower scores than late-loss ADLs (e.g. eating). The ADL Hierarchy Scale provides six categories ranging from no impairment to total dependence (Morris *et al.*, 1999).
- *Cognitive Performance Scale*: The Cognitive Performance Scale (CPS) combines six items on memory impairment, level of consciousness, and executive function/daily decision-making, to produce a scale with seven levels from intact to very severe impairment. A variety of validation studies have demonstrated that the CPS is highly correlated with the Folstein Mini-Mental Status Examination (Morris *et al.*, 1994).
- *CHESS Scale*: The Changes in Health, End-stage Disease and Signs and Symptoms (CHESS) scale was designed to identify individuals at risk of serious decline. It can serve as an outcome indicator where the objective of care and services is to minimize problems related to declines in function. CHESS, originally developed for use in the nursing home, has been adapted for use with the MDS-HC. It uses six items to create a five-point scale. In both the nursing home and home-care populations, there is clear differentiation of all six levels of CHESS scores, and higher levels are predictive of adverse outcomes like mortality, hospitalization, pain, caregiver stress, and poor self-rated health (Hirdes *et al.*, 2003).
- *Depression Rating Scale*: The count of seven MDS depression items has been validated in a comparison of the DRS with the Hamilton Depression Rating Scale and the Cornell Scale for Depression. Compared to DSM-IV major or minor depression diagnoses, the DRS was 91% sensitive and 69% specific at a cutoff score of 3 out of 7 (Burrows *et al.*, 2000).
- *IADL Involvement Scale*: This scale is based upon a sum of seven items: meal preparation, ordinary housework, managing finances, medications, phone use, shopping, and transportation. Individual items are summed to produce a scale that ranges from 0 to 42, with higher scores indicating greater difficulty in performing instrumental activities.
- *Pain Scale*: The Pain Scale was originally developed for use in nursing homes and later translated for use with the MDS-HC. The scale uses two items to create a four-level score that has been shown to be highly predictive of pain in nursing-home residents as measured on the Visual Analogue Scale (Fries *et al.*, 2001).

Reports that combine these scales, potentially with individual items (such as diagnoses or services received) and other measures (e.g., case-mix categories; see the following text) can be useful both at the individual (clinical) level and when summarized for programs or populations. At the individual level, a summary profile can provide a "cover sheet" for a patient's chart or a "transfer document" that would follow a patient to another care setting: hospital, nursing home, and so on. For example, the Province of Ontario, Canada is experimenting with the "Personal Health Profile" that provides a one-page abstract of the home-care MDS, outlining key clinical points of interest to a nursing home admitting this individual. There is value also at an aggregate level, to describe those enrolled and cared for in a program. For example, the State of Michigan has used profiles of its home- and community-based programs to understand differences among the several agencies statewide providing services, and to compare those maintained with home care and those in nursing homes.

Case mix

Case mix is the identification of individuals' characteristics related to the cost of their care. In this application, the goal is to use MDS items in a system that can measure which individual uses more care and to measure the cost of this care. Initially, case-mix development was aimed at improving our understanding of the cost differences between nursing homes. Rapidly, it became clear that facilities varied in the range and distribution of types of residents for whom they cared, and that a method for relating resident characteristics to resource use was central to understanding underlying differences in the cost structures of nursing homes. Moreover, with the successful US implementation of the Diagnosis-Related Groups (Fetter *et al.*, 1991) case-mix system for acute care hospitals in the mid-1980s, the development of case-mix classification systems for all types of institutional providers became of immediate interest for the design of government payment systems. It was recognized that payment systems that recognize varying care needs of patients will, all other things being equal, promote more equitable provision of resources appropriate to patient needs.

The most used (MDS-based) nursing-home case-mix system is the Resource Utilization Groups (RUGs). The latest version, RUG-III, is part of the federal system for paying nursing homes under Medicare as well as almost a half of all state-funded systems in the United States; it is also used in Catalonia (Spain) and is to be implemented in three Canadian provinces and Iceland.

RUG-III (Fries *et al.*, 1994) is the algorithm that used 107 MDS items to group the nursing-home residents to

explain resource use – per diem wage-weighted hours and minutes spent by facility staff caring for residents. The system incorporates up to three dimensions in describing a resident. The first dimension indicates one of the seven major types of nursing-home residents (Special Rehabilitation, Extensive Care, Special Care, Clinically Complex, Cognitively Impaired, Behavioral Problems, and Reduced Physical Functions, in decreasing order of resource use). The second dimension is an ADL index, a summary measure of functional capability, produced by combining four ADL measures (toileting, eating, transfer, and bed mobility). Although ADLs are the most effective measures in explaining resource use, they demonstrate even greater statistical power within defined major types of residents. Also, four ADLs are sufficient; additional ADLs provide little marginal information about resource use. The final dimension describes particular services (such as nursing rehabilitation) or problems (such as behavior). In combination, a total of 44 mutually exclusive RUG-III groups are formed.

Associated with each of the RUG-III groups is a case-mix index, a relative measure of the cost of caring for an individual in this group. Across the 44 groups, there is over a nine-to-one difference in this measure.

This range of resource use argues well for the appropriateness of incorporating case mix in payment systems. Nevertheless, the design of such payment systems is considerably more complex than simply the technical incorporation of case-mix. A few of the issues that need to be addressed include determination of the cost centers to be adjusted by case mix; whether the system will be historic cost-based or pricing; the design of incentives, for example, for discharge, admission of heavy care residents, or other desired facility behaviors.

While most focus historically has been on the use of case mix solely for payment system design, it can assist in facility management (e.g., helping identify trends in the types of residents admitted), staffing decisions (e.g., balancing wards compared to the staff assigned), comparing facilities, and serving as a single measure to best capture the differences in the mix of patients across facilities in statistical analyses (e.g., as a case-mix adjustor for quality indicators).

The use of RUG-III for cross-national comparisons has been greatly enhanced by a series of studies in different European and Pacific-rim nations, demonstrating that it appropriately distinguished the types of resident and that the relative relationship represented by the case-mix indexes holds across nations and care settings, the ratio of care times between residents from two RUG-III groups will be the same (Carpenter *et al.*, 1997). RUG-III thus is an important MDS scale for international comparisons.

There are case-mix systems developed as well for home care, assisted living, and mental health. The home-care system – RUG-III/HC – is a close parallel to the nursing-home RUG-III, thus permitting case-mix comparison of these two populations (Björkgren *et al.*, 2000).

Quality of Care

The MDS addresses quality of care issues in several manners. First, it has been mandated, designed, and implemented to help clinical staff better understand the needs of the residents under their care. With a comprehensive picture of the clinical, functional, social, and mental needs of their residents, staff can use the RAP system to focus on key problem areas and put in place an appropriate plan of care. Thus, the MDS can help *produce* quality of care. Second, items in the MDS can be combined to measure characteristics and outcomes of care that form the indicators of quality of care. In the United States, the CMS and others have moved to the use of MDS-derived Quality Indicators as both a teaching tool to advance quality and as a consumer tool to help families make better choices. We discuss this second use here in more detail.

At the facility level, what stands out is the challenge of simultaneously providing good to superior care in multiple outcome areas. Most of the problems assessed in the MDS do not necessarily relate to one another. Thus, if a facility gears up to provide superior pressure ulcer or restraint reduction care, these efforts will not by themselves carry over into good care in the areas of mood, pain, and delirium. To be a good to superior facility, staff will have to have reasonable clinical knowledge in a wide variety of areas. To achieve this objective will require lower staff turnover, a commitment to education, an active quality care initiative (e.g., a multiple problem CQI effort), staff buy-in at the highest levels, a true focus on the resident as the key to one's business effort, and accurate assessment of resident performance.

Key to this effort has been the emergence of validated quality indicators (QIs), constructed from resident-level clinical data from the MDS resident assessments and aggregated to the facility level. These QIs characterize the performance of nursing facilities on key measures of quality. According to this logic, facilities, state surveyors, purchasers of care, and family members can use performance measures to guide their understanding of the performance characteristics of different facilities. When problematic scores are found, families may be best advised to seek alternative homes for their loved ones, surveyors can focus on those clinical areas in which the home appears to be most deficient, and facilities can use these same data to target care problems for continuous quality improvement efforts.

Measures of nursing-home quality have been proposed and used by researchers in the past, but generally only for a small number of facilities or in select groups of facilities (Mor *et al.*, 1997a). Also, these measures were based upon aggregate data obtained about a nursing home, to compare the rate of events between facilities with various characteristics (Zinn, 1994). Two major efforts have developed quality indicators (QIs) based on the MDS and the appropriate case-mix adjustment mechanisms. The initial work by Zimmerman and colleagues (Zimmerman *et al.*, 1995) has more recently been expanded to a national study to design and validate nursing-home QIs: the CMS-funded MEGA Study (Morris *et al.*, 2002).

Multiple steps were involved in creating and validating QIs: relevant clinical events were identified (e.g., a fall, a stage 2 or higher pressure ulcer, or a decline in ADLs); the interval over which the events were to be measured was established (e.g., 90 days); the occurrence of these events among nursing-home residents over the specified time period was evaluated (e.g., too low a rate of occurrence would have negated the utility of an indicator); appropriate covariate adjustors were identified, to ensure that differential admission policies across facilities was not the cause for inter-facility variation in the rates; and, finally, the indicators were demonstrated valid, in that they were driven by facility processes of care rather than just measuring random occurrences.

The MEGA study QIs are multidimensional, encompassing clinical, functional, psychosocial, and other aspects of resident health and well-being. While single, simple composite measures would be attractive, this does not seem to be an adequate representation of quality. The MEGA team recommended that CMS utilize several QIs from each domain for purposes of public reporting, quality monitoring, and performance improvement.

In total, the MEGA study identified or created 45 quality indicators. Only two QIs had very low prevalence ("New insertion of indwelling catheter" and "Failure to improve and manage delirium" were below 5%); other QI rates ranged between 5 and 92% in nursing facilities. Of the remaining indicators, 13 of the chronic care indicators and four of the post-acute care indicators were judged to have quite a substantial process of care validation.

The chronic care quality indicators with the highest level of validity include (note: some represent multiple QIs, for high, low, or combined risk residents):

- Prevalence of indwelling catheter
- Bladder/bowel incontinence
- Urinary tract infections
- Infections
- Inadequate pain management
- Pressure ulcers
- Late-loss ADL worsening
- ADL worsening
- Locomotion worsening
- Improvement in walking
- Worsening bladder continence.

Four post-acute care quality indicators are highly valid, including:

- Failure to improve and manage delirium
- Inadequate pain management
- Failure to improve during early post-acute period
- Improvement in walking.

Quality indicators have several potential uses including: by facilities in management, for example in a continuous quality assurance system; by government agencies in targeting poor quality facilities for more intense quality of care surveys; by nursing-home organizations in identifying best care practices; and by consumers in identifying the best nursing homes for their loved ones. As an example of the last application, the CMS website now displays MDS-based QIs for all US nursing homes. There is ongoing research to determine whether the availability of such information actually affects consumer decisions.

Eligibility

MDS-HC data can also be used in screening systems intended to identify appropriate care pathways for clients. One issue that has most concerned policymakers has been the rising demand for long-term care services and the resulting costs. As a result, policymakers, advocates, and providers have been faced with the increasingly difficult task of prioritizing target population and allocating increasingly scarce public resources in a fair and equitable manner. Even in the absence of a financial objective, decisions need to be made as to the best setting for caring for an individual.

The data contained in an MDS – nursing home, home care, and so on – can support systematic, standardized methods for such screening and resource allocation activities. While some may be concerned about such use, there are two major advantages. First, the criteria can be developed objectively and scientifically, and are subject to scrutiny and refinement. Second, these systems should never be used without an appeal mechanism to address unusual cases. While appeals could be seen as a way to avoid the whole eligibility system, with both screening and assessment data these decisions can be tracked and used to distinguish between inappropriate "overrides" and potential improvements in the eligibility algorithms.

Several different screening tools currently available include:

MAPLe (Method for Assessing Priority Level): This screening system defines five priority levels that relate to the risk of adverse outcomes. Clients in the low priority level have no major functional, cognitive, behavioral, or environmental problems. Thus, they can be considered self-reliant. The high priority level is based on the presence of ADL impairment, cognitive impairment, wandering, behavior problems, and the client's status on the nursing-home risk CAP. Clients in the high priority level are nearly nine times more likely to be admitted to a long-term care facility than are the low priority clients. MAPLe also predicts caregiver stress (Hirdes *et al.*, 2002).

MI Choice: This 32-question screening tool is derived from the MDS-HC instrument and was developed for the Michigan Department of Community Health. The scoring algorithm groups individuals in one of five levels of care: nursing home, home care, intermittent personal care, homemaker, and information and referral services. The screen can be used over the phone to identify persons who are not likely to meet health, cognitive, and functional criteria for home care or institutional services. This enables expensive in-person assessment resources to be targeted to persons who have

been identified by the screener as more likely to qualify as medically eligible for assistance. During the assessment process, MI Choice can also serve as a complement to the assessor's clinical insights and the individual's preferences about the most appropriate care setting (Fries *et al.*, 2002).

Resource utilization groups (RUG-III, RUG-III/HC): As described earlier, these are case-mix systems, identifying client groups that reflect the relative cost of services they are likely to consume. However, they can also enable decision-makers to identify groups of people who can be considered presumptively eligible for a particular service or benefit. In the US Medicare Prospective Payment System, certain RUG-III categories are determined to meet the Medicare eligible requirements (rehabilitation of skilled nursing services). RUG-III/HC will be used in Michigan to determine eligibility for nursing home or equivalent home- and community-based care.

Outcome Measures and Program Evaluation

Many MDS items or scales, taken from an individual assessment or from the contrast of two assessments of the same individual over a period of time, can serve as outcome measures. Three representative examples of the many possible ones include:

- The presence of any fall in the past 90 days is a negative outcome that is included in the nursing home and other MDSs. Similarly, hospitalization, the presence of pain, decubitus ulcers, loneliness, environmental problems, elder abuse, and so on, are all potentially useful inputs.
- Decline in continence when comparing the level on one assessment to a prior assessment 90 days earlier. One could similarly track declines (or improvements!) in isolation (how much of the time alone during the day), stamina, compliance with medication, and so on.
- Decline in cognition can also be detected as the change in a scale (e.g., the Cognitive Performance Scale) from one assessment to the next. Similarly, one could track overall ADL or IADL function, body mass index, depression, and so on.

An example is the report by Landi *et al.* (1999), which demonstrated a decline from 44% to 26% in the number of clients hospitalized from five home-care agencies in two Italian provinces, using comparisons before and after the implementation of the RAI-HC. Also, Gambassi found that ACE inhibitor therapy (vs. digoxin) for congestive heart failure improved survival and ADL function even for patients over age 85, individuals systematically underrepresented in randomized trials.

The research to derive quality indicators, which are designed around these same outcome measures, can often provide risk adjustment to be sure that populations are compared on similar grounds.

Research

Archives accumulated from the use of MDS assessments can provide data for a range of research topics from clinical and epidemiological to policy. Assessments can be considered by themselves to understand the constellation of clinical problems of individuals; linked with other assessments of the same individual to represent longitudinal trajectories; accumulated by facility, program, region, or nation; and, potentially linked with cost or other identifying characteristics (e.g., census level information to provide a regional "denominator" number of elderly persons, or nonprofit ownership of a facility). The breadth of domains in the MDS assessments provide appropriate measures for many areas of interest, as well as critical covariates to adjust for sample or population differences.

As of 2004, over 400 research articles were listed on the interRAI website. A few examples of these include:

- cross-national comparison of antidepressant use in nursing-home residents
- racial differences in the use of nursing homes
- accelerated decline in centenarians
- the effect of funding changes (e.g., the Balanced Budget Act of 1997) on access to post-acute care.
- risk factors (including race, age, and dementia) in the detection of pain.

There are several advantages to the use of MDS data for research. First, the data meets reasonable reliability standards. Second, there are a large number of observations available, making even rare population numerous, and permitting stratification or control group selection even on multiple characteristics. Third, there are a large number of facilities or agencies represented so that even if this is the appropriate level of analysis (e.g., for contrasting facilities or programs), there are sufficient numbers for strong statistical power. Fourth, the full population is represented and sampling error is eliminated. Fifth, when MDS systems are implemented as part of clinical care, then multiple assessments of the same individual are performed, and longitudinal trajectories and outcome measures can be developed. Finally, multiple years' worth of data are accumulated, so that temporal trends can be visualized.

Multiple Uses of MDS Data

The advantages listed earlier are the result of MDS systems being implemented as part of the standard care process in a setting. In the past, these types of "administrative" data sets, produced as a by-product of the delivery of care, have had low esteem in health policy research. Much of their reputation was well deserved. They have traditionally had most of the following characteristics:

- poor definitions in the instruments, leading to unreliability and lack of validity;

- no "owner" who gains value from the data and is able to promulgate accuracy;
- perceived as "paperwork" and "busy-work" by (overworked) staff who have no personal or professional stake in data accuracy and often never see them used for any discernable purpose;
- little monitoring of data quality or the completeness of assessments;
- no external audit of a facilities' assessments.

The MDS avoids many of these problems by its direct link to managing the care of nursing-home residents. With a central "core" based in clinical care, and performed by professionals responsible for the care of the resident, there are strong incentives to provide accurate information. This provides the foundation for the assessment and its accuracy: which responsible clinician wouldn't do the best job possible in the care they provide? However, once these data are available, motivated and collected for this primary purpose, all the other uses described earlier are valuable yet virtually free by-products.

The addition of alternative uses for the data makes those involved with an assessment system into interested "owners". For example, if the data are used for case-mix payment, quality assurance, staffing decisions, and so on, then facility management will be invested in assuring that the assessment is performed. Further, such multiple uses of the data can directly encourage their accuracy. For instance, consider an assessment item such as pressure ulcers. It is an indicator of a resident whose care is expensive, both for the care of the ulcer and for the other conditions that such a sick patient would have. Therefore, a facility paid under a case-mix payment system (e.g., one based on RUG-III) would get more money if a pressure ulcer was reported. But pressure ulcers are often also used as one of the indicators of poor quality of care, thereby encouraging under-reporting. Use of the MDS item on pressure sores simultaneously for both case-mix and for quality provides counterbalancing forces to encourage accurate assessment of this item. There are, of course, also substantial threats to the accuracy of MDS data. Multiple uses, while potentially providing offsetting incentives, also provide potential bias if individuals cannot see (or are not convinced of) them. The time to complete the MDS is substantial, especially for qualified staff who are often in short supply, potentially resulting in poor assessment or missing data. Staff turnover and inadequate training may mean that assessments are poorly done or incorrectly computerized. While many of these can be addressed through training, auditing programs, improved staffing and careful research methodology, they remain a concern for any research effort.

IMPLEMENTATIONS OF MDS INSTRUMENTS

The MDS instruments have been adopted for use in multiple settings around the world. A limited selection of these includes:

- the nursing-home MDS has been adopted as the national assessment system for Iceland;
- in addition to the mandate that all nursing homes use the MDS, 10 US states have adopted the MDS-HC (home care) and applications for determining eligibility;
- the Province of Ontario, Canada, has adopted the nursing-home, home-care, and mental health MDS instruments province-wide; six other Canadian provinces/territories have or are planning to adopt these instruments as well;
- the General Assembly of Spitex (the Swiss home-care association) has decided to implement the MDS-HC across the entire nation by the end of 2006;
- the MDS-HC has been adopted for use throughout Hong Kong and is one of three recommended assessment systems for home care in Japan;
- both the MDS and MDS-HC are being implemented nationwide in Estonia;
- the MDS-HC is used throughout two regions of Italy.

Several of these implementations are discussed in Fries and Fahey (2003). With these multiple implementations, cross-national data are becoming available to compare, on a common measurement basis, care provided to elderly persons around the world. Prior studies have been handicapped by the lack of detailed information about individuals, measured in a consistent manner. An example of such new studies includes the results of the Aged in Home-Care Project (*AdHOC*) which collected information on 3785 individuals residing in 11 European nations. These data showed that the provision of formal care to people with similar dependency varies extremely widely, with very little formal care in Italy, and more than twice as much as the average across all levels of dependency in the United Kingdom (Carpenter *et al.*, 2004).

KEY POINTS

- Resident Assessment Instrument/Minimum Data Set provides comprehensive assessment of elderly residents in nursing homes.
- MDS provides basis for individualized care planning.
- Other Minimum Data Sets available for home- and community-based and institutional settings, for post-acute, palliative, and mental health.
- Data can be used for multiple purposes, including case-mix measurement, quality indicators, eligibility, and policy research.
- RAI/MDS assessment systems have been implemented in multiple nations, enabling cross-nation comparisons.

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Appendix

Conversion of SI Units to Standard Units

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BLOOD BIOCHEMISTRY

Investigation	SI units	Conversion factor	Standard units
Alpha-feto protein	0.0–20 μg/l	1.0	0.0–20 ng/ml
Ammon. Nitrogen	<40 μmol/l	1.4	15–45 μg/dl
Ascorbate	23–114 μmol/l	0.0176	0.4–2 mg/dl
Bicarbonate	24–30 mmol/l	1.0	24–30 m eq/l
Bilirubin (total)	2–17 μmol/l	0.059	0.12–1.0 mg/dl
Calcium	2.15–2.6 mmol/l	4.1	8.8–10.7 mg/dl
Cholesterol (WHO recommended range)	<5.2 mmol/l	38.6	<199 mg/dl
HDL Cholesterol	>1.0 mmol/l	38.6	>38.0 mg/dl
LDL Cholesterol	1.00–4.00 mmol/l	38.6	38–153 mg/dl
Chloride	98–107 mmol/l	1.0	98–107 m eq/l
Copper	12–21 μmol/l	6.4	76–134 μg/dl
Corticosteroid am	170–750 nmol/l	0.036	6.27 μg/dl
pm	50–200 nmol/l		2–8 μg/dl
Creatinine	50–120 nmol/l	0.013	0.65–1.2 mg/dl
Ferritin	18–300 μg/l	1.0	18–300 ng/ml
Fibrinogen	1.0–4.0 g/l	100	100–400 mg/dl
Folate	>1.4 μg/l	1.0	>1.4 ng/ml
Glucose (Random)	3.3–5.5 mmol/l	18	54–190 mg/dl
(Fasting)	<6.1 mmol/l		50–100 mg/dl
Iron	10.0–36 μmol/l	5.7	57–205 μg/dl
Iron binding capacity	45–70 μmol/l	5.6	250–390 μg/dl
Lactate	0.67–1.8 mmol/l	9.0	6–16 mg/dl
Lead	0.5–2.0 μmol/l	20	10–14 μg/dl
Magnesium	0.7–1.07 mmol/l	2.4	1.7–2.6 mg/dl
Osmolality	280–300 mmol/kg	1.0	280–300 m Osm/kg
Phosphorus	0.8–1.5 mmol/l	3.1	2.5–4.3 mg/dl

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Investigation	SI units	Conversion factor	Standard units
Potassium	3.3–5.0 mmol/l	1.0	3.3–5.0 m eq/l
Protein (total)	58–80 g/l	0.1	5.8–8.0 g/dl
Albumen	38–50 g/l	0.1	3.8–5.0 g/dl
Globulin	18–36 g/l	0.1	1.8–3.6 g/dl
Immunoglobins			
Ig A	0.9–4.5 g/l	100	90–450 mg/dl
Ig M M	0.45–1.8 g/l		45–180 mg/dl
F	0.5–2.2 g/l		50–220 mg/dl
Ig G	7–19 g/l		700–1900 mg/dl
Sodium	136–145 mmol/l	1.0	136–145 m eq/l
Thyroxine	9.6–26.5 pmol/l	0.78	7.5–18.7 μg/dl
Transferrin	1.70–3.70 g/l	0.01	170–370 μg/dl
Triodothyronine (T3)	1.2–3.5 nmol/l	66	80–230 ng/dl
TSH	0.35–5.0 m U/l	1.0	0.35–5.0 μu/ml
Triglycerides	0.57–1.70 mmol/l	88.6	50–151 mg/dl
Urea	2.3–6.9 mmol/l	6	14–41 mg/dl
Vitamin B12	160–920 ng/l	1.0	160–920 pg/ml

URINE BIOCHEMISTRY

Investigation	SI units	Conversion factor	Standard units
Calcium	2.5–7.5 mmol/24 h	40	100–300 mg/dl
Creatinine	9–17 mmol/24 h	0.111	1.0–2.0 g/24 h
Hydroxyproline	0.08–0.25 mmol/24 h	125	10–35 mg/24 h
Phosphate	15–50 mmol/24 h	0.033	0.5–1.5 g/24 h
Potassium	25–100 mmol/24 h	1	25–100 m eq/24 h
Sodium	40–220 mmol/24 h	1	40–220 m eq/24 h

HEMATOLOGY

Investigation	SI units	Conversion factor	Standard units
Hemoglobin	11.5–16.5 g/l	1	1.15–1.65 g/dl
RBC	$3.80–5.80 \times 10^{12}$/l	0.001	$3.80–5.80 \times 10^{6}$/mm^3
WBC	$4.0–11.0 \times 10^{9}$/l	0.001	$4.0–11.0 \times 10^{3}$/mm^3
Platelets	$150–400 \times 10^{9}$/l	0.001	$150–400 \times 10^{3}$mm^3

Index

Notes
Abbreviations

CABG – coronary artery bypass grafting
COPD – chronic obstructive pulmonary disease
DIC – disseminated intravascular coagulation
MCI – mild cognitive impairment
MND – motor neuron disease
NIPPV – noninvasive positive pressure ventilation
NSAIDs – nonsteroidal anti-inflammatory drugs (NSAIDs)

American spelling have been used in this index, for example anemia
Cardiac Trials are indexed under their acronyms.
Page numbers in **bold** refer to boxes or tables
Page numbers in *italics* refer to figures

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